Effects of soft tissue augmentation procedures on peri-implant health or disease: A systematic review and meta-analysis

Thoma, Daniel S ; Naenni, Nadja ; Figuero, Elena ; Hämmerle, Christoph H F ; Schwarz, Frank ; Jung, Ronald E ; Sanz-Sánchez, Ignacio

Abstract: OBJECTIVE To review the dental literature in terms of soft tissue augmentation procedures and their influence on peri-implant health or disease in partially and fully edentulous patients. METHODS A MEDLINE search from 1966 to 2016 was performed to identify controlled clinical studies comparing soft tissue grafting versus no soft tissue grafting (maintenance) or two types of soft tissue grafting procedures at implant sites. The soft tissue grafting procedures included either an increase of keratinized tissue or an increase of the thickness of the peri-implant mucosa. Studies reporting on the peri-implant tissue health, as assessed by bleeding or gingival indices, were included in the review. The search was complemented by an additional hand search of all selected full-text articles and reviews published between 2011 and 2016. The initial search yielded a total number of 2,823 studies. Eligible studies were selected based on the inclusion criteria (finally included: four studies on gain of keratinized tissue; six studies on gain of mucosal thickness) and quality assessments conducted. Meta-analyses were applied whenever possible. RESULTS Soft tissue grafting procedures for gain of keratinized tissue resulted in a significantly greater improvement of gingival index values compared to maintenance groups (with or without keratinized tissue) [n = 2; WMD = 0.863; 95% CI (0.658; 1.067); p < .001]. For final marginal bone levels, statistically significant differences were calculated in favor of an apically positioned flap (APF) plus autogenous grafts versus all control treatments (APF alone; APF plus a collagen matrix; maintenance without intervention [with or without residual keratinized tissue]) [n = 4; WMD = -0.175 mm; 95% CI: (-0.313; -0.037); p = .013]. Soft tissue grafting procedures for gain of mucosal thickness did not result in significant improvements in bleeding indices over time, but in significantly less marginal bone loss over time [WMD = 0.110; 95% CI: 0.067; 0.154; p < .001] and a borderline significance for marginal bone levels at the study endpoints compared to sites without grafting. CONCLUSIONS Within the limitations of this review, it was concluded that soft tissue grafting procedures result in more favorable peri-implant health: (i) for gain of keratinized mucosa using autogenous grafts with a greater improvement of bleeding indices and higher marginal bone levels; (ii) for gain of mucosal thickness using autogenous grafts with significantly less marginal bone loss.

DOI: https://doi.org/10.1111/clr.13114

Thoma, Daniel S; Naenni, Nadja; Figuero, Elena; Hämmerle, Christoph H F; Schwarz, Frank; Jung, Ronald E; Sanz-Sánchez, Ignacio (2018). Effects of soft tissue augmentation procedures on peri-implant health or disease: A systematic review and meta-analysis. Clinical Oral Implants Research, (29 Suppl):32-49.
DOI: https://doi.org/10.1111/clr.13114

Effects of soft tissue augmentation procedures on peri-implant health or disease – a systematic review and meta-analysis

Thoma DS,[1] Naenni N,[1] Figuero E,[2] Hämmerle CHF,[1] Schwarz F,[3] Jung RE,[1] Sanz-Sanchez I[2]

Key words: Systematic review, dental implant, bleeding on probing, periodontal probing pocket depth, peri-implant mucositis, peri-implantitis, bleeding on probing, gingival index, complication, soft tissue, subepithelial connective tissue graft, free gingival graft

Running title: Soft tissue grafting and peri-implant health

Address for correspondence: Daniel S. Thoma, PD Dr. med. dent.
Clinic of Fixed and Removable Prosthodontics and Dental Material Science
University of Zurich
Plattenstrasse 11
CH-8032 Zurich, Switzerland
Phone: +41 44 634 32 57
Fax: +41 44 634 43 05
e-mail: daniel.thoma@zzm.uzh.ch

[1] Clinic of Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich, Zurich, Switzerland
[2] ETEP (Etiology and Therapy of Periodontal Diseases) Research Group, University Complutense, Madrid, Spain.
[3] Department of Oral Surgery, Universitätsklinikum Düsseldorf, Düsseldorf, Germany

Abstract

Objective: To review the dental literature in terms of soft tissue augmentation procedures and their influence on peri-implant health or disease in partially and fully edentulous patients.

Methods: A MEDLINE search from 1966 – 2016 was performed to identify controlled clinical studies comparing soft tissue grafting versus no soft tissue grafting (maintenance) or two types of soft tissue grafting procedures at implant sites. The soft tissue grafting procedures included either an increase of keratinized tissue or an increase of the thickness of the peri-implant mucosa. Studies reporting on the peri-implant tissue health, as assessed by bleeding or gingival indices, were included in the review. The search was complimented by an additional hand search of all selected full-text articles and reviews published between 2011 and 2016. The initial search yielded a total number of 2823 studies. Eligible studies were selected based on the inclusion criteria (finally included: 4 studies on gain of keratinized tissue; 6 studies on gain of mucosal thickness) and quality assessments conducted. Meta-analyses were applied whenever possible.

Results: Soft tissue grafting procedures for gain of keratinized tissue resulted in a significantly greater improvement of gingival index values compared to maintenance groups (with or without keratinized tissue) [n=2; WMD=0.863; 95% CI (0.658; 1.067); $p<0.001$]. For final marginal bone levels, statistically significant differences were calculated in favor of an apically positioned flap (APF) plus autogenous grafts versus all control treatments (APF alone; APF plus a collagen matrix; maintenance without intervention (with or without residual keratinized tissue)) [n=4; WMD=-0.175mm; 95% CI: (-0.313; -0.037); $p=0.013$]. Soft tissue grafting procedures for gain of mucosal thickness did not result in significant improvements of bleeding indices over time, but in significantly less marginal bone loss over time [WMD=0.110; 95% CI: 0.067; 0.154; $p<0.001$] and a borderline significance for marginal bone levels at the study endpoints compared to sites without grafting.

Conclusions: Within the limitations of this review it was concluded that soft tissue

grafting procedures result in more favorable peri-implant health: i) for gain of keratinized mucosa using autogenous grafts with a greater improvement of bleeding indices and higher marginal bone levels; ii) for gain of mucosal thickness using autogenous grafts with significantly less marginal bone loss.

Introduction

Soft tissue grafting procedures are increasingly performed for a number of indications in conjunction with dental implant therapy (Thoma et al., 2014). Major clinical indications include recession coverage, gain of keratinized tissue (KT) and augmentation of soft tissue volume (STV) (Lorenzo et al., 2012) (Basegmez et al., 2012, Thoma et al., 2016, Roccuzzo et al., 2014). These periodontal plastic surgical procedures have been recommended to establish short and long-term favorable biological, functional and esthetic outcomes. From a biological point of view, scientific evidence reports controversial data for the width of KT (Lin et al., 2013, Wennstrom and Derks, 2012). A lack of KT was not considered to be crucial in maintaining the health of peri-implant soft tissues (Wennstrom et al., 1994), to be associated with more bone loss (Chung et al., 2006) or to be more prone to peri-implant disease (Roos-Jansaker et al., 2006). Further studies reported, however, that a wider zone of KT may better preserve soft and hard tissue stability (Bouri et al., 2008), may be more favorable for the long-term maintenance of dental implants (Kim et al., 2009) and may result in better oral hygiene and less recession over time (Schrott et al., 2009). From an esthetic point of view, a number of *in vitro* and clinical studies demonstrated a critical threshold value of 2mm mucosal thickness for implant-borne reconstruction and reconstructive materials less discoloration of the soft tissues (Ioannidis et al., 2016, Jung et al., 2008, Thoma et al., 2015, Jung et al., 2007), as well as superior esthetic outcomes compared to implant sites without grafting (Kan et al., 2009, Cornelini et al., 2008). Moreover, an increased soft tissue thickness (thick biotype) may decrease the risk for recessions with immediate implants (Evans and Chen, 2008). Surgical procedures to augment soft tissue volume were therefore recommended in the esthetic zone mainly from an esthetic point of view and to compensate for volume loss following tooth extraction and implant therapy with immediate or delayed placement protocols (Schneider et al., 2011, Cosyn et al., 2013, Thoma et al., 2016). From a biological point of view, no threshold value for a

specific soft tissue thickness could be defined according to a recent systematic review (Akcali et al., 2016). Still, the major goal of implant therapy is to obtain long-term peri-implant health based on stable peri-implant soft tissue dimensions, low bleeding indices and stable marginal bone levels. In summary, there is a lack of scientific recommendations whether or not to perform surgical procedures for gain of KT and for gain of mucosal thickness to establish peri-implant health and to limit the incidence of peri-implant disease. Neither do clinical suggestions exist for a specific soft tissue transplant to obtain more favorable outcomes. This question can only be answered by (randomized) controlled clinical trials comparing implant sites with and without soft tissue grafting and/or studies comparing different soft tissue transplants and techniques and reported outcome measures assessing peri-implant health.

The objective of the present systematic review was to assess the effect of soft tissue grafting procedures to increase either the width of keratinized tissue or the mucosal thickness at dental implant sites in comparison to implant sites without soft tissue grafting procedures or with different grafting materials/transplants in terms of peri-implant health.

