Efficacy of soft tissue augmentation around dental implants and in partially edentulous areas: a systematic review

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Abstract: AIM: To review the dental literature in terms of efficacy of soft tissue augmentation procedures around dental implants and in partially edentulous sites. METHODS: A Medline search was performed for human studies augmenting keratinized mucosa (KM) and soft tissue volume around implants and in partially edentulous areas. Due to heterogeneity in between the studies, no meta-analyses could be performed. RESULTS: Nine (KM) and eleven (volume) studies met the inclusion criteria. An apically positioned flap/vestibuloplasty (APF/V) plus a graft material [free gingival graft (FGG)/subepithelial connective tissue graft (SCTG)/collagen matrix (CM)] resulted in an increase of keratinized tissue (1.4-3.3 mm). Statistically significantly better outcomes were obtained for APF/V plus FGG/SCTG compared with controls (APF/V alone; no treatment) (p < 0.05). For surgery time and patient morbidity, statistically significantly more favourable outcomes were reported for CM compared to SCTGs (p < 0.05) in two randomized controlled clinical trials (RCTs), even though rendering less keratinized tissue. SCTGs were the best-documented method for gain of soft tissue volume at implant sites and partially edentulous sites. Aesthetically at immediate implant sites, better papilla fill and higher marginal mucosal levels were obtained using SCTGs compared to non-grafted sites. CONCLUSIONS: An APF/V plus FGG/SCTG was the best-documented and most successful method to increase the width of KM. APF/V plus CM demonstrated less gain in KM, but also less patient morbidity and surgery time compared to APF/V plus SCTG based on two RCTs. Autogenous grafts (SCTG) rendered an increase in soft tissue thickness and better aesthetics compared to non-grafted sites.

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Efficacy of soft tissue augmentation around dental implants and in partially edentulous areas – a systematic review

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soft tissue augmentation, keratinized tissue, soft tissue volume, subepithelial connective tissue graft, free gingival graft, allogenic dermal matrix graft, vestibuloplasty, collagen matrix, dental implant

Running title:
Soft tissue grafting – a systematic review

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Clinical relevance

Scientific rationale for the study: the aim of this systematic review was to assess the efficacy of soft tissue augmentation procedures to gain keratinized mucosa around dental implants and to increase the soft tissue volume around implants and in partially edentulous areas.

Principal findings: An apically positioned flap/vestibuloplasty (APF/V) plus a graft material was considered a successful treatment concept resulting for gain of keratinized mucosa. The amount of keratinized mucosa could statistically significantly be increased combining an APF/V with autogenous tissue (FGG=free gingival graft)/SCTG=subepithelial connective tissue graft) when compared to control groups (no treatment, APF/V alone). The use of collagen matrices (CM) reduced surgery time and patient morbidity, but rendered less gain of keratinized mucosa compared to the use of autogenous tissue (SCTG). Autogenous grafts (SCTG/FGG) rendered a two- and three-dimensional gain of soft tissue thickness at implant sites and partially edentulous sites.

Practical implications: Larger evidence is available for APF/V plus autogenous tissue (FGG/SCTG) and supports these procedures for gain of keratinized mucosa. If surgery time and patient morbidity are considered, APF/V plus CM may be recommended as an alternative treatment modality, even though rendering less gain in keratinized mucosa and being less documented. For soft tissue volume increase, the use of autogenous grafts (SCTG/FGG) has to be considered as gold standard. No soft tissue substitute materials can be recommended for this procedure.
**Conflict of interest and source of funding statement**

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Abstract

**Aim:** To review the dental literature in terms of efficacy of soft tissue augmentation procedures around dental implants and in partially edentulous sites.

**Methods:** A Medline search was performed for human studies augmenting keratinized mucosa and soft tissue volume around implants and in partially edentulous areas. Relevant studies were identified and statistics reported for meta-analyses including weighted mean differences with 95% confidence intervals.

**Results:** Nine (keratinized mucosa) and eleven (volume) studies met the inclusion criteria. An apically positioned flap/vestibuloplasty (APF/V) plus a graft material (FGG/SCTG/CM) (FGG=free gingival graft/SCTG=subepithelial connective tissue graft/CM=collagen matrix) resulted in an increase of up to 4mm of keratinized mucosa. Based on meta-analysis, statistically significantly better outcomes were obtained for APF/V plus FGG/SCTG compared to controls (APF/V alone; no treatment) (p<0.05). For surgery time and patient morbidity, statistically significantly better outcomes were reported for collagen matrices (CM) compared to SCTGs (p<0.05), even though rendering less keratinized tissue. SCTGs were the best-documented method for gain of soft tissue volume at implant sites and partially edentulous sites. Esthetically at immediate implant sites, better papilla fill and higher marginal mucosal levels were obtained using SCTGs compared to non-grafted sites.

