Comparison between Subepithelial Connective Tissue Graft and De-epithelialized Gingival Graft: A systematic review and a meta-analysis

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Abstract

Aim: Sup-epithelial connective tissue graft (SCTG) and de-epithelialized gingival graft (DGG) approaches have been investigated with a focus on post-operative morbidity but not from a clinical outcome standpoint. The aim of this systematic review was to systematically investigate the literature for coronally advanced flaps (CAFs) combined with SCTG or DGG.

Material and Methods: Electronic and hand searches were performed to identified randomized controlled trials (RCTs) investigating the treatment of gingival recession (GRs) using CAF, with at least a 1-year of follow-up. The primary outcome was the mean root coverage (mRC), while the secondary outcomes included recession reduction (Rec Red), keratinized tissue (KT) gain, probing depth (PD) change, and clinical attachment level (CAL) gain.

Results: Ten RCTs with a total of 408 gingival recessions were included. The meta-analysis demonstrated that CAF + DGG is associated with superior mRC, Rec Red, KT gain, PD reduction and CAL gain. The mRC for SCTG and DGG at 1-year was 89.3% and 94.0% respectively, while the mean difference of the other clinical parameters between the two approaches was within 1 mm in favor of the DGG group.

Conclusions: Limited evidence is available when comparing the two techniques, however the usage of DGG may be considered as the preferred technique of choice for autologous CTG harvesting when incorporated with a CAF.

Keywords: gingival recession, connective tissue graft, mucogingival surgery, meta-analysis, systematic review

Introduction

Treatment of aesthetic defects in isolated and multiple gingival recessions (GRs) using a coronally advanced flap (CAF) has been widely demonstrated as a predictable approach (Cairo *et al.*, 2016b; Cairo *et al.*, 2014). Similarly, the beneficial effects of adding an autologous connective tissue graft (CTG) to CAF have been extensively reported (Zucchelli *et al.*, 2014c; Cairo *et al.*, 2016a; Pini-Prato *et al.*, 2010). Consequently, CAF + CTG has been long recognized as the gold standard for root coverage procedures (Zucchelli *et al.*, 2015; Cairo *et al.*, 2014), especially when the gingival biotype is thin or the keratinized tissue (KT) around the GR is minimal or even absent (Leong *et al.*, 2011). It can also be speculated that the more favorable long-term results provided by CAF+CTG, compared to CAF alone, might partially be due to the facilitation of the creeping attachment effect by the increased gingival thickness (Pini-Prato *et al.*, 2010).

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Although several connective tissue substitutes have been proposed to overcome patient morbidity and the need for a second surgical site (de Queiroz Cortes *et al.*, 2006; Stefanini *et al.*, 2016), these alternative grafting materials have not been able to demonstrate comparable or better outcomes than autologous CTGs (Cairo *et al.*, 2014; Chambrone *et al.*, 2015; Cairo *et al.*, 2016b).

Autologous CTGs can be harvested from the palate, edentulous areas, or the maxillary tuberosity. The palate is the most common donor site and the most investigated in the literature. The palatal harvesting technique was introduced in 1966 by Nabers (1966) making it possible to increase KT around teeth and facilitating better oral hygiene. Efforts have been made to minimize the invasiveness of the palatal harvesting approach. Edel (1974) proposed a "trap-door" technique aimed at creating a palatal flap that can be repositioned to allow for healing by primary intention. Langer & Langer (1985) introduced a palatal flap approach that allowed for harvesting of sub-epithelial connective tissue graft (SCTG) with a small band of epithelium that minimizes patient morbidity. Several modifications of these incision approaches have also been described (Harris, 1997; Bruno, 1994). In an attempt to avoid vertical incisions, the "envelope" technique was designed using a single horizontal incision (Hurzeler *et al.*, 1999; Lorenzana *et al.*, 2000). Lorenzana & Allen (2000) suggested a modification of the parallel incision technique in order to minimize post-operative complications. Nonetheless, over-thinning of the palatal flap can often be encountered, leading to wound sloughing. The single incision technique ensures a consistent thickness of the flap and the harvesting of a "deeper" connective tissue graft which usually includes the periosteum layer (Lorenzana and Allen, 2000).