Material and Methods

Protocol development and eligibility criteria

A detailed protocol was developed and followed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Liberati et al., 2009, Moher et al., 2009).

PICO questions

Population: systemically healthy patients with dental implants

Intervention: soft tissue grafting procedures to increase the keratinized tissue or the mucosal thickness at dental implant sites

Comparison: implant sites without soft tissue grafting procedures or with (a) different grafting materials/transplants

Outcome:

- Primary outcome: peri-implant health measured by a bleeding index or gingival index
- Secondary outcomes: probing pocket depth values, marginal bone level changes, plaque index, time-point of intervention, type of material

Focused questions

In systemically healthy patients with dental implants, what is the effect of soft tissue grafting procedures to increase the width of keratinized tissue or the mucosal thickness at dental implant sites in comparison to implant sites without soft tissue grafting procedures or with different grafting materials/transplants in terms of peri-implant health?

Search strategy

An electronic MEDLINE (PubMed) search was performed for controlled clinical studies, including articles published from January 1, 1966 up to July 31, 2016 in the Dental literature. The search was limited to the English, German and Spanish language. Additionally, full text articles of narrative and systematic reviews on similar topics published between January 2011 and July 2016 were obtained. An additional hand search was performed identifying relevant studies by screening these reviews and the reference list of all obtained full-text articles.

Search Terms

The following search terms were applied:

("acellular dermal matrix" OR "dermal matrix allograft" OR "alloderm" OR "keratinized gingiva" OR "keratinized tissue" OR "soft tissue graft" OR "subepithelial connective tissue graft" OR "connective tissue"(MeSH term) OR "free gingival graft" OR "human fibroblast-derived dermal substitute" OR "dermagraft" OR "apligraf" OR "collagen matrix" OR "extracellular membrane" OR "gingival autograft" OR "attached gingiva" OR "attached mucosa" OR "keratinized mucosa" OR "soft tissue augmentation" OR "soft tissue transplantation" OR "vestibuloplasty" (MeSH term) OR "ridge augmentation" OR "soft tissue correction" OR "apically positioned flap")

AND

("dental implants" (MeSH term) OR "jaw, edentulous, partially" (MeSH term) OR "pontic" (MeSH term) OR "implant sites" OR "bleeding on probing" OR "sulcus bleeding index")

Inclusion criteria

Clinical publications were considered if all of the following criteria were suitable: i) human trials with a minimum amount of 10 patients (5 per group), ii) any controlled clinical study (CCT), iii) follow-up of at least 3 months, iv) reported outcome

measures following the surgical intervention for gain of keratinized tissue or gain of mucosal thickness around dental implants including any peri-implant bleeding index/parameter, and vii) patients needed to have been examined clinically.

Exclusion criteria

In vitro and preclinical studies, case series, case reports and reports based on questionnaires, interviews and charts were excluded from the review as well as all studies not meeting the inclusion criteria. Moreover, studies dealing with treatment of recession defects and increase of keratinized tissue around teeth and soft tissue volume at pontic sites were not considered.

Selection of studies

Two authors (DT, NN) independently screened the titles derived from the online search based on the inclusion criteria. Disagreements were solved by discussion. Subsequently, the abstracts of the selected titles were obtained and screened for meeting the inclusion criteria. If no abstract was available, the abstract of the printed article was used. Thereafter, full-text articles of the selected abstracts were obtained. If title and abstract did not provide sufficient information regarding the inclusion criteria, the full text was obtained as well. Again, disagreements were resolved by discussion and Cohen's Kappa-coefficient was calculated as a measure of agreement between the 2 readers.

The final selection based on inclusion/exclusion criteria was made for the full text articles. For this purpose, Materials and Methods, Results and Discussion of these studies were screened by two reviewers (DT, NN) and double-checked. Any questions that came up during the screening were discussed between the authors to aim for consensus. In case potential publications did not report (in detail) on peri-implant bleeding indices/parameters, authors were contacted and asked if they could provide additional data.

Data extraction and method of analysis

All data were extracted independently by two reviewers (DTH, NN) using data extraction tables. Any disagreements were thereafter discussed to aim for consensus.

Information on the following parameters was extracted: author(s), year of publication, study setting, study design, number of patients, age range, mean age, gender, drop outs, mean follow-up and range, periodontal status, smoking habits, systemic condition, type of intervention (test and control(s)), implant system, number of implants, number of implant failures, implant survival rate, probing depth (PD), bleeding on probing (BOP) or any other bleeding index, plaque index (PlI) or any other gingival index, mid-facial mucosal level (MML), width of keratinized tissue (KT), mucosal thickness (MT), marginal bone levels (MBL).

The primary outcome included bleeding on probing (BOP) or any other bleeding/gingival index at the follow-up time-point(s). Secondary outcomes were probing depth (PD), plaque index (PlI), mid-facial mucosal level (MML), width of keratinized tissue (KT), mucosal thickness (MT), marginal bone level (MBL) (changes).

Quality Assessment

Two reviewers (DT, NN) independently evaluated the methodological quality of all included studies using the Cochrane Collaboration's tool for assessing risk of bias in randomized controlled clinical studies including six domains/questions (Higgins et al., 2011). The same tool was applied for controlled clinical trials, hereby omitting questions 2, 3 and 4. Again, disagreements were discussed to aim for consensus.

Statistical Analysis

To summarize and compare studies, mean and standard deviation (SD) values (change final-baseline and final data) were directly pooled and analyzed with weighted mean differences (WMDs) and 95% confidence intervals (CIs). In case of

studies with more than two arms, each intervention was compared against the control group. Study-specific estimates were pooled with both the fixed and random-effect models (DerSimonian and Laird, 1986) and the random-effect model results were presented.

Two groups of meta-analyses were performed based on the type of intervention:

- Interventions directed to increase the width of keratinized tissue (KT). The data for the control group were obtained from implants with xenogeneic soft tissue grafting or from implants with maintenance alone (no soft tissue grafting), whereas the test group comprised of the data from groups with autogenous soft tissue grafting procedures. In addition, a subgroup analysis was carried out on the selected outcome variables using the type of control procedures [apically position flap/vestibuloplasty (APF), maintenance (alveolar mucosa, keratinized mucosa (>0mm, >2mm, <2mm)), apically positioned flap and collagen matrix (XCM)] as explanatory variable.

- Interventions directed to augment the mucosal thickness (MT). In that case, the data for the control group were obtained from implants without soft tissue grafting, whereas the test group comprised of the data from groups with grafting procedures.

The statistical heterogeneity among studies was assessed using the Q test according to Dersimonian and Laird as well as the I2 index (Higgins et al., 2003), thus reporting the percentage of variation in the global estimate that was attributable to heterogeneity (I2=25%: low; I2=50%: moderate; I2=75%: high heterogeneity).

The publication bias was evaluated using the Begg´s and Egger´s tests for small-study effects for gingival index change (in case of KT) and for BOP change (in case of MT). A sensitivity analysis of the meta-analysis results was also performed.

A Forest Plot was created to illustrate the effects in the meta-analysis of the different studies and the global estimation. STATA® (StataCorp LP, Lakeway Drive, College Station, Texas, USA) intercooled software was used to perform all analyses. Statistical significance was defined as a p value <0.05.

Results

Study characteristics

The electronic search identified a total of 2823 titles (for details refer to Figure 1). From assessing the titles, 2579 were excluded after discussion (inter-reader agreement k=0.75 ± 0.31). The resulting number of abstracts obtained was 244. Out of these, 194 were excluded (inter-reader agreement k=0.67 ± 0.31). Subsequently, 50 full text articles were obtained including 20 review articles. The additional hand search provided three more studies for gain of mucosal thickness (Migliorati et al., 2015, Cosyn et al., 2016, Bienz et al., 2017). Finally, 10 articles met the inclusion criteria, 4 articles for gain of keratinized tissue and 6 publications for gain of mucosal thickness (Table 1).

Exclusion of studies

The authors of potentially excluded full texts were contacted to provide, if available, additional data. Reasons for excluding studies (n=23, see reference list "List of excluded full-text articles and the reason for exclusion") after reading the full texts were: insufficient data (e.g. no clinical parameters obtained/reported (BOP)) (17 studies), case reports (3), submerged implants (no data on implants) (1), no control group (1), no soft tissue grafting performed (1) (see list of excluded studies).

Quality assessment of the included studies

Table 2 summarizes the results of the quality assessment of the 10 included studies. Four of the included studies were RCTs (Yoshino et al., 2014, Migliorati et al., 2015, Lorenzo et al., 2012, Basegmez et al., 2013) and the full checklist (Cochrane

Collaboration's tool for assessing the risk of bias) was applied, whereas for the remaining 6 studies (all CCTs), questions 2, 3 and 4 were omitted.

Keratinized tissue

The two included RCTs (Lorenzo et al., 2012, Basegmez et al., 2012) had a low risk of bias for all questions (random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessments, outcome data, reporting). The two CCTs were judged as having an unclear (Buyukozdemir Askin et al., 2015) or high (Roccuzzo et al., 2016) risk of selection (random sequence generation) bias. There was insufficient information regarding randomization allocation in one study (Buyukozdemir Askin et al., 2015), whereas in the other study, patients were allocated to a specific treatment according to the clinician's judgment (Roccuzzo et al., 2016). Concerning outcome and reporting bias, both CCTs were judged having a low risk.