**Conclusions:** An APF/V plus FGG/SCTG was the best-documented and most successful method to increase the width of keratinized mucosa. APF/V plus CM demonstrated less gain in keratinized mucosa, but also less patient morbidity and surgery time compared to APF/V plus SCTG based on two randomized controlled clinical trials. Autogenous grafts (SCTG) rendered an increase in soft tissue thickness and better esthetics compared to non-grafted sites.
Introduction

Plastic periodontal procedures to augment keratinized tissue and to increase soft tissue volume are well described (Cairo et al., 2008, Thoma et al., 2009). These procedures are indicated to establish functional and biological stability around teeth and implants, mainly in conjunction with reconstructive therapy. The question whether or not there is a need for keratinized tissue to maintain periodontal health around teeth and peri-implant health around dental implants has been controversially discussed in the literature citing a number of parameters to be considered: i) establishment and maintenance of biological health, ii) prevention of recession, iii) esthetics and, iv) cleansibility of the reconstruction (Hoelscher and Simons, 1994, Marquez, 2004, Mehta and Lim, 2010, Wennstrom and Derks, 2012). For dental implants, clinical evidence suggests that a lack of keratinized mucosa (KM) may not be crucial in maintaining the health of peri-implant soft tissues (Wennstrom et al., 1994), may not be associated with more bone loss (Chung et al., 2006) or that despite the presence of KM, peri-implantitis may occur (Roos-Jansaker et al., 2006). In contrast, more recent clinical studies concluded that a wider zone of KM 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 that a lack of KM may result in poorer oral hygiene and greater soft tissue recession (Schrott et al., 2009). This resulted in a clinical recommendation of 2mm for the width of keratinized mucosa (Adibrad et al., 2009, Bengazi et al., 1996), a dimension similar to the zone of keratinized gingiva recommended to be adequate around teeth (Lang and Loe, 1972). Treatment-wise, plastic procedures to augment keratinized tissue include an apically positioned flap or a vestibuloplasty procedure (Thoma et al., 2009, Palacci and Nowzari, 2008). This can be performed prior to implant placement, simultaneously with second stage surgery or post insertion of the final reconstruction. Moreover, in order to compensate for hard and soft tissue deficits in localized defects, soft tissue volume augmentation is mainly indicated for esthetic reasons and to facilitate oral hygiene in pontic areas (Seibert, 1983a, Pini-Prato et al., 2004). In these sites, the classic procedures include the use of free gingival grafts (FGG), subepithelial connective grafts (SCTG) and various types of roll and pedicle flaps (Seibert, 1983b, Studer et al., 2000, Batista et al., 2001, Cho, 1998, Breault et al., 2004). In conjunction with dental implants, plastic augmentative procedures were recommended to enhance the thickness of the soft tissues simultaneously with implant placement or during the healing phase of the implants (Speroni et al., 2010, Grunder, 2000, Schneider et al., 2011). Clinical studies demonstrated various techniques to be successful, resulting in greater flexibility for the choice of the reconstruction material, better esthetic outcomes with respect to the color of the peri-implant tissues, maintenance or even improvement of the marginal mucosal height and higher papillae.
scores (Jung et al., 2008, Speroni et al., 2010, Cornelini et al., 2008, Kan et al., 2009). From a functional point of view however, there is still a lack of scientific evidence whether or not thicker peri-implant soft tissues result in better long-term success and survival rates of dental implants.

Since controversy still exists with respect to the efficacy of soft tissue augmentation and new materials were evaluated more recently, there is a strong need to critically assess the dental literature for optimized procedures and graft materials in terms of soft tissue augmentation.

Therefore, the aim of the present systematic review was to assess dental literature focusing on the efficacy of soft tissue augmentation procedures to increase the width of the keratinized mucosa around dental implants and to increase the soft tissue volume around implants and in partially edentulous areas.
Materials 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).

Focused question

What is the efficacy of different soft tissue augmentation methods in terms of i) increasing the width of keratinized mucosa, and ii) gain in soft tissue volume around implants and in partially edentulous areas?

Search strategy

A Medline (PubMed) search was performed for human studies, including articles published from January 1, 1966 up to May 15, 2013 in the dental literature. The search was limited to the English and German language. The search was complemented by manual searches of the reference list of all selected full-text articles. Additionally, full text articles of reviews published in the same time period were obtained. An additional hand search was performed searching for relevant studies by screening these reviews.

Search Terms

The following search terms were selected: “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” 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” OR “ridge augmentation” OR “soft tissue correction” OR “apically positioned flap” AND “dental implants” OR “Jaw, Edentulous, Partially” OR “pontic” (all MeSH terms)

The search was limited to language (english, german), „human trial“ (MeSH term, clinical studies), and “Dental Journals”. Additionally, the MeSH terms: “case reports”, “clinical trial”, “comparative study”, “controlled clinical trial”, “randomized controlled trial”, “meta-analysis”, “review” and “systematic reviews” were used.
**Inclusion criteria**

The applied inclusion criteria were different for studies dealing with gain of keratinized mucosa or gain of soft tissue volume.

**Increase in width of keratinized mucosa**

Any case series, cohort study, controlled clinical trial and randomized controlled clinical trial with at least 5 patients was included. A follow-up period of at least 3 months was required for the primary outcome “gain in keratinized mucosa”. The reported treatment outcomes had to include either clinical and/or histological measures of the width of keratinized mucosa. The primary outcome of the studies had to be localized gain in width of keratinized mucosa.

**Augmentation of soft tissue volume around dental implant and in partially edentulous areas**

For studies focusing on soft tissue volume gain, any prospective case series, cohort study, controlled clinical trial and randomized controlled clinical trial with at least 5 patients was included. The minimal follow-up time was 3 months for the primary outcome “gain in soft tissue volume”. The reported treatment outcomes had to include either clinical and/or histological measures of the soft tissue volume.

The minimal follow-up time (3 months) for the primary outcome variables chosen in this systematic review is based on a lack of a scientific data with long-term results and in line with a previously published systematic review (Thoma et al., 2009).