CTG harvested with techniques that allow the palatal flap to be repositioned is generally defined as sub-epithelial connective tissue graft (SCTG). These approaches generally obtain the tissue from the premolar area (Zuhr *et al.*, 2014). However, when the palatal fibromucosa thickness is inadequate, this technique should be avoided (Zucchelli and Mounssif, 2015).

Considering that healing by secondary intention is not associated with increased post-operative discomfort (Zucchelli *et al.*, 2010), Zucchelli and coworkers introduced the de-epithelialized gingival graft (DGG); in which it is harvested as a free gingival graft, then extra-orally de-epithelialized (Zucchelli *et al.*, 2010). This technique permits palatal harvesting regardless of fibromucosa thickness. Connective tissue obtained using the DGG technique is considered more stable and contains less fatty and glandular tissue than SCTG (Bertl *et al.*, 2015; Zucchelli *et al.*, 2010). In fact, a histologic study on cadavers by Bertl *et al.* (2015) demonstrated that the composition of the CTG depends entirely on the harvesting approach, where the harvesting location had no influence on the composition. DGG was found to be primarily composed of lamina propria with large amounts of fibrous connective tissue, while SCTG comprised palatal submucosa, which essentially contained a greater amount of fatty and glandular tissue (Bertl *et al.*, 2015).

Epithelial differentiation is influenced by the underlying connective tissue (Bertl *et al.*, 2015), as demonstrated by Karring *et al.* (1975) in an animal model. It is thus reasonable to assume that the composition of the underlying connective tissue can affect the outcome of the bilaminar root coverage procedure, as well as influence the amount of KT gain. Therefore, the aim of this systematic review was to investigate the outcomes of CAF combined with SCTG versus DGG.

Material and Methods

Study Registration

The review protocol was registered and allocated the identification number (CRD42017080861) in the PROSPERO International Prospective Register of Systematic Reviews hosted by the National Institute for Health Research, University of York, Centre for Reviews and Dissemination.

Patient, Intervention, Comparison, Outcome (PICO) Question

This systematic review utilized the Preferred Reporting Items Systematic review and Meta-Analyses (PRISMA) statement and checklist (Moher *et al.*, 2009), as well as the patient, intervention, comparison, outcomes (PICO) method.

P: Patients receiving a CTG for single or multiple gingival recession (GR) defects (Miller I and II) without loss of inter-dental bone (Miller, 1985a)
I: CAF + DGG
C: CAF + SCTG.
O: Recession reduction, mean root coverage (mRC), keratinized tissue (KT) gain, probing depth (PD) reduction, clinical attachment level (CAL) gain.

Information Sources

Electronic and manual literature searches were performed by three independent reviewers (LT, AR, MT) using the databases MEDLINE (PubMed) and EMBASE. Potential articles were examined in full-text by three reviewers (LT, AR, MT) independently, and the articles' eligibility for this review was confirmed after discussion. Disagreements were resolved by consult with an additional investigator (HLW). The level of agreement between the reviewers regarding study inclusion was calculated using k statistics.

Screening Process

The MEDLINE/PubMed search was performed on 14/12/17 using the following strategy:

- ((“connective tissue”[MeSH Terms] OR (“connective”[All Fields] AND “tissue”[All Fields]) OR “connective tissue”[All Fields]) AND (“transplants”[MeSH Terms] OR “transplants”[All Fields] OR “graft”[All Fields])) AND (“humans”[MeSH Terms] AND English[lang] AND jsubsetd[text])
- (coronally[All Fields] AND positioned[All Fields] AND (“surgical flaps”[MeSH Terms] OR (“surgical”[All Fields] AND “flaps”[All Fields]) OR “surgical flaps”[All Fields] OR “flap”[All Fields])) AND english[Language] AND (“humans”[MeSH Terms] AND jsubsetd[text])
- (coronally[All Fields] AND advanced[All Fields] AND (“surgical flaps”[MeSH Terms] OR (“surgical”[All Fields] AND “flaps”[All Fields]) OR “surgical flaps”[All Fields] OR “flap”[All Fields])) AND (“humans”[MeSH Terms] AND English[lang] AND jsubsetd[text]).

The EMBASE search was completed on 14/12/17 using the following strategy:

- ‘english’:la AND coronally AND advanced AND flap AND connective AND tissue AND graft) AND ‘human’/de AND ‘article’/it.

The search on the Cochrane Oral Health Group Trials Register was performed on 14/12/17 using the following strategy:

- “Gingival Recession” [Search All Text] AND “Root Coverage” [Search All Text].