For group imbalance and radiographic bias, the risks were considered to be low (Buyukozdemir Askin et al., 2015) or unclear (Roccuzzo et al., 2016). Clinician bias was either unclear (Buyukozdemir Askin et al., 2015) or low (Roccuzzo et al., 2016). Both did not perform a sample size calculation (Table 2).

Further factors that influenced bias were high patient numbers in both and a long follow-up period of 10 years in the latter study (Roccuzzo et al., 2016). All other included studies had follow-up periods between 6 and 12 months.

No publication bias was observed for GI change (main outcome variable) with the Egger test (p=0.450) and with the Begg test (0.308).

Mucosal thickness

The two included RCTs (Migliorati et al., 2015, Yoshino et al., 2014) were judged as having a low risk for selection bias since a block randomization generated by a

statistician or a computer generated random list were used. Concerning allocation concealment and blinding of researchers, both studies were considered to have an unclear risk since insufficient information was provided. One study was judged with a low risk, although the procedure did not allow the surgeon to be blinded for the treatment (Migliorati et al., 2015). Detection, attrition and reporting bias were of low risk except for the blinding of the outcome assessment (Yoshino et al., 2014). Here all data were gathered by a non-blinded single examiner (Yoshino et al., 2014) and thus, the detection bias was judged as unclear.

The random sequence allocation (selection bias) was judged as high risk in all four CCTs as they did either not explain the reason for the different treatment options (Bianchi and Sanfilippo, 2004) or the patients were divided into the groups upon the clinicians judgment (Fenner et al., 2016, Bienz et al., 2017, Cosyn et al., 2016). Attrition and outcome bias were considered to have a low risk of bias in all four studies. Further bias were judged with a low risk (Cosyn et al., 2016, Bianchi and Sanfilippo, 2004) and unclear risk due to a single examiner collecting the data (Fenner et al., 2016), no sample size calculation and retrospective study design (Fenner et al., 2016, Bienz et al., 2017). (Table 2)

No publication bias for BOP changes was detected by Begg ($p>0.05$) or Egger tests ($p=0.767$). The sensitivity analyses for this outcome showed that the exclusion of a single study did not substantially alter any estimate.

Included studies

The 10 studies that met the inclusion criteria are presented in Table 1. Four studies were randomized controlled trials (RCTs) published between 2012 and 2014. Five studies were prospective, controlled clinical studies (CCTs), whereas one study was performed as a retrospective CCT (Bienz et al., 2017). All CCTs were published between 2004 and 2017. The studies were performed at University settings (n=7) or in private practice (n=2), whereas one study did not report on the setting. That

particular study was designed as a two-center study (Lorenzo et al., 2012), whereas the remaining 9 studies were single-center studies. The observation period and the reported data in all studies was at least 6 months.

Keratinized tissue

The 4 studies (2 RCTs, 2 CCTs) for gain of keratinized tissue reported on a cohort of 234 patients with a mean age of 56.8 (SD 6.7) years. Fifty-eight percent of the patients were females. No patients dropped out in three studies, whereas one study had a drop-out rate of 20% (Roccuzzo et al., 2016). All patients were systemically and periodontally healthy at the beginning of the investigations except in one study (Basegmez et al., 2012). In that particular study, patients were included if they presented signs of mucositis. Two studies only included non-smokers, one study light smokers (<10 cigarettes per day) (Lorenzo et al., 2012) and one study did not report on smoking habits (Roccuzzo et al., 2016). The overall number of implants included in the studies amounted to 276 and no implant loss was reported (100% implant survival rate) in any of the groups and studies. The mean follow-up time was 36 months (range 6-120 months).

Interventions

The timing of the surgical interventions varied between the studies in terms of the time-span following implant placement. The procedures, however, were always performed after the insertion of the final reconstructions. The therapeutic interventions were therefore indicated and performed in patients with existing implants and reconstructions. This included more specifically: implants with i) signs of mucositis and a width of KT ≤1.5mm (Basegmez et al., 2012), ii) a width of KT ≤2mm (Buyukozdemir Askin et al., 2015), iii) a width of ≤1mm (Lorenzo et al., 2012) or iv) no KM (Roccuzzo et al., 2016).

The types of surgical interventions were as follows: i) an apically positioned flap or vestibuloplasty procedure alone (APF), ii) an APF plus a free gingival graft (FGG), iii)

an APF plus a collagen matrix (XCM) or iv) no treatment (maintenance without intervention) with or without residual keratinized tissue.

Effect of grafting procedure on peri-implant health

Bleeding on probing (BOP) / Gingival index (GI)

Two studies reported on "bleeding on probing" (BOP) (Buyukozdemir Askin et al., 2015, Roccuzzo et al., 2016), whereas three studies reported on "gingival index" (GI) (Loe and Silness, 1963). Final BOP values at the study endpoint were reported to range between 23% and 27% without observing a significant difference between the groups with or without soft tissue grafting in a long-term study (Roccuzzo et al., 2016). In a second study, mean baseline values of 85% (with autogenous soft tissue grafting) and 40-95% (without soft tissue grafting) and mean study endpoint values of 30% (with autogenous soft tissue grafting) and 25-95% (without soft tissue grafting) were reported. The changes over time were significant, favoring the group with autogenous soft tissue grafting (Buyukozdemir Askin et al., 2015).

Meta-analyses on study endpoint BOP values revealed no statistically significant difference between groups with and without soft tissue grafting [n=2; WMD=0.004; 95% CI (-0.117; 0.125; p=0.95]. There appeared to be a tendency, however, favoring grafting with autogenous transplants compared to maintenance within the alveolar mucosa alone [n=1; WMD=0.060; 95% CI (-0,124; 0,244); p=0.523).

Mean GI values ranged from 0.50-1.34 (with soft tissue grafting) /0.35-1.43 (no soft tissue grafting) at baseline to 0.28-0.65 (with soft tissue grafting) /0.20-1.32 (no soft tissue grafting) after follow-up periods of 6 to 12 months (Table 3). Meta-analysis revealed significant differences between investigated groups for change in GI values ($p<0.001$). When comparing change of GI values over time between treatment with an autogenous graft versus maintenance (with or without keratinized tissue), there was a significant difference in favor of the soft tissue grafting group [n=2; WMD=0.863; 95% CI (0.658; 1.067); $p<0.001$] (Buyukozdemir Askin et al.,

2015).

Based on the same study, soft tissue grafting lead to significantly reduced final GI values compared to a maintenance group without grafting in sites with a width of keratinized tissue <2mm [n=1; WMD=0.670; 95% CI (0.436; 0.904); p<0.001] (Buyukozdemir Askin et al., 2015).

Probing depth

Probing depth (PD) values did not change significantly over time between the different treatment groups and based on meta-analyses. Mean PD values ranged from 1.97mm to 3.09mm (with soft tissue grafting) / from 1.76mm to 3.25mm (no soft tissue grafting) at baseline and from 2.08mm to 3.18mm (with soft tissue grafting) / from 1.60mm to 3.62mm (no soft tissue grafting) after 6 to 120 months (Table 3). Comparing final PD values for group APF versus APF plus autogenous tissue resulted in significantly lower values favoring group APF plus autogenous tissue [n=1; WMD=0.440; 95% CI (0.223; 0.657); p<0.001].

Marginal bone level changes

Marginal bone level and the respective changes were reported in one out of four studies (Buyukozdemir Askin et al., 2015), whereas one study reported on final values only (Roccuzzo et al., 2016). In the first study, no significant differences were observed over time between sites with or without soft tissue grafting based on meta-the analysis on marginal bone loss [n=1; WMD=-0.025; 95% CI (-0.108; 0.058); p=0.553]. Mean marginal bone level changes were 0.16mm (with soft tissue grafting) and 0.21mm (for maintenance with <2mm KT) and 0.15mm (for maintenance with >2mm KT) during an observation period of 6 months (Table 3).

Statistically significant differences were noted for final marginal bone levels in favor of APF plus autogenous grafts versus all control treatments (apically positioned flap

or vestibuloplasty procedure alone (APF); APF plus a collagen matrix (XCM); no treatment (maintenance without intervention) with or without residual keratinized tissue) [n=4; WMD=-0.175; 95% CI: (-0.313; -0.037); p=0.013. These differences were predominantly based on the differences between APF plus autogenous grafts versus maintenance within keratinized tissue [n=3; WMD=-0.213; 95% CI (-0.373; -0.054); p=0.009).

Plaque index

Three studies reported plaque index values at baseline and at follow-up time-points of 6 to 12 months (Basegmez et al., 2012, Buyukozdemir Askin et al., 2015, Roccuzzo et al., 2016) (Table 3). In two studies, a significant benefit with lower plaque values was observed following the surgical intervention to increase KT (Roccuzzo et al., 2016, Buyukozdemir Askin et al., 2015), whereas one study reported a significant decrease of the plaque index over time, but no significant difference compared to the untreated control group at baseline and at 12 months (Basegmez et al., 2013). Meta-analysis for these data indicated significant differences in final PlI values when comparing APF plus autogenous grafts versus with maintenance (KT<2mm), favoring the grafted group [n=1; WMD=0.240; 95% CI (0.002; 0.478); p=0.049]. Performing a grafting procedure reduced PlI value changes comparing maintenance groups (KT<2mm or >2mm) and APF versus APF plus autogenous grafts [n=3; WMD=0.354; 95% CI (0.228; 0.480); p<0.001).