**Exclusion criteria**

Studies not meeting all inclusion criteria were excluded from the review. Publications dealing with the following topics were also excluded: in vitro studies, preclinical (animal) studies, studies dealing with the treatment of recession defects, studies augmenting keratinized tissue around teeth only, studies augmenting soft tissue in fully edentulous patients, studies where the effect of soft tissue augmentation surgery could not be extracted from the data (e.g. combination of guided bone regeneration and soft tissue augmentation).

**Selection of studies**

Titles derived from this broad search were independently screened by 2 authors (DT, BB) based on the inclusion criteria. Disagreements were resolved by discussion. Cohen’s Kappa-coefficient was used as a measure of agreement between the 2 readers. Following this, abstracts of all titles agreed on by both authors were obtained, and screened for meeting the inclusion criteria. If no abstract was available in the database, the abstract of the printed article was used. The selected articles were then obtained in
full text. If title and abstract did not provide sufficient information regarding the inclusion criteria, the full report was obtained as well. Again, disagreements were resolved by discussion.

Finally, the selection based on inclusion/exclusion criteria was made for the full text articles. For this purpose Material and Methods, and Results of these studies were screened. This step was again carried out independently by 2 readers. Disagreements were resolved by discussion.

Data extraction
Two reviewers independently extracted the data using data extraction tables. Any disagreements were resolved by discussion aiming for consensus.

Quality assessment
A quality assessment of the included randomized controlled clinical trials and controlled clinical studies was performed independently by two reviewers (BB, DTH) according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011) (Higgins and Green, 2011). Three main quality criteria were assessed: allocation concealment, blinding treatment outcomes to outcome examiners and completeness of follow-up. The studies were then rated to have a low risk of bias (all 3 criteria met) or a high risk of bias (one or more criteria not met).

Statistical Analysis
A test of heterogeneity was calculated to determine whether fixed or random effects models should be used for pooling of studies. Studies were pooled with inverse-variance weighting, and between study heterogeneity was estimated with the DerSimonian-Laird estimator. Meta-analyses were performed to compare treatment vs. no treatment, treatment a vs. treatment b and treatment a vs. treatment b vs. treatment c.
Results

Study characteristics
The electronic search identified a total of 2396 titles (for details, refer to Fig. 1). From assessing the titles, 2283 were excluded (inter-reader agreement $k = 0.98 \pm 0.48$). The resulting number of abstracts obtained was 113, out of which 83 were excluded (inter-reader agreement $k = 0.98 \pm 0.25$). Thirty full-text articles were obtained, 7 articles were further excluded after reading full text. Finally, including studies found through hand searching, 9 studies of keratinized tissue and 11 studies of soft tissue volume articles met the inclusion criteria.

Exclusion of studies
The reasons for excluding studies (7) after full text was obtained were: no reported or insufficient clinical details (n=3), an insufficient number of patients (n=1), only hard tissue augmentation (n=2) and soft tissue augmentation in combination with implant placement and guided bone regeneration (n=1). Details are provided in Table 1.

Included studies
The 20 studies that met the inclusion criteria are presented in Table 2 - 5. Table 2 and 4 represent data for “keratinized tissue augmentation studies” (9 studies) and Table 3 and 5 refer to clinical studies regarding “soft tissue volume” (11 studies).

Increase in width of keratinized mucosa
Patient-based treatment outcomes for the width of keratinized tissue retrieved from 9 studies are presented in Table 2 and 4. Three studies were designed as randomized controlled trials (RCT), two as controlled clinical trials (CCT) and the rest of four studies were case series reports. 198 patients were treated for gain of keratinized tissue around the implants. The methods and techniques used for gain of keratinized tissue included no treatment, vestibuloplasty, APF/V (apically positioned flap/vestibuloplasty) in combination with autogenous tissues (FGG=free gingival graft), SCTG=subepithelial connective tissue graft) and APF/V in combination with allogenic grafts (ADMG) or collagen matrices (CM). The mean follow up period was 16.2 months (6-48). The main reason for treating the patients encompassed a lack of or an inadequate with of attached gingival/keratinized tissue. In summary, three studies were eligible for comparison using meta-analyses. The hypothesis of the heterogeneity test could not be rejected ($p=0.43$), therefore a fixed effects model was chosen.

Quality assessment
The quality assessment of the included studies revealed a high risk of bias for all included studies except for the three RCTs (Sanz et al., 2009, Basegmez et al., 2012, Lorenzo et al., 2012).
Treatment outcomes

Width of keratinized tissue

A total of 7 studies (3 RCTs, 2 CCTs, 2 case series) reported on the width of augmented keratinized tissue; three studies could be compared for mean gain in keratinized tissue using meta-analyses. Four studies investigated the efficacy of collagen matrices (Mucograft®, Geistlich, Switzerland and Collatape®, Zimmer Dental, USA) or an acellular dermal matrix graft (SureDerm™, Hans Biomed Corp, Korea) compared to autogenous grafts (FGG, SCTG) for augmenting the band of keratinized tissue. In two RCTs, the application of a CM demonstrated a gain of keratinized tissue as effective and predictable as the gold standard, an autogenous SCTG (Sanz et al., 2009, Lorenzo et al., 2012). One study evaluated the changes in width of keratinized tissue following APF/V, APF/V plus CM and APF/V plus FGG. After 3-4 weeks, the FGG cases showed a greater increase in keratinized tissue, while the APF/V plus CM demonstrated a more physiologic and a more favorable morphology than the APF/V only cases (Lee et al., 2010). In addition, one study reported on the effects of different time-points for performing FGGs (Stimmelmayr et al., 2011). In this study no statistical significance (p=0.562) in width of keratinized tissue between FGGs performed at the time of implant placement or at the time of uncovering the implants (Stimmelmayr et al., 2011). Three studies were eligible for meta-analyses (Sanz et al., 2009, Lorenzo et al., 2012, Lee et al., 2010). The I-square value of 0% demonstrated homogeneity between the two studies (p=0.4252). The overall estimate for mean difference in width of keratinized tissue was -0.32mm (95% CI -0.67mm; 0.03mm) in favor of the control groups (control sites using autogenous tissue compared to APF/V plus CM). The resulting forest plot diagram is displayed in Figure 2.