Furthermore, a manual search through periodontics-related journals, including *Journal of Dental Research, Journal of Clinical Periodontology, Journal of Periodontology, Journal of Periodontal Research and International Journal of Periodontics & Restorative Dentistry,* from January 2016 to December 2017, was performed. The references of all the articles were reviewed in full text to identify all other available articles. A manual search of the related journals, including a complete search of *Journal of Clinical Periodontology, Journal of Periodontal Research, Journal of Periodontology,* and *International Journal of Periodontics and Restorative Dentistry* was also performed. Finally, previous systematic reviews investigating root coverage procedures for single recessions (Roccuzzo *et al.,*. 2002, Oates *et al.,*. 2003, Pagliaro *et al.,*. 2003, Clauser *et al.,*. 2003, Al-Hamdan *et al.,*. 2003, Gapski *et al.,*. 2005, Hwang & Wang 2006, Cheng *et al.,*. 2007, Chambrone *et al.,*. 2008, Cairo *et al.,*. 2008, Chambrone *et al.,*. 2009a,b, 2010, Ko & Lu 2010, Chambrone *et al.,*. 2012, Fu *et al.,*. 2012, Buti *et al.,*. 2013, Cairo *et al.,*. 2014, Cheng *et al.,*. 2015, Tatakis *et al.,*. 2016, Atieh *et al.,* 2016, Guan *et al.,* 2016, Cairo *et al.,*, 2016) were also screened for article identification. Moreover, when necessary, authors were contacted to obtain further information regarding the harvesting approach.

Types of Intervention:

CAF + CTG for the treatment of single or multiple buccal recessions was considered.

SCTG harvesting approaches aim to achieve primary intention healing by raising a palatal flap which rests closely above the wound after harvesting the CTG. Based on the number of incisions, SCTG harvesting techniques can be classified as envelope, L-technique or trap door approach. On the other hand, DGG involves an open wound that will heal via secondary intention. This was conducted similar as free gingival graft but have more thickness, once harvested, the overlying epithelium is then removed extra-orally to obtain a CTG. Figure 1 illustrates these two different harvesting approaches.

Measured Outcomes:

Primary outcomes:

- Evaluation of the recession depth reduction (Rec Red) and the mean root coverage (mRC)

Secondary outcomes:

- Change in the width of keratinized tissue (KT), expressed as KT gain in millimeters obtained by comparing the KT at follow-up and KT at baseline
- Change in mid-buccal probing pocket depth (PD) after root coverage
- Change in clinical attachment level (CAL)

Design of the included studies and Eligibility Criteria:

In this systematic review, only prospective randomized controlled clinical trials (RCTs), including a split-mouth model, for the treatment of single or multiple gingival recessions with CAF, of at least 1-year duration, were considered. Either the test or control group of each selected study was included in the article if the following inclusion criteria were met:

- CTG alone (not combined with biologic agents).
- Palatal harvesting technique clearly explained or a citation of the technique is provided.
- Follow-up ≥ 12 months
- Miller’s class I and/or II
- Root coverage procedure in a single surgery
- Patients without previous history of soft tissue graft surgery