Superiority of one grafting procedure/material over others /gain in width of keratinized tissue (KT)

Three treatment modalities (autogenous tissue, collagen matrix, apically positioned flap (AFP)) were used in the four included studies and compared with

regular maintenance of implant sites with more than 2mm, less than 2mm or no keratinized tissue. Statistically significant differences favoring APF plus autogenous tissue were observed for final PPD values (vs. APF) only ($p<0.001$). All other parameters did not reveal to favor any treatment in terms of peri-implant health. These data were derived from one clinical study and a reported observation period of 6 months.

Mucosal thickness

The 6 studies (2 RCTs, 4 CCTs) reporting on surgical interventions for gain of mucosal thickness included 260 patients with a mean age of 50.5 (±4.6) years (Table 1). Fifty-three percent of the patients were females. The mean drop-out rate was 5% (0% in three studies). All patients were, systemically and periodontally healthy. One study, however, did not report on the general and periodontal health of the patients (Bianchi and Sanfilippo, 2004). Smoking habits were <15 cigarettes per day ((Bianchi and Sanfilippo, 2004), <6 cigarettes per day (Migliorati et al., 2015, Fenner et al., 2016, Bienz et al., 2017) or non-smokers only (Yoshino et al., 2014, Cosyn et al., 2016). The overall number of implants assessed amounted to 260 at baseline and 246 at the follow-up examinations. No implants were reported to be lost (100% implant survival rate) in any of the groups and studies. The mean follow-up time was 40.5 months (range 12-86 months).

Interventions

In 5 studies, immediate implants were placed, whereas in one study, delayed implant placement was performed (Bienz et al., 2017). The mucosal thickness was increased at implant placement (Yoshino et al., 2014, Migliorati et al., 2015, Bianchi and Sanfilippo, 2004) or >3 months post implant placement (Cosyn et al., 2016, Fenner et al., 2016, Bienz et al., 2017). All procedures were therefore performed prior to the insertion of the final reconstructions. The therapeutic interventions were

reported to be indicated: i) to prevent recessions and compensate for volume deficiency (Cosyn et al., 2016), ii) to facilitate tissue adaptation at implant placement (Bianchi and Sanfilippo, 2004), iii) for esthetic purposes and to compensate for volume deficiencies (Fenner et al., 2016, Bienz et al., 2017) or iv) not further mentioned (Yoshino et al., 2014, Migliorati et al., 2015).

The type of surgical interventions was as follows: i) immediate implant placement without soft tissue grafting, ii) delayed implant placement without soft tissue grafting, iii) immediate implant placement plus simultaneous subepithelial connective tissue graft (SCTG), iv) immediate implant placement plus delayed SCTG or v) delayed implant placement plus delayed SCTG.

Effect of grafting procedure on peri-implant health

Bleeding on probing (BOP)

Four studies (Fenner et al., 2016, Migliorati et al., 2015, Bienz et al., 2017, Cosyn et al., 2016) reported on BOP values. Mean values ranged between 20-35% (autogenous soft tissue grafting); 21-40% (no grafting) at baseline and 20-56% (autogenous soft tissue grafting); 33-46% (no grafting) after a mean follow-up of 57 months (Table 3). Meta-analysis did not demonstrate any significant influence of grafting procedures on BOP values compared to control groups, neither for changes over time nor for endpoint values.

Probing depth

In five studies, no significant effect after soft tissue volume augmentation was observed, with mean PD values ranging from 2.50mm-3.45mm (with grafting); from 2.50mm-3.20mm (without grafting) at baseline to 3.67mm-4.09mm (with grafting); 3.20mm-3.97mm (without grafting) after a mean of 57 months (Table 3). One study reported a significant benefit (lower PD values) following an increase in mucosal thickness (Bianchi and Sanfilippo, 2004). In that particular study, 27% of the test implant sites (immediate implants with soft tissue grafting) as compared to 45% of the control implant sites (without soft tissue grafting) had PD values >3mm (Bianchi and Sanfilippo, 2004). Meta-analysis did not reveal any significant differences regarding PD between grafted (autogenous graft) and control groups (no grafting).

Marginal bone level changes

Marginal bone level changes and final values were reported in two out of four studies (Yoshino et al., 2014, Migliorati et al., 2015). Final values were reported in two studies (Yoshino et al., 2014, Fenner et al., 2016) (Table 3). Groups without soft tissue grafting lost significantly more marginal bone over time than groups with grafting (WMD=0.110; 95% CI: 0.067; 0.154; $p<0.001$). Meta-analysis

demonstrated a borderline significance favoring soft tissue grafting [n=2; WMD=0.249; 95% CI (-0.001; 0.500); p=0.051] for final marginal bone levels.

Plaque index

Plaque values were assessed in all six of the included studies. None of the studies reported any significant differences between implants sites that had undergone a soft tissue grafting procedure and the respective control (non-grafted) sites. Moreover, plaque index values remained stable independent of any surgical intervention, the timing of soft tissue grafting (at implant placement or staged) and study design (CCT or RCT) with reported mean follow-up periods between 12 and 108 months (Table 3). Similar results were obtained applying meta-analysis, finding no statistically significant differences for change of PlI values between grafted and non-grafted groups [n=1; WMD=0.020; 95% CI (-0.174; 0.214); p=0.840].

Superiority of one grafting procedure/material over others

In all 6 included studies, subepithelial connective tissue grafts were used to increase the mucosal thickness. No other materials such as soft tissue substitutes were applied. No superiority of any treatment modality could therefore be calculated. The time-point of implant placement as well as the time-point of soft tissue grafting differed between the studies. Due to heterogeneity in terms of study design (CCT, RCT) and reported outcome measures, an ideal time-point for implant placement in conjunction with soft tissue augmentation (immediate, early, delayed) or soft tissue grafting (simultaneous with implant placement or staged) could not be assessed.

Discussion

The present systematic review assessed the influence of soft tissue grafting procedures on peri-implant health. The outcomes revealed that soft tissue grafting using autogenous tissue for gain of keratinized tissue results in i) a significant decrease of BOP and GI values and significantly lower GI values at the study endpoint compared to maintenance groups; ii) significantly lower PD values compared to APF alone; iii) significantly higher marginal bone levels at the study endpoint compared to control groups; iv) a significant decrease of PlI values and significantly lower PlI values at the study endpoint compared to control groups. Soft tissue grafting using SCTGs to augment the mucosal thickness resulted in i) no significant improvement over time nor at the study endpoint for BOP, PD and PlI values; ii) significantly less marginal bone loss over time and a borderline significance for marginal bone levels at the study endpoints compared to sites without grafting.

Keratinized tissue

Various procedures and materials were evaluated in the past to augment keratinized tissue around teeth and dental implants predominantly with the purpose to obtain health of periodontal and peri-implant tissues (Thoma et al., 2009, Thoma et al., 2014). BOP and GI values are considered valuable measurements to assess peri-implant health (Heitz-Mayfield, 2008, Salvi and Lang, 2004, Zitzmann and Berglundh, 2008). These values also serve as indicators for changes of the biological peri-implant environment and the development of peri-implant mucositis, a reversible disease of the peri-implant tissues (Jepsen et al., 2015, Salvi et al., 2012). In case of increased or increasing BOP and GI values, various surgical techniques were proposed to increase the width of keratinized tissue, thereby establishing peri-implant health and thus preventing the development of peri-implant disease. Data based on the present meta-analyses revealed a significant improvement for the

primary outcome BOP/GI over time and significantly lower GI values at the follow-up time-points following grafting with autogenous tissue. Moreover, PD and PlI values decreased and marginal bone levels were higher for groups with surgical interventions. These results demonstrate that soft tissue grafting procedure result in biologic benefits compared to control groups and thereby justify the surgical interventions. This is in line with previous publications using a retro- or prospective design (Bouri et al., 2008, Schrott et al., 2009). Data from more recent systematic reviews on the topic of keratinized tissue gain around dental implants, were more controversial and not able to fully support these surgical interventions to maintain or enhance peri-implant health (Chiu et al., 2015, Gobbato et al., 2013, Wennstrom and Derks, 2012). The observed clinical benefit (based on the present systematic review) in favor of soft tissue grafting procedure might in part be explained by the fact that the presence of keratinized tissue results in a more stable seal around the implant neck that facilitates the ability of the patients to clean the reconstructions and to limit bacterial infiltration. This is in line with a recent clinical study demonstrating that implant sites with less than 2 mm of keratinized tissue were more prone to brushing discomfort, plaque accumulation, and peri-implant soft tissue inflammation compared to implant sites with ≥2 mm of keratinized tissue (Souza et al., 2016).

Even though for various transplants and soft tissue substitutes (autogenous tissue, collagen matrix, apically positioned flap (AFP)) were evaluated in the included studies, comparative analyses of different procedures revealed significantly more favorable data for APF plus autogenous tissue versus APF alone only. All other assessed parameters did not show any benefit of one treatment modality over another. Hence, clinical recommendations can only be made for APF plus autogenous tissue and not for any other treatment modality at the current moment.

The obtained data need to some extent be interpreted with caution based on a number of facts: i) heterogeneity between the studies in terms of groups, assessed outcome measures, follow-up time-points and, ii) the inclusion of CCT trials and the

respective high risk of bias for the majority of the questions related to the quality assessment. Heterogeneity between the studies not only encompassed the study design (RCT vs. CCT), but further included the number of patients, sites, the assessed outcome measures (BOP, GI), the time-point of the clinical examination and the follow-up period. These limitations resulted in few outcomes that were eligible for meta-analyses based on few included studies and heterogeneous study designs.