Percent shrinkage or contraction of keratinized tissue

Two RCTs (Sanz et al., 2009, Basegmez et al., 2012) and one case series (Park, 2006) reported postoperative shrinkage or contraction of augmented tissue. All studies found shrinkage of the augmented grafts (SCTG, CM, ADMG, FGG). Only one study reported on % mean graft contraction, revealing more favorable results for the autogenous control group (SCTG; 59.7%) compared to a CM group (67.2%) at 30 days (Sanz et al., 2009).

Width of attached mucosa

One RCT study (Basegmez et al., 2012) reported on the efficacy of two techniques (APF/V+FGG or APF/V alone) for increasing the amount of keratinized tissue around the implants. Sixty-four patients with 64 implants with a minimal keratinized tissue (<1.5 mm) and signs of peri-implant mucositis were randomly assigned and treated. The result demonstrated that the width of the attached mucosa and the final gains in the FGG group were significantly greater than in the APF/V group (Basegmez et al., 2012).
**Immobilized mucosa**

In order to extend the immobilized mucosa, a case series (Lauer et al., 1996) reported on an APF/V procedure in combination with implant placement using transalveolar sutures to increase the stability of the lingual peri-implant soft tissue. More immobilized mucosa was obtained lingually compared to a control group of six patients with no APF/V (Lauer et al., 1996).

**Surgery time**

Two RCT studies reported on total surgery time spent to increase the width of keratinized tissue (Sanz et al., 2009, Lorenzo et al., 2012). Surgery time spent in both studies was less in the CM group compared to the SCTG group. These differences were statistically significantly different in both studies. The results of the two studies could be pooled, again with a fixed effects model (test for heterogeneity: I-square value=0% p-value 0.591). The resulting mean difference in surgery time (minutes) was -14.78 (95% CI -19.4842; -10.0682) in favor of the test groups (CM) compared to the control groups (autogenous tissue). The corresponding forest plot is shown in Figure 3.

**Patient-reported outcomes**

Two RCT studies assessed the postoperative pain (Sanz et al., 2009, Lorenzo et al., 2012). In both studies, patient morbidity was evaluated using a visual analogue scale (VAS, with a grading of 0-10) through a questionnaire whilst the perception of pain was measured based on the utilization of the intake of a postoperative analgesic. Comparable results with less morbidity in the CM groups were observed in both studies. At 10 days, patients in the SCTG group had higher mean pain scores compared to the CM group. These differences were statistically significant. In addition, the amount of anti-inflammatory medication (ibuprofen) needed by patients during postoperative was statistically significantly higher in the SCTG group compared to CM group (Sanz et al., 2009).

**Augmentation of soft tissue volume**

Eleven studies met the inclusion criteria as they report on soft tissue volume (Table 3 and 5). Two studies were designed as randomized control trials (RCT), three as controlled clinical trials (CCT) and the remaining six studies were case series reports. In total, 295 patients with 320 sites were treated to enhance the soft tissue volume around implants and in partially edentulous areas. The mean follow-up period was 14.5 months (range 1-108 months). In four of the studies grafting procedures were performed to augment localized alveolar ridge defects (Allen et al., 1985, Studer et al., 2000, Batista et al., 2001, Akcali et al., 2013), while in the remaining studies, soft tissue was grafted at the day of implant placement (Bianchi and Sanfilippo, 2004, Cornelini et al., 2008, Kan...
et al., 2009, Wiesner et al., 2010, Simion et al., 2012) and/or during the healing period of the implant (Speroni et al., 2010, Schneider et al., 2011, Simion et al., 2012). The methods and surgical techniques used for increasing soft tissue volume included: immediate implant placement with SCTG, hydroxylapatite graft, a collagen matrix in combination with a growth factor (platelet-derived growth factor-BB=PDGF-BB), allogenic dermal matrix graft (ADMG), a SCTG (alone) and a palatal vascularized interpositional periosteal-connective tissue graft (VIPCG). No meta-analysis could be performed due to heterogeneity in the study design and treatment modalities.

Quality assessment
The quality assessment of the included studies revealed a high risk of bias for all included studies except for one RCT (Wiesner et al., 2010).