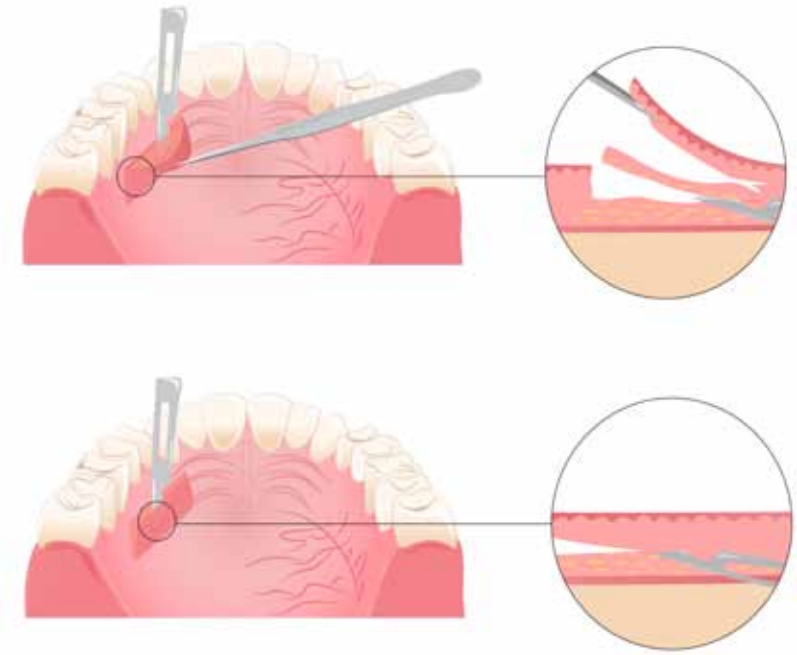


Figure 1. Schematic illustration of the different harvesting technique and graft composition between a) SCTG and b) DGG. The SCTG harvesting technique requires a layer of connective tissue to be maintained within the primary palatal flap to avoid its dehiscence. Thus, the harvested CTG comes from the deeper area of the palate, close to the periosteal layer. The DGG harvesting technique is based on the harvesting of a superficial layer that includes both epithelium and connective tissue. The CTG is then obtained by the extra-oral de-epithelialization.

Correspondingly, articles were excluded based on the following criteria:

- Heavy smokers (more than 20 cigarettes/day) (Cortellini *et al.*, 2009)
- Two-step surgery
- Follow-up < 1 year
- Studies reporting outcomes of only one specific tooth (e.g. 1 premolar)
- CAF + CTG combined with other agents such as enamel matrix derivatives (EMD), platelet rich plasma (PRP) etc.
- Harvesting technique not mentioned or not clearly explained.
- Varying harvesting technique across the study procedures
- Flap design different from a conventional CAF (i.e. CAF without de-epithelialization of the papillae, CAF where the CTG was left exposed, CAF positioned at CEJ without overcorrection of the flap, etc.) (Zucchelli *et al.*, 2000; de Sanctis *et al.*, 2007)
- Studies that treated gingival recession entirely associated with non-carious cervical lesions
- Recruitment of patients from a previous published article
- Retrospective studies

Statistical Analyses

Data from the papers that met the inclusion criteria were extracted by three investigators (LT, AR, MT). The primary outcome was the reduction in recession depth (Rec Red), and the secondary outcomes were the reduction in probing depth (PD), gain in keratinized tissue (KT), gain in clinical attachment level (CAL), and the percentage of root coverage (mRC). The pooled weighted mean (WM) and the 95% confidence interval (CI) of all variables were estimated using a computer software (Comprehensive Meta-analysis Version 2, Biostat, Englewood, NJ, USA). Random effects meta-analyses of the selected studies were applied to avoid any bias being caused by methodological differences among studies. Due to a lack of RCTs to compare CTG to DGG directly, for each outcome measurement, tissue grafting with different techniques (CTG and DGG) were meta-analyzed and reported separately. The contributions of each article to the primary outcome and the secondary outcomes were weighed based on the sample size. Forest plots were produced to graphically represent WM and 95% CI in primary and secondary outcomes for all included studies using number of treated defects as the analysis unit. Heterogeneity among studies was assessed with p value of chi-square test as well as I^2 test, and a p value less than 0.05 represents significant heterogeneity. The reporting of these meta-analyses adhered to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (Moher *et al.*, 2009).

Quality and Risk of Bias Assessment

Quality assessment was based on the published full-text articles and was performed independently by two investigators (AR and LT). The Cochrane Risk of Bias Tool for Randomized Controlled Trials was used to evaluate RCTs (Higgins *et al.*, 2011), by addressing questions in the following areas: (1) appropriate population size; (2) definitions of inclusion and exclusion; (3) the presence of randomization; (4) methods of allocation concealment; (5) masking of examiners; (6) appropriately reported any incomplete outcome data; and (7) a lack of selective outcome reporting. The potential risk of bias was categorized as low if a study provided detailed information of all parameters above. Moderate risk was considered if a study failed to provide information on only one of the parameters, whereas if a study showed missing information of >2 parameters, the study was categorized as having a high risk of bias.