Moreover, the literature is scarce in terms of controlled clinical studies comparing surgical procedures for gain of keratinized tissue including the, from a biologic point of view, most important outcome of inflammation (BOP/GI) at peri-implant sites. This is rather surprising and was the predominant reason for exclusion (in 17 out of 23) of full text articles. Efforts should therefore be undertaken to include such outcome measures in future randomized controlled clinical trials.

Mucosal thickness

Soft tissue grafting procedures intended to increase the mucosal thickness were predominantly performed to improve the esthetic outcome and to compensate for existing volume deficiencies (Cosyn et al., 2013, Bienz et al., 2017, Fenner et al., 2016). Only recently, similar procedures were proposed to target a biologic effect, e.g., minimizing marginal bone loss around dental implants (Linkevicius et al., 2015). In all included clinical studies of the present systematic review, autogenous connective tissue grafts were used and control groups included non-grafted implant sites. The primary outcome of the present systematic review, assessing BOP/GI values, could not demonstrate any significant influence of soft tissue grafting procedure on peri-implant health or disease. Consequently, such surgical interventions might, at the moment and based on very scarce clinical data, not be recommended to positively influence the peri-implant tissues on the biologic level. Interestingly, marginal bone level changes (significant) and endpoint levels (borderline significant), however, demonstrated more favorable results for groups with soft tissue grafting compared to untreated controls. This is in line with short-

term results from a clinical study where the presence of a thick (both originally existing and after augmentation with an allograft) peri-implant mucosa led to higher marginal bone levels compared to implant sites with a thin mucosa (Linkevicius et al., 2015).

Meta-analyses were based on three eligible studies reporting on changes (two studies) and final marginal bone levels (two studies). These results underline, to some extent, that the data need to be interpreted with caution due to heterogeneity in study design (RCT vs. CCT) and a limited number of included studies. Moreover, the reported borderline significance for final marginal bone levels favoring soft tissue grafting is based on one long-term (7.2-years) study indicating a benefit (Fenner et al., 2016) and a second study reporting a negative effect (Yoshino et al., 2014) of SCTGs on peri-implant marginal bone levels at a 1-year follow-up. These results were not statistically significant in the original publications, whereas they were borderline significant based on the meta-analysis and must be interpreted with caution due to varying follow-up periods.

Limitations of the systematic review

The present systematic review covered a new area of research area and the number of publications found through online and hand search was therefore limited. The database "MEDLINE" was selected for the electronic search and thus the search was based on one database only, although knowing that more databases exist. One might thus speculate that more scientific data exists and might therefore consider this a limitation of the present systematic review. This possible lack was, however, compensated by an additional hand search that included the thorough screening of narrative and systematic review articles, and the reference lists of all obtained full-text articles, even the ones that were later excluded. No further hand-search of journals was performed though.

Additionally, the unit of analysis was pooled for the meta-analysis for the sake of the small number of included studies. Although most of the included studies had analyzed their data on the patient level, two studies had used the implant as the unit

of analysis. From a methodological point of view this is an important limitation, since implant-level analysis tends to under-estimate the confidence intervals for the pooled estimate, yielding to an inflated type-I error.

The initial search (limited to one database only and the absence of a grey literature search) provided a relatively high number of potentially eligible studies. Most of these studies, however, did not provide data on bleeding indices, even after contacting the corresponding authors, as their primary focus was esthetics or changes of marginal bone levels (Cornelini et al., 2008, Grunder, 2011, Linkevicius et al., 2015). Given these to some extent limited data, clinical recommendations include that in general, the clinician may consider the use of autogenous soft tissue grafting to promote peri-implant soft tissue health or marginal bone levels at implant sites with insufficient soft tissue dimensions. It is anticipated that plaque control is better facilitated in the presence of >2mm of keratinized tissue. In case an increase of keratinized tissue is desired around a dental implant, the clinician should consider performing a free gingival graft. In the esthetic zone, when an increase in mucosal thickness around implant sites displaying volume deficiencies is desired, clinicians should consider connective tissue grafting procedures to promote greater stability of interproximal marginal bone levels.

Conclusions

Soft tissue grafting procedures can be recommended to improve peri-implant health. For gain of keratinized tissue, the use of an apically positioned flap in conjunction with autogenous grafts resulted in a greater improvement of bleeding indices and higher marginal bone levels. For gain of mucosal thickness, the use of autogenous grafts resulted in significantly less marginal bone loss over time, but no improvement of further clinical parameters (e.g. bleeding indices).

Conflict of interest, source of funding and acknowledgments

The authors report no conflict of interest. This work was funded by the Clinic of Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich and the ETEP (Etiology and Therapy of Periodontal Diseases) Research Group, University Complutense, Madrid, Spain.

List of Reviews

Bassetti, M., Kaufmann, R., Salvi, G. E., Sculean, A. & Bassetti, R. (2015) Soft tissue grafting to improve the attached mucosa at dental implants: A review of the literature and proposal of a decision tree. *Quintessence Int* **46,** 499-510. doi:10.3290/j.qi.a33688.

Brito, C., Tenenbaum, H. C., Wong, B. K., Schmitt, C. & Nogueira-Filho, G. (2014) Is keratinized mucosa indispensable to maintain peri-implant health? A systematic review of the literature. *J Biomed Mater Res B Appl Biomater* **102,** 643-650. doi:10.1002/jbm.b.33042.

Chiu, Y. W., Lee, S. Y., Lin, Y. C. & Lai, Y. L. (2015) Significance of the width of keratinized mucosa on peri-implant health. *J Chin Med Assoc* **78,** 389-394. doi:10.1016/j.jcma.2015.05.001.

Esposito, M., Maghaireh, H., Grusovin, M. G., Ziounas, I. & Worthington, H. V. (2012a) Interventions for replacing missing teeth: management of soft tissues for dental implants. *Cochrane Database Syst Rev***,** Cd006697. doi:10.1002/14651858.CD006697.pub2.

Esposito, M., Maghaireh, H., Grusovin, M. G., Ziounas, I. & Worthington, H. V. (2012b) Soft tissue management for dental implants: what are the most effective techniques? A Cochrane systematic review. *Eur J Oral Implantol* **5,** 221-238.

Gallucci, G. O., Grutter, L., Chuang, S. K. & Belser, U. C. (2011) Dimensional changes of peri-implant soft tissue over 2 years with single-implant crowns in the anterior maxilla. *J Clin Periodontol* **38,** 293-299. doi:10.1111/j.1600-051X.2010.01686.x.

Gobbato, L., Avila-Ortiz, G., Sohrabi, K., Wang, C. W. & Karimbux, N. (2013) The effect of keratinized mucosa width on peri-implant health: a systematic review. *Int J Oral Maxillofac Implants* **28,** 1536-1545. doi:10.11607/jomi.3244.

Hsu, Y. T., Shieh, C. H. & Wang, H. L. (2012) Using soft tissue graft to prevent mid-facial mucosal recession following immediate implant placement. *J Int Acad Periodontol* **14,** 76-82.

Khzam, N., Arora, H., Kim, P., Fisher, A., Mattheos, N. & Ivanovski, S. (2015) Systematic Review of Soft Tissue Alterations and Esthetic Outcomes Following Immediate Implant Placement and Restoration of Single Implants in the Anterior Maxilla. *J Periodontol* **86,** 1321-1330. doi:10.1902/jop.2015.150287.

Kim, D. M. & Neiva, R. (2015) Periodontal soft tissue non-root coverage procedures: a systematic review from the AAP Regeneration Workshop. *J Periodontol* **86,** S56-72. doi:10.1902/jop.2015.130684.

Lee, C. T., Tao, C. Y. & Stoupel, J. (2016) The Effect of Subepithelial Connective Tissue Graft Placement on Esthetic Outcomes After Immediate Implant Placement: Systematic Review. *J Periodontol* **87,** 156-167. doi:10.1902/jop.2015.150383.

Levine, R. A., Huynh-Ba, G. & Cochran, D. L. (2014) Soft tissue augmentation procedures for mucogingival defects in esthetic sites. *Int J Oral Maxillofac Implants* **29 Suppl,** 155-185. doi:10.11607/jomi.2014suppl.g3.2.

Lin, G. H., Chan, H. L. & Wang, H. L. (2013) The significance of keratinized mucosa on implant health: a systematic review. *J Periodontol* **84,** 1755-1767. doi:10.1902/jop.2013.120688.

Lin, G. H., Chan, H. L. & Wang, H. L. (2014) Effects of currently available surgical and restorative interventions on reducing midfacial mucosal recession of immediately placed single-tooth implants: a systematic review. *J Periodontol* **85,** 92-102. doi:10.1902/jop.2013.130064.

Poskevicius, L., Sidlauskas, A., Galindo-Moreno, P. & Juodzbalys, G. (2015) Dimensional soft tissue changes following soft tissue grafting in conjunction with implant placement or around present dental implants: a systematic review. *Clin Oral Implants Res*. doi:10.1111/clr.12606.