Treatment outcomes
Volume increase measured by two-dimensional methods
Four studies reported horizontal and/or vertical changes in soft tissue volume following soft tissue grafting procedures using stents and periodontal probes or endodontic instruments to measure the changes over time. In a case series, localized alveolar defects in eight patients with 18 sites were treated with ADMG. A gain in vertical ridge width of 0.61mm (SD 0.77) and in horizontal ridge width of 1.72mm (SD 0.59) was reported during the course of 6 months (Batista et al., 2001). A newly developed collagen matrix was evaluated in a prospective case series, using the matrix in combination with a growth factor (PDGF-BB) at the day of implant placement or at second stage surgery (Simion et al., 2012). The obtained gains in ridge width ranged between 0.35mm and 2.14mm with standard deviations of up to 3.27mm at 4 months depending on the level where the measurements were taken using a stent and an endodontic instrument. Since no other treatment modalities were tested, neither the effect of the collagen matrix alone nor the effect of the growth factor can be estimated (Simion et al., 2012). Three years after grafting with SCTGs at the day of implant uncovering, 14 sites in 14 patients demonstrated a mean gain of 1.4mm in mucosal thickness in a subsequent case series (Speroni et al., 2010). The only RCT reporting on soft tissue volume increase following grafting at implant placement, tested the effect of SCTGs vs. no treatment in 10 patients in a split-mouth design (Wiesner et al., 2010). Statistically significant more favorable outcomes were obtained using SCTGs (mean thickness of 3.2mm±0.42mm) compared to sites not receiving soft tissue grafting (1.9mm±0.32mm).

Volume increase measured by three-dimensional methods
Only three studies reported truly three-dimensional changes of the soft tissue volume following grafting. In the first one, the Moiré method was used to calculate the volume changes following grafting with two types of autogenous tissue grafts in localized alveolar defects (Studer et al., 2000). The study demonstrated a volume gain between 159 mm³ (SCTG; SD = 80) and 104 mm³ (FGG; SD = 31). The differences between the two treatment modalities were statistically significant in favor of the SCTG group, while untreated defects showed a slight increase in volume of 6mm³ (SD = 5.4), which was statistically significantly different compared to the two test groups using autogenous tissue (Studer et al., 2000). In a more recent RCT, SCTGs were compared to VIPCGs (interpositional connective tissue grafts) for augmentation of localized alveolar defects (Akcali et al., 2013). A more advanced technique was used to calculate the volume changes and revealed statistically significant more volume for VIPCG-treated sites (1.18mm; range 0.16mm to 1.75mm) compared to free SCTGs (0.63mm; 0.28mm-1.22mm). In a case series, SCTGs were used during the healing phase of implants in 16 sites and patients (Schneider et al., 2011). The mean increase due to grafting was 0.55mm with a standard deviation of 0.53mm after 4 weeks of healing (Schneider et al., 2011).

**Shrinkage**

In a case series, 21 patients with 26 localized alveolar defects were treated either with a SCTG or hydroxylapatite implants. All sites with SCTG demonstrated some shrinkage within the first 4-6 weeks, but the augmented sites remained stable for three years. In all but 2 sites (out of 12) treated with hydroxylapatite implants, no shrinkage was observed (Allen et al., 1985). The shrinkage of the horizontal ridge width amounted to 41.4% over 6 months when localized alveolar defects were augmented with ADMGs in a case series (Batista et al., 2001). This is in line with results from a RCT comparing SCTGs (shrinkage 47% after 6 months) with similar defects to VIPCG= Interpositional connective tissue grafts (shrinkage of 6.4% only) (Akcali et al., 2013).

**Esthetic outcomes**

The Jemt score (Jemt, 1997) was used to evaluate the esthetic outcomes in two studies (Cornelini et al., 2008, Kan et al., 2009). Both studies demonstrated favorable results for soft tissue grafting with higher papilla scores during the course of the study (2.15 years; (Kan et al., 2009) and significantly better outcomes (higher papilla scores) compared to sites without grafting for immediate implants combined with SCTGs (Cornelini et al., 2008). The same two studies also evaluated the position of the mucosal margin compared to neighboring teeth. Similar to the Jemt scores, a more favorable outcome with a higher mean facial line was observed after 2.15 years (Kan et al., 2009), while
grafted sites revealed significantly higher mucosal margin levels for grafted sites after 12 months (Cornelini et al., 2008).

Additional outcome parameters
Additional outcome measures included the amount of keratinized mucosa, the stability of the emergence profile, the patient satisfaction (all in Bianchi and Sanfilippo, 2004) and the tissue biotype changes (Kan et al., 2009).
Discussion
The present systematic review focused on the question whether there is superiority of one method over others for soft tissue grafting around implants and in partially edentulous spaces. For keratinized tissue, nine studies were included and three of them could be compared using meta-analyses. For the augmentation of soft tissue volume, a final number of 11 studies met the inclusion criteria. Due to heterogeneity between the studies, no meta-analysis could be performed.