Results

The search results are depicted in Figure 2. Ten RCTs completely fulfilled the present systematic review's inclusion criteria (Azaripour *et al.*, 2016; Kuis *et al.*, 2013; McGuire *et al.*, 2003; McGuire *et al.*, 2010; Roman *et al.*, 2013; Tunaliota *et al.*, 2015; Zucchelli *et al.*, 2010; Zucchelli *et al.*, 2014a; Zucchelli *et al.*, 2014b; Zucchelli *et al.*, 2014c) (Table 1, Data S2). Rejected studies, and the reason for exclusion, are summarized in supplement Table 2 (Data S3).

Bias assessment

The results of bias risk assessment for the included RCTs, using The Cochrane Risk of Bias Tool, are summarized in table 2; 6 studies were considered to have a low risk of bias (Azaripour *et al.*, 2016; Roman *et al.*, 2013; Zucchelli *et al.*, 2010; Zucchelli *et al.*, 2014a; Zucchelli *et al.*, 2014b; Zucchelli *et al.*, 2014c) and 4 studies were considered to have a moderate risk of bias (Kuis *et al.*, 2013; McGuire and Nunn, 2003; McGuire and Scheyer, 2010; Tunaliota *et al.*, 2015).

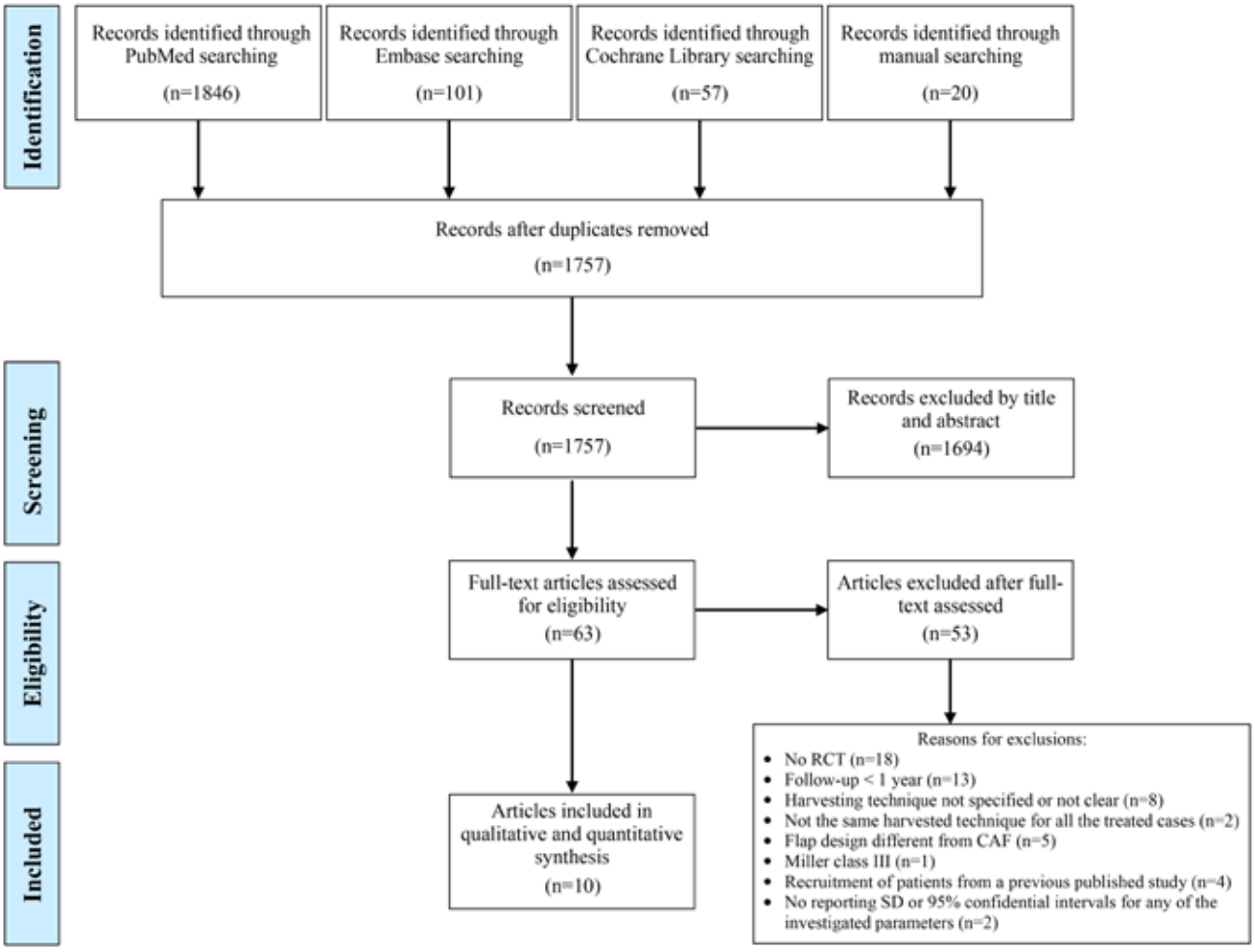


Figure 2. PRISMA flowchart

Table 1. General overview of the included studies

Study	Design	Patients (N)	Smokers	Follow-up (years)	Treatment	Recession type	Harvesting approach - CTG type
Azaripour *et al.* (2016)	Mono-centre, double-blind RCT	Recruited: 40 Drop-outs: 0	No	1	CAF + SCTG (control) MMTT + SCTG (test)	Single or multiple	Trap door technique – SCTG
Kuis *et al.* (2013)	Split-mouth RCT	Recruited: 37 Drop-outs: 0	No	1	CAF (control) CAF + CTG (test)	Single	Trap door technique – SCTG
Kuis *et al.* (2013)	Split-mouth RCT	Recruited: 37 Drop-outs: 0	No	5	CAF (control) CAF + CTG (test)	Single	Trap door technique – SCTG
McGuire & Nunn (2003)	Single-center, split-mouth RCT	Recruited: 20 Drop-outs: 3	No	1	CAF + CTG (control) CAF + EMD (test)	Single	Envelope technique – SCTG