Rotundo, R., Pagliaro, U., Bendinelli, E., Esposito, M. & Buti, J. (2015) Long-term outcomes of soft tissue augmentation around dental implants on soft and hard tissue stability: a systematic review. *Clin Oral Implants Res* **26 Suppl 11,** 123-138. doi:10.1111/clr.12629.

Thoma, D. S., Buranawat, B., Hammerle, C. H., Held, U. & Jung, R. E. (2014a) Efficacy of soft tissue augmentation around dental implants and in partially edentulous areas: a systematic review. *J Clin Periodontol* **41 Suppl 15,** S77-91. doi:10.1111/jcpe.12220.

Thoma, D. S., Muhlemann, S. & Jung, R. E. (2014b) Critical soft-tissue dimensions with dental implants and treatment concepts. *Periodontol 2000* **66,** 106-118. doi:10.1111/prd.12045.

Wennstrom, J. L. & Derks, J. (2012) Is there a need for keratinized mucosa around implants to maintain health and tissue stability? *Clin Oral Implants Res* **23 Suppl 6,** 136-146. doi:10.1111/j.1600-0501.2012.02540.x.

Wu, Q., Qu, Y., Gong, P., Wang, T., Gong, T. & Man, Y. (2015) Evaluation of the efficacy of keratinized mucosa augmentation techniques around dental implants: a systematic review. *J Prosthet Dent* **113,** 383-390. doi:10.1016/j.prosdent.2014.10.001.

Included articles

Keratinized tissue

Basegmez, C., Ersanli, S., Demirel, K., Bolukbasi, N. & Yalcin, S. (2012) The comparison of two techniques to increase the amount of peri-implant attached mucosa: free gingival grafts versus vestibuloplasty. One-year results from a randomised controlled trial. *Eur J Oral Implantol* **5,** 139-145.

Buyukozdemir Askin, S., Berker, E., Akincibay, H., Uysal, S., Erman, B., Tezcan, I. & Karabulut, E. (2015) Necessity of keratinized tissues for dental implants: a clinical, immunological, and radiographic study. *Clin Implant Dent Relat Res* **17,** 1-12. doi:10.1111/cid.12079.

Lorenzo, R., Garcia, V., Orsini, M., Martin, C. & Sanz, M. (2012) Clinical efficacy of a xenogeneic collagen matrix in augmenting keratinized mucosa around implants: a randomized controlled prospective clinical trial. *Clin Oral Implants Res* **23,** 316-324. doi:10.1111/j.1600-0501.2011.02260.x.

Roccuzzo, M., Grasso, G. & Dalmasso, P. (2016) Keratinized mucosa around implants in partially edentulous posterior mandible: 10-year results of a prospective comparative study. *Clin Oral Implants Res* **27,** 491-496. doi:10.1111/clr.12563.

Mucosal thickness

Bianchi, A. E. & Sanfilippo, F. (2004) Single-tooth replacement by immediate implant and connective tissue graft: a 1-9-year clinical evaluation. *Clin Oral Implants Res* **15,** 269-277. doi:10.1111/j.1600-0501.2004.01020.x.

Bienz, S. P., Jung, R. E., Sapata, V. M., Hammerle, C. H., Husler, J. & Thoma, D. S. (2017) Volumetric changes and peri-implant health at implant sites with or without soft tissue grafting in the esthetic zone, a retrospective case-control study with a 5-year follow-up. *Clin Oral Implants Res*. doi:10.1111/clr.13013.

Cosyn, J., Eghbali, A., Hermans, A., Vervaeke, S., De Bruyn, H. & Cleymaet, R. (2016) A 5-year prospective study on single immediate implants in the aesthetic zone. *J Clin Periodontol* **43,** 702-709. doi:10.1111/jcpe.12571.

Fenner, N., Hammerle, C. H., Sailer, I. & Jung, R. E. (2016) Long-term clinical, technical, and esthetic outcomes of all-ceramic vs. titanium abutments on implant supporting single-tooth reconstructions after at least 5 years. *Clin Oral Implants Res* **27,** 716-723. doi:10.1111/clr.12654.

Migliorati, M., Amorfini, L., Signori, A., Biavati, A. S. & Benedicenti, S. (2015) Clinical and Aesthetic Outcome with Post-Extractive Implants with or without Soft

Tissue Augmentation: A 2-Year Randomized Clinical Trial. *Clin Implant Dent Relat Res* **17,** 983-995. doi:10.1111/cid.12194.

Yoshino, S., Kan, J. Y., Rungcharassaeng, K., Roe, P. & Lozada, J. L. (2014) Effects of connective tissue grafting on the facial gingival level following single immediate implant placement and provisionalization in the esthetic zone: a 1-year randomized controlled prospective study. *Int J Oral Maxillofac Implants* **29,** 432-440. doi:10.11607/jomi.3379.

Excluded articles and reason for exclusion

Anderson, L. E., Inglehart, M. R., El-Kholy, K., Eber, R. & Wang, H. L. (2014) Implant associated soft tissue defects in the anterior maxilla: a randomized control trial comparing subepithelial connective tissue graft and acellular dermal matrix allograft. *Implant Dent* **23,** 416-425. doi:10.1097/id.0000000000000122.

reason for exclusion: insufficient data (no clinical parameters)

Baltacioglu, E., Bagis, B., Korkmaz, F. M., Aydin, G., Yuva, P. & Korkmaz, Y. T. (2015) Peri-Implant Plastic Surgical Approaches to Increasing Keratinized Mucosa Width. *J Oral Implantol* **41,** e73-81. doi:10.1563/aaid-joi-d-13-00170.

reason for exclusion: insufficient data

Barone, R., Clauser, C., Grassi, R., Merli, M. & Prato, G. P. (1998) A protocol for maintaining or increasing the width of masticatory mucosa around submerged implants: a 1-year prospective study on 53 patients. *Int J Periodontics Restorative Dent* **18,** 377-387.

reason for exclusion: insufficient data (no BOP reported)

Boardman, N., Darby, I. & Chen, S. (2016) A retrospective evaluation of aesthetic outcomes for single-tooth implants in the anterior maxilla. *Clin Oral Implants Res* **27,** 443-451. doi:10.1111/clr.12593.

reason for exclusion: insufficient data (BOP not reported)

Cornelini, R., Barone, A. & Covani, U. (2008) Connective tissue grafts in postextraction implants with immediate restoration: a prospective controlled clinical study. *Pract Proced Aesthet Dent* **20,** 337-343.

reason for exclusion: insufficient data

Cosyn, J., De Bruyn, H. & Cleymaet, R. (2013a) Soft tissue preservation and pink aesthetics around single immediate implant restorations: a 1-year prospective study. *Clin Implant Dent Relat Res* **15,** 847-857. doi:10.1111/j.1708-8208.2012.00448.x.

reason for exclusion: insufficient data (clinical parameters evaluated but not reported)

Cosyn, J., Eghbali, A., Hanselaer, L., De Rouck, T., Wyn, I., Sabzevar, M. M., Cleymaet, R. & De Bruyn, H. (2013b) Four modalities of single implant treatment in the anterior maxilla: a clinical, radiographic, and aesthetic evaluation. *Clin Implant Dent Relat Res* **15,** 517-530. doi:10.1111/j.1708-8208.2011.00417.x.

reason for exclusion: no soft tissue grafting performed

Fagan, M. C., Owens, H., Smaha, J. & Kao, R. T. (2008) Simultaneous hard and soft tissue augmentation for implants in the esthetic zone: report of 37 consecutive cases. *J Periodontol* **79,** 1782-1788. doi:10.1902/jop.2008.080034.

reason for exclusion: insufficient data

Fischer, K. R., Fickl, S., Mardas, N., Bozec, L. & Donos, N. (2014) Stage-two surgery using collagen soft tissue grafts: clinical cases and ultrastructural analysis. *Quintessence Int* **45,** 853-860. doi:10.3290/j.qi.a32511.

reason for exclusion:(only two patients treated)

Grunder, U. (2011) Crestal ridge width changes when placing implants at the time of tooth extraction with and without soft tissue augmentation after a healing period of 6 months: report of 24 consecutive cases. *Int J Periodontics Restorative Dent* **31,** 9-17.

reason for exclusion: insufficient data (no measurements of clinical parameters performed)

Kolerman, R., Nissan, J., Mijiritsky, E., Hamoudi, N., Mangano, C. & Tal, H. (2016a) Esthetic assessment of immediately restored implants combined with GBR and free connective tissue graft. *Clin Oral Implants Res*. doi:10.1111/clr.12755.

reason for exclusion: insufficient data

Kolerman, R., Nissan, J., Rahmanov, A., Zenziper, E., Slutzkey, S. & Tal, H. (2016b) Radiological and Biological Assessment of Immediately Restored Anterior Maxillary Implants Combined with GBR and Free Connective Tissue Graft. *Clin Implant Dent Relat Res*. doi:10.1111/cid.12417.

reason for exclusion: no control

Kovacs, A. F., Wallowy, P., Stefenelli, U. & Landau, S. (2013) Periimplant changes in different transplanted soft tissues around loaded endosseous implants in patients after oral tumor surgery. *Implant Dent* **22,** 650-655. doi:10.1097/01.id.0000433935.76603.0a.

reason for exclusion: insufficient data

Lee, K. H., Kim, B. O. & Jang, H. S. (2010) Clinical evaluation of a collagen matrix to enhance the width of keratinized gingiva around dental implants. *J Periodontal Implant Sci* **40,** 96-101. doi:10.5051/jpis.2010.40.2.96.