Increase in width of keratinized tissue
Gain of keratinized tissue
Seven studies specifically reported on various techniques and materials to augment keratinized tissue around dental implants. In all studies, the width of keratinized tissue could be successfully augmented. Due to a large heterogeneity between the studies, with some studies missing control groups and different time-points applying the soft tissue grafting (simultaneous with implant placement, during the healing phase of the implants and after the insertion of the final reconstruction), it is difficult to recommend a specific technique. The selection of the included studies also demonstrates advances and trends in clinical research. In older studies, either an APF/V alone or in combination with autogenous tissue harvested from the patient’s palate was the treatment of choice (Lauer et al., 1996, ten Bruggenkate et al., 1991). The main disadvantage of using autogenous tissue results from the morbidity associated with the harvesting procedure and the subsequent healing. Research has therefore focused on alternative materials and techniques. In one of the studies, a human-derived ADMG was applied (Park, 2006). This material has been documented extensively in dentistry in various fields, such as for gain of keratinized tissue around teeth, for recession coverage, for gain of keratinized mucosa around dental implants and for volume increase (Wei et al., 2000, Aichelmann-Reidy et al., 2001, Batista et al., 2001, Carney et al., 2012). The advantage of using alternative materials is documented with less patient morbidity compared to autogenous tissue for gain of keratinized gingiva (Griffin et al., 2006). Around dental implants, the combination of an APF/V and ADMG was successful to augment keratinized tissue (Park, 2006). However, due to the lack of a control group, any comparison to the gold standard (autogenous tissue) is missing. No further included studies were using this material. In contrast, a number of human studies used ADMG for gain of keratinized tissue. High shrinkage rates were reported during healing around teeth (Wei et al., 2000) and the tissue, histologically resembled scar tissue (Wei et al., 2002). More recently, collagen matrices were developed and extensively evaluated in preclinical and clinical studies (Rocchietta et al., 2012, Jung et al., 2011, Thoma et al., 2012a, Vignoletti et al., 2011, Jung et al., 2013, Jepsen et al., 2013). Three of the included studies reported on the use of two types of collagen matrices (Sanz et al., 2009, Lee et al., 2010, Lorenzo et al.,
In all three studies, autogenous tissue served as a control group. The increase in width of keratinized tissue with a range of 1.8mm to 2.3mm indicates a successful use of both CM types. Still, the meta-analysis revealed inferiority of the collagen matrices in all three studies compared to control groups with autogenous tissue. Clinically, the WMD of -0.32mm only may be negligible. This may even more serve as part of the discussion, since alternative devices (e.g. CM) can significantly reduce patient morbidity, reduce the overall treatment time and slightly improve esthetics compared to control groups (Griffin et al., 2006, Sanz et al., 2009, Lorenzo et al., 2012, Thoma et al., 2012a). In one study, the width of keratinized mucosa was reported as gain in width of attached mucosa (Basegmez et al., 2012). While at teeth, the keratinized tissue (i.e. the gingiva) consist of two parts, the attached gingiva and the free gingiva, at implant sites, no such terms exist. The dimension of the keratinized tissue appears to be similar at teeth and implant sites, but a clear soft tissue attachment to implants has yet to be reported (Berglundh and Lindhe, 1996). It may therefore be speculated that the reported attached mucosa represents the keratinized mucosa found in other studies.

**Percent shrinkage and contraction of keratinized tissue**

The changes in width over time following the initial augmentation procedure is of great importance and serves as a reliable mean to estimate the predictability of the applied technique. Therefore, the overall contraction or shrinkage over time needs to be evaluated. Three studies reported on these outcomes and revealed that independently of the applied surgical technique or material used to augment, a certain loss of the initially augmented width has to be accepted. This ranged quite extensively in the present systematic review, with one study reporting only 2% of shrinkage over 12 months (Basegmez et al., 2012), while the remaining two studies reported shrinkage rates higher than 50% at one or six months (Park, 2006, Sanz et al., 2009). The variability may be due to the use of different techniques (vestibuloplasty according to Edlan & Mejchar, APF/V), different observation time-points (1, 6 and 12 months), differences in graft materials (CM, FGG, SCTG) and different indications (inadequate width of keratinized mucosa, inadequate width of attached mucosa, peri-implant mucositis). Other influences such as the thickness of the graft, which appears to be important when augmenting keratinized tissue around teeth (Mormann et al., 1981) and the lack of a prevascularization (for CM compared to autogenous tissue) could not be evaluated due to a low number of include studies reporting these outcomes.

**Surgery time**

As reported above, the gain in width of keratinized mucosa is not the only outcome parameter that may favor one over the other technique. In two RCTs, the overall treatment time was calculated and clearly demonstrated that by avoiding the use of
autogenous tissue and the associated harvesting procedure, the surgery time can be significantly reduced (Sanz et al., 2009, Lorenzo et al., 2012). The meta-analysis revealed a mean difference of roughly 15 minutes in favor of the CM groups. This has to be considered as a major advantage for the use of alternative devices and may be directly correlated with the postoperative healing and the patient morbidity.

**Patient-reported outcomes**
The postoperative complications of soft tissue grafting procedure include bleeding, swelling as major contributors (Wessel and Tatakis, 2008, Dordick et al., 1976b, Dordick et al., 1976a, Griffin et al., 2006, Farnoush, 1978, Del Pizzo et al., 2002). Several studies evaluated the patient morbidity following gingival augmentation. The data are not conclusive, but predominantly demonstrate less morbidity associated with soft tissue substitutes compared to autogenous tissue (McGuire et al., 2008, Griffin et al., 2006, McGuire and Nunn, 2005). Only two included studies provided data of postoperative pain in the present review. The information derived from the two RCTs clearly demonstrates superiority with less morbidity for soft tissue substitutes compared to autogenous tissue (Sanz et al., 2009, Lorenzo et al., 2012). Data were provided by questionnaires and the intake of pain killer medication in the follow-up. Since both studies were not designed as split-mouth studies, the data are conclusive and more relevant than data obtained in previous studies. In older studies, split-mouth designs appeared to confuse patients, making it difficult to differentiate between two sites (McGuire and Nunn, 2005, McGuire et al., 2008). Therefore, in a previous systematic review on soft tissue grafting procedures, no benefit was shown for soft tissue substitutes (Thoma et al., 2009). The outcomes on patient morbidity are of major relevance and might help to thrive the choice for a grafting material towards soft tissue substitutes in the future.