McGuire & Scheyer (2010)	Single-masked, split-mouth RCT	Recruited: 25 Drop-outs: 0	No	1	CAF + CTG (control) CAF + XCM (test)	Single	SCTG
Roman *et al.* (2013)	Parallel, double-blind RCT	Recruited: 42 Drop-outs: 0	Yes (if ≤ 10 cigarettes/day)	1	CAF + CTG (control) CAF + CTG + EMD (test)	Single	Envelope technique – SCTG
Tunali *et al.* (2015)	Split-mouth RCT	Recruited: 10 Drop-outs: 0	No	1	CAF + CTG (control) CAF + L-PRF (test)	Multiple	Envelope technique – SCTG
Zucchelli *et al.* (2010)	Double-center, double-blind RCT	Recruited: 50 Drop-outs: 0	Yes (if ≤ 10 cigarettes/day)	1	CAF + SCTG (control) CAF + DGG (test)	Single or multiple	Trap door technique – SCTG Epithelialized gingival graft – DGG
Zucchelli *et al.* (2014a)	Double-masked, parallel design RCT	Recruited: 50 Drop-outs: 0	Yes (if ≤ 10 cigarettes/day)	1	CAF + CTG (control) CAF + CTG + LST removal (test)	Single or multiple	Epithelialized gingival graft – DGG
Zucchelli *et al.* (2014b)	Double-masked, parallel design RCT	Recruited: 60 Drop-outs: 0	Yes (if ≤ 10 cigarettes/day)	1	CAF + "big" CTG (control) CAF + "small" CTG (test)	Single	Epithelialized gingival graft – DGG
Zucchelli *et al.* (2014c)	Double-blinded, parallel design RCT	Recruited: 50 Drop-outs: 0	Yes (if ≤ 10 cigarettes/day)	1	CAF (control) CAF + CTG (test)	Multiple	Epithelialized gingival graft – DGG
Zucchelli *et al.* (2014c)	Double-blinded, parallel design RCT	Recruited: 50 Drop-outs: 0	Yes (if ≤ 10 cigarettes/day)	5	CAF (control) CAF + CTG (test)	Multiple	Epithelialized gingival graft – DGG

Note. RCT: Randomized Controlled Trial; CAF: Coronally Advanced Flap; SCTG: Subepithelial Connective Tissue Graft; DGG: De-epithelialized Gingival Graft; MMTT: Modified Microsurgical Tunnel Technique; EMD: Emdogain; L-PRF: Leukocyte and Platelet-Rich Fibrin; LST: Labial Submucosal Tissue