reason for exclusion: (nine patients)

Narayan, S. J., Singh, P. K., Mohammed, S. & Patel, R. K. (2015) Enhancing the zone of keratinized tissue around implants. *J Indian Prosthodont Soc* **15,** 183-186. doi:10.4103/0972-4052.158083.

reason for exclusion: (report of two cases)

Rungcharassaeng, K., Kan, J. Y., Yoshino, S., Morimoto, T. & Zimmerman, G. (2012) Immediate implant placement and provisionalization with and without a connective tissue graft: an analysis of facial gingival tissue thickness. *Int J Periodontics Restorative Dent* **32,** 657-663.

reason for exclusion: insufficient data

Schallhorn, R. A., McClain, P. K., Charles, A., Clem, D. & Newman, M. G. (2015) Evaluation of a porcine collagen matrix used to augment keratinized tissue and increase soft tissue thickness around existing dental implants. *Int J Periodontics Restorative Dent* **35,** 99-103. doi:10.11607/prd.1888.

reason for exclusion: insufficient data

Schmitt, C. M., Moest, T., Lutz, R., Wehrhan, F., Neukam, F. W. & Schlegel, K. A. (2015) Long-term outcomes after vestibuloplasty with a porcine collagen matrix (Mucograft(R)) versus the free gingival graft: a comparative prospective clinical trial. *Clin Oral Implants Res*. doi:10.1111/clr.12575.

reason for exclusion: insufficient data

Schmitt, C. M., Tudor, C., Kiener, K., Wehrhan, F., Schmitt, J., Eitner, S., Agaimy, A. & Schlegel, K. A. (2013) Vestibuloplasty: porcine collagen matrix versus free gingival graft: a clinical and histologic study. *J Periodontol* **84,** 914-923. doi:10.1902/jop.2012.120084.

reason for exclusion: insufficient data

Stimmelmayr, M., Stangl, M., Edelhoff, D. & Beuer, F. (2011) Clinical prospective study of a modified technique to extend the keratinized gingiva around implants in combination with ridge augmentation: one-year results. *Int J Oral Maxillofac Implants* **26,** 1094-1101.

reason for exclusion: insufficient data

Thoma, D. S., Zeltner, M., Hilbe, M., Hammerle, C. H., Husler, J. & Jung, R. E. (2016) Randomized controlled clinical study evaluating effectiveness and safety of a volume-stable collagen matrix compared to autogenous connective tissue grafts for soft tissue augmentation at implant sites. *J Clin Periodontol*. doi:10.1111/jcpe.12588.

reason for exclusion: submerged implants

Tunkel, J., de Stavola, L. & Khoury, F. (2013) Changes in soft tissue dimensions following three different techniques of stage-two surgery: a case series report. *Int J Periodontics Restorative Dent* **33,** 411-418. doi:10.11607/prd.0616.

reason for exclusion: insufficient data

Wiesner, G., Esposito, M., Worthington, H. & Schlee, M. (2010) Connective tissue grafts for thickening peri-implant tissues at implant placement. One-year results from an explanatory split-mouth randomised controlled clinical trial. *Eur J Oral Implantol* **3,** 27-35.

reason for exclusion: insufficient data

References

Akcali, A., Trullenque-Eriksson, A., Sun, C., Petrie, A., Nibali, L. & Donos, N. (2016) What is the effect of soft tissue thickness on crestal bone loss around dental implants? A systematic review. *Clin Oral Implants Res*. doi:10.1111/clr.12916.

Basegmez, C., Ersanli, S., Demirel, K., Bolukbasi, N. & Yalcin, S. (2012) The comparison of two techniques to increase the amount of peri-implant attached mucosa: free gingival grafts versus vestibuloplasty. One-year results from a randomised controlled trial. *Eur J Oral Implantol* **5,** 139-145.

Basegmez, C., Karabuda, Z. C., Demirel, K. & Yalcin, S. (2013) The comparison of acellular dermal matrix allografts with free gingival grafts in the augmentation of peri-implant attached mucosa: a randomised controlled trial. *Eur J Oral Implantol* **6,** 145-152.

Bianchi, A. E. & Sanfilippo, F. (2004) Single-tooth replacement by immediate implant and connective tissue graft: a 1-9-year clinical evaluation. *Clin Oral Implants Res* **15,** 269-277. doi:10.1111/j.1600-0501.2004.01020.x.

Bienz, S. P., Jung, R. E., Sapata, V. M., Hammerle, C. H., Husler, J. & Thoma, D. S. (2017) Volumetric changes and peri-implant health at implant sites with or without soft tissue grafting in the esthetic zone, a retrospective case-control study with a 5-year follow-up. *Clin Oral Implants Res*. doi:10.1111/clr.13013.

Bouri, A., Jr., Bissada, N., Al-Zahrani, M. S., Faddoul, F. & Nouneh, I. (2008) Width of keratinized gingiva and the health status of the supporting tissues around dental implants. *Int J Oral Maxillofac Implants* **23,** 323-326.

Buyukozdemir Askin, S., Berker, E., Akincibay, H., Uysal, S., Erman, B., Tezcan, I. & Karabulut, E. (2015) Necessity of keratinized tissues for dental implants: a clinical, immunological, and radiographic study. *Clin Implant Dent Relat Res* **17,** 1-12. doi:10.1111/cid.12079.

Chiu, Y. W., Lee, S. Y., Lin, Y. C. & Lai, Y. L. (2015) Significance of the width of keratinized mucosa on peri-implant health. *J Chin Med Assoc* **78,** 389-394. doi:10.1016/j.jcma.2015.05.001.

Chung, D. M., Oh, T. J., Shotwell, J. L., Misch, C. E. & Wang, H. L. (2006) Significance of keratinized mucosa in maintenance of dental implants with different surfaces. *J Periodontol* **77,** 1410-1420. doi:10.1902/jop.2006.050393.

Cornelini, R., Barone, A. & Covani, U. (2008) Connective tissue grafts in postextraction implants with immediate restoration: a prospective controlled clinical study. *Pract Proced Aesthet Dent* **20,** 337-343.

Cosyn, J., De Bruyn, H. & Cleymaet, R. (2013) Soft tissue preservation and pink aesthetics around single immediate implant restorations: a 1-year prospective study. *Clin Implant Dent Relat Res* **15,** 847-857. doi:10.1111/j.1708-8208.2012.00448.x.

Cosyn, J., Eghbali, A., Hermans, A., Vervaeke, S., De Bruyn, H. & Cleymaet, R. (2016) A 5-year prospective study on single immediate implants in the aesthetic zone. *J Clin Periodontol* **43,** 702-709. doi:10.1111/jcpe.12571.

DerSimonian, R. & Laird, N. (1986) Meta-analysis in clinical trials. *Control Clin Trials* **7,** 177-188.

Evans, C. D. & Chen, S. T. (2008) Esthetic outcomes of immediate implant placements. *Clin Oral Implants Res* **19,** 73-80. doi:10.1111/j.1600-0501.2007.01413.x.

Fenner, N., Hammerle, C. H., Sailer, I. & Jung, R. E. (2016) Long-term clinical, technical, and esthetic outcomes of all-ceramic vs. titanium abutments on implant supporting single-tooth reconstructions after at least 5 years. *Clin Oral Implants Res* **27,** 716-723. doi:10.1111/clr.12654.

Gobbato, L., Avila-Ortiz, G., Sohrabi, K., Wang, C. W. & Karimbux, N. (2013) The effect of keratinized mucosa width on peri-implant health: a systematic review. *Int J Oral Maxillofac Implants* **28,** 1536-1545. doi:10.11607/jomi.3244.

Grunder, U. (2011) Crestal ridge width changes when placing implants at the time of tooth extraction with and without soft tissue augmentation after a healing period of 6 months: report of 24 consecutive cases. *Int J Periodontics Restorative Dent* **31,** 9-17.

Heitz-Mayfield, L. J. (2008) Peri-implant diseases: diagnosis and risk indicators. *J Clin Periodontol* **35,** 292-304. doi:10.1111/j.1600-051X.2008.01275.x.

Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., Savovic, J., Schulz, K. F., Weeks, L., Sterne, J. A., Cochrane Bias Methods, G. & Cochrane Statistical Methods, G. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343,** d5928. doi:10.1136/bmj.d5928.

Ioannidis, A., Cathomen, E., Jung, R. E., Fehmer, V., Husler, J. & Thoma, D. S. (2016) Discoloration of the mucosa caused by different restorative materials - a spectrophotometric in vitro study. *Clin Oral Implants Res*. doi:10.1111/clr.12928.

Jepsen, S., Berglundh, T., Genco, R., Aass, A. M., Demirel, K., Derks, J., Figuero, E., Giovannoli, J. L., Goldstein, M., Lambert, F., Ortiz-Vigon, A., Polyzois, I., Salvi, G. E., Schwarz, F., Serino, G., Tomasi, C. & Zitzmann, N. U. (2015) Primary prevention of peri-implantitis: managing peri-implant mucositis. *J Clin Periodontol* **42 Suppl 16,** S152-157. doi:10.1111/jcpe.12369.