**Augmentation of soft tissue volume**
Compared to a previous systematic review (Thoma et al., 2009), the number of included studies increased with 11 studies finally meeting the inclusion criteria. The difference is due to broader inclusion criteria (implant sites, partially edentulous sites), a number of very recent studies applying new materials and techniques (growth factors, soft tissue substitutes) and the development of new techniques to assess soft tissue volume changes (non-invasive three-dimensional analyses). Still, due to heterogeneity between the studies, no meta-analysis could be performed.

**Volume increase measured by two-dimensional methods**
Four studies reported two-dimensional changes of soft tissue volume applying autogenous tissue (SCTG) and soft tissue substitutes (CM, ADMG) (Batista et al., 2001, Simion et al., 2012, Speroni et al., 2010, Wiesner et al., 2010). The measurements were
performed using endodontic instruments or periodontal probes, mostly with the aid of a standardized stent. The outcomes provided variability with respect to the increase in soft tissue thickness over time with a range of 0.35mm to 3.2mm depending on the location (buccal at different levels, occlusal) and the follow-up time-point (4 months to 3 years). In all studies, a volume increase was obtained independent of the technique and material, but it was also demonstrated that some shrinkage might occur over time. Similar to studies for gain of keratinized tissue, autogenous tissue appears to be the gold standard as it was used most often, but new soft tissue substitutes are being evaluated. Research has strongly focused on the development and testing of alternative devices with collagen matrices being the most promising ones (Thoma et al., 2013). Unlike for gain of keratinized tissue where preclinical and clinical data are published (Jung et al., 2011, Sanz et al., 2009, Lorenzo et al., 2012), collagen matrices for gain of soft tissue volume are scare and mostly documented in vitro and in preclinical studies (Mathes et al., 2010, Thoma et al., 2010, Thoma et al., 2011, Thoma et al., 2012b). Only one clinical study used a collagen matrix (Simion et al., 2012), which was originally designed to serve as a matrix for gain of keratinized tissue and showed only a minimal increase in thickness based on preclinical data (Jung et al., 2011). Therefore, this matrix was combined with a growth factor to enhance the vascularization and the connective tissue formation (Simion et al., 2012). The outcomes of the study demonstrated a short-term increase in soft tissue volume at all levels. Some more data at just one buccal level over 3.5 years, however, revealed that the obtained soft tissue thickness decreased by more than 50% to roughly 0.9mm (Simion et al., 2012). This demonstrates that a soft tissue substitute for soft tissue volume increase may have additional requirements for long-term stability and a successful outcome. In order to overcome these issues and to meet the demands and requirements for soft tissue substitutes, a new modified collagen matrix with cross-linking has been tested over the course of the past years. In vitro and preclinical data are favorable and a direct comparison with the gold standard, the autogenous graft, demonstrated non-inferiority in a canine model (Mathes et al., 2010, Thoma et al., 2010, Thoma et al., 2011, Thoma et al., 2012b). Clinical data however are still lacking.

Volume increase measured by three-dimensional methods

Recent development not only focused on new devices but also on the evaluation of non-invasive methods to assess volumetric changes (Windisch et al., 2007, Fickl et al., 2009, Strebel et al., 2009). Three studies used casts to evaluate the soft tissue volume over time. In all three studies, autogenous tissue was used for volume increase, in two studies for partially edentulous sites (Studer et al., 2000, Akcali et al., 2013), in one for volume increase at implant sites (Schneider et al., 2011). Again, due to heterogeneity, the outcomes could not be compared, but data provide clinically more relevant data since the measurements capture the entire augmented area. The mean augmented thickness
ranged between 0.55mm and 1.18mm, while the remaining study provided an increase of 104mm³ to 159mm³ (Studer et al., 2000). The outcomes at partially edentulous sites are difficult to put into context unless esthetic, functional and/or long-term data are provided. At implant sites, a soft tissue thickness of 2mm appears to be the threshold thickness at the buccal aspect for more esthetic outcomes (Jung et al., 2007, Jung et al., 2008, van Brakel et al., 2011). Unfortunately, the entire soft tissue thickness and suitable esthetic outcome parameters were not provided by the included study (Schneider et al., 2011). Conclusions on whether or not the treatment was successful are difficult to draw.

Shrinkage
Similar to keratinized tissue, the overall shrinkage rate provides data on the reliability of the applied technique and material. Autogenous tissue was reported to shrink by more than 40% in two studies, while a pedicle flap (VIPCG) appears to be more reliable resulting in less shrinkage over time (6.4% at 6 months) (Akcali et al., 2013). Data on soft tissue substitutes were not reported in the included studies.

Esthetic outcomes
There is a huge variety of esthetic factors reported in the literature (Benic et al., 2012). For maximal esthetics, the soft tissue thickness at the buccal aspect of the implant sites and the height of the papillae appears to be the key factors (Thoma et al., 2013). The Jemt score (Jemt, 1997) is considered an easily applicable method to assess the esthetic outcome in the papilla area and provides relevant clinical information on the esthetic outcome at implant sites. Two included studies demonstrated that the use of autogenous tissue combined with immediate placement results in favorable clinical esthetics at one and 2.15 years (Kan et al., 2009, Cornelini et al., 2008). Since one of the studies was designed as a CCT, data on non-grafted sites are included. The outcomes clearly demonstrate that necessity and the superiority of grafted sites resulting in better esthetics over the course of one year (Cornelini et al., 2008).
Conclusion
The present systematic review revealed that for gain of keratinized mucosa at implant sites, various methods and various materials could be used successfully. All applied techniques were based on an APF/V in combination with autogenous tissue (SCTG/FGG) or a soft tissue substitute (ADMG/CM) and rendered a gain in keratinized tissue for an observation period of up to 48 months. In contrast to gingival augmentation, only one study reported on APF/V alone, which might indicate that most studies were commercially funded. However, some shrinkage may occur with all applied grafting materials and may result in a decrease in width of keratinized tissue of more than 50% within a couple of months. For soft tissue volume augmentation, autogenous tissue (SCTG) has to be considered as treatment of choice resulting in an increase in soft tissue thickness at implant sites and in partially edentulous sites. Soft tissue substitute lack clinical data and can currently not be recommended. Again, some shrinkage of the augmented sites has to be considered. From an esthetic point of view, soft tissue volume grafting concomitant with immediate implant placement may result in superior outcomes with respect to papilla height and the level of the marginal mucosa compared to natural teeth and control groups.
Future direction of research