Table 2. General characteristics of the intervention and results

Author & year	Follow-up	Sites	Rec red (mm)	KT gain (mm)	PD increase (mm)	CAL change (mm)	mRC (%)
Azaripour *et al*. 2016	1	29	2.343(0.68)	0.3 (2.12)	-0.1(1.03)	2.44(1.43)	0.9928
Kuis *et al*. 2013	1	57	2.54 (0.81)	1.3 (1.81)	NA	NA	0.9658
McGuire & Nunn 2003	1	18	4.01 (1.11)	1.56(1.31)	-0.09(1.21)	4.1(1.9)	0.9435
McGuire & Scheyer 2010	1	25	3.18 (0.37)	1.2 (1.82)	0.23(0.90)	2.95(1)	0.9930
Roman *et al*. 2013	1	21	2.91 (1.67)	1.34(1.4)	-0.04(0.80)	2.95(2.08)	0.8975
Tunali *et al*. 2015	1	22	3.05 (0.77)	0.60(0.93)	-0.31(0.62)	3.04(1.75)	0.7641
Zucchelli *et al*. 2010	1	25	3.14 (0.41)	1.92(0.74)	0.12(0.56)	3.02(0.71)	0.9075
Kuis *et al*. 2013	5	57	2.44 (0.56)	1.37(0.88)	NA	NA	0.9230
Zucchelli *et al*. 2010	1	25	3.4 (0.81)	2.12(0.52)	0.2(0.5)	3.2(0.91)	0.9551
Zucchelli *et al*. 2014c	1	76	3.02 (0.6)	1 (0.44)	-0.04(0.26)	3.01(0.62)	0.9587
Zucchelli *et al*. 2014b (control)	1	30	3.8 (0.92)	2.50(0.73)	0.20(0.54)	3.60(1.06)	0.9669
Zucchelli *et al*. 2014b (test)	1	30	3.66 (0.96)	2.17(0.59)	0.16(0.53)	3.26(0.78)	0.9632
Zucchelli *et al*. 2014a (control)	1	25	3.08 (1.12)	2.2 (1.77)	-1.56(1)	4.6(1.41)	0.8280
Zucchelli *et al*. 2014a (test)	1	25	3.68 (1.11)	1.56(1.1)	-1.6(0.96)	5.24(1.76)	0.9787
Zucchelli *et al*. 2014c	5	76	3.06 (0.6)	1.71(0.51)	0.11(0.32)	2.87(0.64)	0.9714

Note. Rec red: Recession reduction; KT gain: Keratinized Tissue gain; PD: probing depth; CAL: Clinical Attachment Level; mRC: mean Root Coverage

Qualitative analysis

Six articles used the SCTG approach (3 envelope technique, 2 trap door technique and 1 article did not specify the SCTG harvesting approach) (Azaripour *et al*., 2016; McGuire and Nunn, 2003; McGuire and Scheyer, 2010; Roman *et al*., 2013; Tunaliota *et al*., 2015; Kuis *et al*., 2013), 3 articles used the DGG approach (Zucchelli *et al*., 2014a; Zucchelli *et al*., 2014b; Zucchelli *et al*., 2014c) and 1 article used both techniques (trap door technique for the SCTG group and DGG for the test group) (Zucchelli *et al*., 2010). 199 (3 drop-outs) patients were included in the SCTG group and 185 in the DGG group. In total, 197 gingival recessions were treated with CAF + SCTG and 211 with CAF + DGG. Eight RCTs reported a 1-year follow-up period (Azaripour *et al*., 2016; McGuire and Nunn, 2003; McGuire and Scheyer, 2010; Roman *et al*., 2013; Tunaliota *et al*., 2015; Zucchelli *et al*., 2010; Zucchelli *et al*., 2014a; Zucchelli *et al*., 2014b), while 2 articles, one belonging to each study group, followed up with the patients for 5 years (Kuis *et al*., 2013; Zucchelli *et al*., 2014c). Four studies had a split-mouth design (Kuis *et al*., 2013; McGuire and Nunn, 2003; McGuire and Scheyer, 2010; Tunaliota *et al*., 2015). Five out of 10 studies did not recruit smokers (Azaripour *et al*., 2016; Kuis *et al*., 2013; McGuire and Nunn, 2003; McGuire and Scheyer, 2010; Tunaliota *et al*., 2015), while the remaining also included light smokers (≤ 10 cigarettes/day) (Roman *et al*., 2013; Zucchelli *et al*., 2010; Zucchelli *et al*., 2014a; Zucchelli *et al*., 2014b; Zucchelli *et al*., 2014c). Five articles used CAF for single recessions (Kuis *et al*., 2013; McGuire and Nunn, 2003; McGuire and Scheyer, 2010; Roman *et al*., 2013; Zucchelli *et al*., 2014b), 2 articles treated multiple recessions (Tunaliota *et al*., 2015; Zucchelli *et al*., 2014c) and remaining 3 treated both localized and multiple recessions (Azaripour *et al*., 2016; Zucchelli *et al*., 2010; Zucchelli *et al*., 2014a).