Jung, R. E., Holderegger, C., Sailer, I., Khraisat, A., Suter, A. & Hammerle, C. H. (2008) The effect of all-ceramic and porcelain-fused-to-metal restorations on marginal peri-implant soft tissue color: a randomized controlled clinical trial. *Int J Periodontics Restorative Dent* **28,** 357-365.

Jung, R. E., Sailer, I., Hammerle, C. H., Attin, T. & Schmidlin, P. (2007) In vitro color changes of soft tissues caused by restorative materials. *Int J Periodontics Restorative Dent* **27,** 251-257.

Kan, J. Y., Rungcharassaeng, K., Morimoto, T. & Lozada, J. (2009) Facial gingival tissue stability after connective tissue graft with single immediate tooth replacement in the esthetic zone: consecutive case report. *J Oral Maxillofac Surg* **67,** 40-48. doi:10.1016/j.joms.2009.07.004.

Kim, B. S., Kim, Y. K., Yun, P. Y., Yi, Y. J., Lee, H. J., Kim, S. G. & Son, J. S. (2009) Evaluation of peri-implant tissue response according to the presence of keratinized mucosa. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **107,** e24-28. doi:10.1016/j.tripleo.2008.12.010.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., Clarke, M., Devereaux, P. J., Kleijnen, J. & Moher, D. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of Internal Medicine* **151,** W65-94.

Lin, G. H., Chan, H. L. & Wang, H. L. (2013) The significance of keratinized mucosa on implant health: a systematic review. *J Periodontol* **84,** 1755-1767. doi:10.1902/jop.2013.120688.

Linkevicius, T., Puisys, A., Linkeviciene, L., Peciuliene, V. & Schlee, M. (2015) Crestal Bone Stability around Implants with Horizontally Matching Connection after Soft Tissue Thickening: A Prospective Clinical Trial. *Clin Implant Dent Relat Res* **17,** 497-508. doi:10.1111/cid.12155.

Loe, H. & Silness, J. (1963) Periodontal Disease in Pregnancy. I. Prevalence and Severity. *Acta Odontol Scand* **21,** 533-551.

Lorenzo, R., Garcia, V., Orsini, M., Martin, C. & Sanz, M. (2012) Clinical efficacy of a xenogeneic collagen matrix in augmenting keratinized mucosa around implants: a randomized controlled prospective clinical trial. *Clin Oral Implants Res* **23,** 316-324. doi:10.1111/j.1600-0501.2011.02260.x.

Migliorati, M., Amorfini, L., Signori, A., Biavati, A. S. & Benedicenti, S. (2015) Clinical and Aesthetic Outcome with Post-Extractive Implants with or without Soft Tissue Augmentation: A 2-Year Randomized Clinical Trial. *Clin Implant Dent Relat Res* **17,** 983-995. doi:10.1111/cid.12194.

Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* **62,** 1006-1012. doi:10.1016/j.jclinepi.2009.06.005.

Roccuzzo, M., Gaudioso, L., Bunino, M. & Dalmasso, P. (2014) Surgical treatment of buccal soft tissue recessions around single implants: 1-year results from a prospective pilot study. *Clin Oral Implants Res* **25,** 641-646. doi:10.1111/clr.12149.

Roccuzzo, M., Grasso, G. & Dalmasso, P. (2016) Keratinized mucosa around implants in partially edentulous posterior mandible: 10-year results of a prospective comparative study. *Clin Oral Implants Res* **27,** 491-496. doi:10.1111/clr.12563.

Roos-Jansaker, A. M., Renvert, H., Lindahl, C. & Renvert, S. (2006) Nine- to fourteen-year follow-up of implant treatment. Part III: factors associated with peri-implant lesions. *J Clin Periodontol* **33,** 296-301. doi:10.1111/j.1600-051X.2006.00908.x.

Salvi, G. E., Aglietta, M., Eick, S., Sculean, A., Lang, N. P. & Ramseier, C. A. (2012) Reversibility of experimental peri-implant mucositis compared with experimental gingivitis in humans. *Clin Oral Implants Res* **23,** 182-190. doi:10.1111/j.1600-0501.2011.02220.x.

Salvi, G. E. & Lang, N. P. (2004) Diagnostic parameters for monitoring peri-implant conditions. *Int J Oral Maxillofac Implants* **19 Suppl,** 116-127.

Schneider, D., Grunder, U., Ender, A., Hammerle, C. H. & Jung, R. E. (2011) Volume gain and stability of peri-implant tissue following bone and soft tissue augmentation: 1-year results from a prospective cohort study. *Clin Oral Implants Res* **22,** 28-37. doi:10.1111/j.1600-0501.2010.01987.x.

Schrott, A. R., Jimenez, M., Hwang, J. W., Fiorellini, J. & Weber, H. P. (2009) Five-year evaluation of the influence of keratinized mucosa on peri-implant soft-tissue health and stability around implants supporting full-arch mandibular fixed prostheses. *Clin Oral Implants Res* **20,** 1170-1177. doi:10.1111/j.1600-0501.2009.01795.x.

Souza, A. B., Tormena, M., Matarazzo, F. & Araujo, M. G. (2016) The influence of peri-implant keratinized mucosa on brushing discomfort and peri-implant tissue health. *Clin Oral Implants Res* **27,** 650-655. doi:10.1111/clr.12703.

Thoma, D. S., Benic, G. I., Zwahlen, M., Hammerle, C. H. & Jung, R. E. (2009) A systematic review assessing soft tissue augmentation techniques. *Clin Oral Implants Res* **20 Suppl 4,** 146-165. doi:10.1111/j.1600-0501.2009.01784.x.

Thoma, D. S., Brandenberg, F., Fehmer, V., Knechtle, N., Hammerle, C. H. & Sailer, I. (2015) The Esthetic Effect of Veneered Zirconia Abutments for Single-Tooth Implant Reconstructions: A Randomized Controlled Clinical Trial. *Clin Implant Dent Relat Res*. doi:10.1111/cid.12388.

Thoma, D. S., Buranawat, B., Hammerle, C. H., Held, U. & Jung, R. E. (2014) Efficacy of soft tissue augmentation around dental implants and in partially edentulous areas: a systematic review. *J Clin Periodontol* **41 Suppl 15,** S77-91. doi:10.1111/jcpe.12220.

Thoma, D. S., Zeltner, M., Hilbe, M., Hammerle, C. H., Husler, J. & Jung, R. E. (2016) Randomized controlled clinical study evaluating effectiveness and safety of a volume-stable collagen matrix compared to autogenous connective tissue grafts for soft tissue augmentation at implant sites. *J Clin Periodontol* **43,** 874-885. doi:10.1111/jcpe.12588.

Wennstrom, J. L., Bengazi, F. & Lekholm, U. (1994) The influence of the masticatory mucosa on the peri-implant soft tissue condition. *Clin Oral Implants Res* **5,** 1-8.

Wennstrom, J. L. & Derks, J. (2012) Is there a need for keratinized mucosa around implants to maintain health and tissue stability? *Clin Oral Implants Res* **23 Suppl 6,** 136-146. doi:10.1111/j.1600-0501.2012.02540.x.

Yoshino, S., Kan, J. Y., Rungcharassaeng, K., Roe, P. & Lozada, J. L. (2014) Effects of connective tissue grafting on the facial gingival level following single immediate implant placement and provisionalization in the esthetic zone: a 1-year randomized controlled prospective study. *Int J Oral Maxillofac Implants* **29,** 432-440. doi:10.11607/jomi.3379.

Zitzmann, N. U. & Berglundh, T. (2008) Definition and prevalence of peri-implant diseases. *J Clin Periodontol* **35,** 286-291. doi:10.1111/j.1600-051X.2008.01274.x.

Figure legends

Figure 1. Search strategy. *For details and reasons for exclusion see reference list ("List of reviews" and "List of excluded full-text articles and the reason for exclusion")

Table legends

Table 1. Study characteristics of the included studies.

MT=mucosal thickness; KT=keratinized tissue; RCT=randomized controlled trial; CCT=clinical controlled trial; CCT*=retrospective CCT

Table 2: Risk-of-bias assessment of the included studies according to the "Cochrane Collaboration's Tool for assessing risk of bias".

1) Authors' judgment; 2) Support for judgment

Table 3: Original data from the included studies.

Table 3a: Study Characteristics and Interventions

RCT= randomized controlled clinical trial; CCT= controlled clinical trial; XCM= xenogeneic collagen matrix; SCTG= connective tissue graft; FGG= free gingival graft; APF= apically positioned flap/vestibuloplasty; KT= keratinized tissue; KT= keratinized mucosa; AM= alveolar mucosa; NR= not reported.

Table 3b: Patient Characteristics and Sample Size

Mean age in months with range or standard deviation (SD);
PI= Plaque Index; GI= Gingival Index; smokers: number of patients;
NR= not reported.

Table 3c: Clinical Parameters

BOP= for Bleeding on Probing; GI= Gingiva Index; PPD= Probing Pocket Depth; mBL= mean marginal bone level; PlI= and Plaque Index. Mean values are given at Baseline (Baseline) and at the respective final follow-up (Final).

for Buyukozdemir et al.:

C1= maintenance with <2mm KT; C2=maintenance >2mm KT)

for Roccuzzo et al:

C1= no treatment (maintenance without intervention) *without* residual keratinized tissue (implants were placed within alveolar mucosa)

C2= no treatment (maintenance without intervention) *with* residual keratinized tissue (implants were placed within keratinized tissue)