The present systematic identified a relatively low number of studies to be included for gain of keratinized tissue around dental implants and for gain of soft tissue volume around dental implants and in partially edentulous sites. Moreover, there was a lack of randomized controlled clinical trials (RCTs), specifically for gain of soft tissue volume. For gain of keratinized tissue, some RCTs were available, but appeared to be fully sponsored by companies, thereby including a greater risk of bias. In order to provide the clinicians with data on optimal techniques and materials, more self-funded studies or studies funded by independent organizations and foundations are needed. Such RCTs would have a great impact for the benefit of patients and clinicians.
Figure legends

Figure 1: Search strategy

Figure 2:
Meta-analyses for gain in width of keratinized tissue. Mean difference (mm) for test minus control. APF = apically positioned flap; SCTG = subepithelial connective tissue graft; FGG = free gingival graft; CM=Collagen matrix; I squared (percentage variation attributable to heterogeneity) = 0%, P =0.4254; CI = confidence interval)

Figure 3:
Meta-analyses for surgery time. Mean difference shorter surgery time (min) for test minus control. APF = apically positioned flap; SCTG = subepithelial connective tissue graft; CM=Collagen matrix; I squared (percentage variation attributable to heterogeneity) = 0%, P =0.591; CI = confidence interval)
References


Table 1. Excluded studies with reason for exclusion

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(CCT = controlled clinical trial; RCT = randomized controlled clinical trial; APF/V = apically positioned flap/vestibuloplasty procedure; SCTG = subepithelial connective tissue graft; FGG = free gingival graft; ADMG = acellular dermal matrix graft; CM = collagen matrix)
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CCT = controlled clinical trial; RCT = randomized controlled clinical trial; SCTG = subepithelial connective tissue graft; FGG = free gingival graft; ADMG = acellular dermal matrix graft; CM = Collagen matrix; PDGF = platelet derived growth factor; VIPCG = Interpositional connective tissue graft.
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12 APF/V and FGG vestibuloplasty according to Edlan & Mejchar

48 APF/V in combination with implant placement
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Table 5: Characteristics of included studies: augmentation of soft tissue volume

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<th>Total number of sites</th>
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<th>Number of sites test</th>
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<th>Number of sites control 1</th>
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<td>Case series</td>
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<td>14</td>
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<td>12</td>
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<td>number of sites control 2</td>
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<td>SCTG</td>
<td>Hydroxylapatite</td>
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<td>shrinkage</td>
<td>14 of 14 sites: shrinkage within first 4-6 weeks, then stable for 3 years</td>
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<td>FGG</td>
<td>untreated defect</td>
<td>soft tissue volume gain in horizontal ridge width (mm)</td>
<td>159 mm³</td>
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<td>ADMG</td>
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<td>NA</td>
<td>48</td>
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<td>immediate implants</td>
<td>NA</td>
<td>papilla Index (Jemt)</td>
<td>19 papillae (score 2); 15 papillae (score 3)</td>
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<td>thick biotype at latest follow-up in all sites</td>
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<td>SCTG</td>
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<td>3D volume measurements based on casts</td>
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<td>NA</td>
<td>3D volume measurements using stents</td>
<td>0.87mm (apical); 2.14mm (central); 0.35mm (occlusal)</td>
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<td>collagen matrix + rhPDGF-BB</td>
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Table 5 continue

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<td>higher values for test group</td>
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<td>22 papillae (score 2); 12 papillae (score 3)</td>
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<td>in favor of test group</td>
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(CCT = controlled clinical trial; RCT = randomized controlled clinical trial; SCTG = subepithelial connective tissue graft; FGG = free gingival graft; ADMG = acellular dermal matrix graft; VIPCG=palatal vascularized interpositional periosteal-connective tissue graft; SD=standard deviation)
first electronic search: 2396 titles

inter-reader agreement
$k = 0.98 \pm 0.48$

independently selected by 2 reviewers and agreed by both: 113 titles
abstracts obtained

inter-reader agreement
$k = 0.98 \pm 0.25$

independently selected by 2 reviewers and agreed by both: 30 abstracts
full text obtained

excluded: 7
keratinized tissue: 3
soft tissue volume: 9
review: 11

further hand searching 6 articles on keratinized tissue (references of full text articles)
further hand searching 2 articles on soft tissue volume (references of full text articles)
further hand searching 2 articles (references of full text articles)

final number of studies included
keratinized tissue: 9
soft tissue volume: 11
review: 13
Figure 2

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<th>Author &amp; Year</th>
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<td>[-0.72; 0.66]</td>
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<td>[-0.67; 0.03]</td>
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More change control

More change test