Quantitative analysis

The summary of the quantitative analysis is outlined in Table 3 and in Table 4.

Percentage of root coverage (mRC)

The WM of the root coverage percentage was 91.7% (95% CI= 82.8% to 96.2%, Fig. 3) and 94.0% (95% CI= 88.2% to 97.1%, Fig. 3) for the CTG and DGG technique, respectively. In addition, the I^2 test was 0% and 0% with a p value for the chi-square test of 0.480 and 0.517 for CTG and DGG technique, respectively, representing a low heterogeneity among the pooled studies.

Recession depth reduction (Rec Red)

The WM of the reduction in recession depth was 3.00mm (95% CI= 2.68mm to 3.31mm, Fig. 4) and 3.43mm (95% CI= 3.11mm to 3.74mm, Fig. 4) for CTG and DGG technique, respectively. In addition, the I^2 test was 32.02% and 0% with a p value for the chi-square test of 0.184 and 0.609 for CTG and DGG technique, respectively, representing a low heterogeneity among the pooled studies.

KT gain

The WM of the KT gain was 1.20mm (95% CI= 0.73mm to 1.67mm, Fig. 3) and 1.92mm (95% CI= 1.29mm to 2.54mm, Fig. 3) for CTG and DGG technique, respectively. In addition, the I^2 test was 0% and 0% with a p value for the chi-square test of 0.595 and 0.776 for CTG and DGG technique, respectively, representing a low heterogeneity among the pooled studies.

Table 3. The results of the bias risk assessment for the included RCTs using The Cochrane Risk of Bias Tool for Randomized Controlled Trials

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addresses	Selective reporting	Other bias	Overall risk of bias
Azaripour *et al*. (2016)	Low	Low	Low	Low	Low	Low	Low	Low
Kuis *et al*. (2013)	Low	Unclear risk	Low	Low	Low	Low	Low	Unclear risk
McGuire & Nunn (2003)	Low	Unclear risk	Low	Low	Low	Low	Low	Unclear risk
McGuire & Scheyer (2010)	Low	Unclear risk	Low	Low	Low	Low	Low	Unclear risk
Roman *et al*. (2013)	Low	Low	Low	Low	Low	Low	Low	Low
Tunali *et al*. (2015)	Low	Unclear risk	Low	Low	Low	Low	Low	Unclear risk
Zucchelli *et al*. (2010)	Low	Low	Low	Low	Low	Low	Low	Low
Zucchelli *et al*. (2014a)	Low	Low	Low	Low	Low	Low	Low	Low
Zucchelli *et al*. (2014b)	Low	Low	Low	Low	Low	Low	Low	Low
Zucchelli *et al*. (2014c)	Low	Low	Low	Low	Low	Low	Low	Low

Table 4. Comparison between CAF + SCTG and CAF + SCTG at 1 year of follow-up

Group	N. of articles	Sites	Rec Red	mRC	KT gain	PD gain	CAL gain
SCTG	7	197	3.08 (2.75 to 3.41)	89.3 (78.6 to 95.0)	1.18 (0.61 to 1.74)	-0.03 (-0.23 to 0.14)*	3.00 (2.68 to 3.32)*
DGG	6	211	3.43 (3.11 to 3.74)	94.0 (88.2 to 97.1)	1.92 (1.29 to 2.54)	-0.39 (-0.78 to -0.01)	3.74 (3.25 to 4.24)
Tot.		408					

Note: * For the SCTG group, the parameters PD gain and CAL gain are based on 6 articles and 140 sites
SCTG: Subepithelial Connective Tissue Graft; DGG: De-epithelialized Gingival Graft; Rec Red: Recession Reduction; mRC: mean Root Coverage; KT gain: Keratinized Tissue gain; PD gain: probing depth gain; CAL gain: Clinical Attachment Loss gain

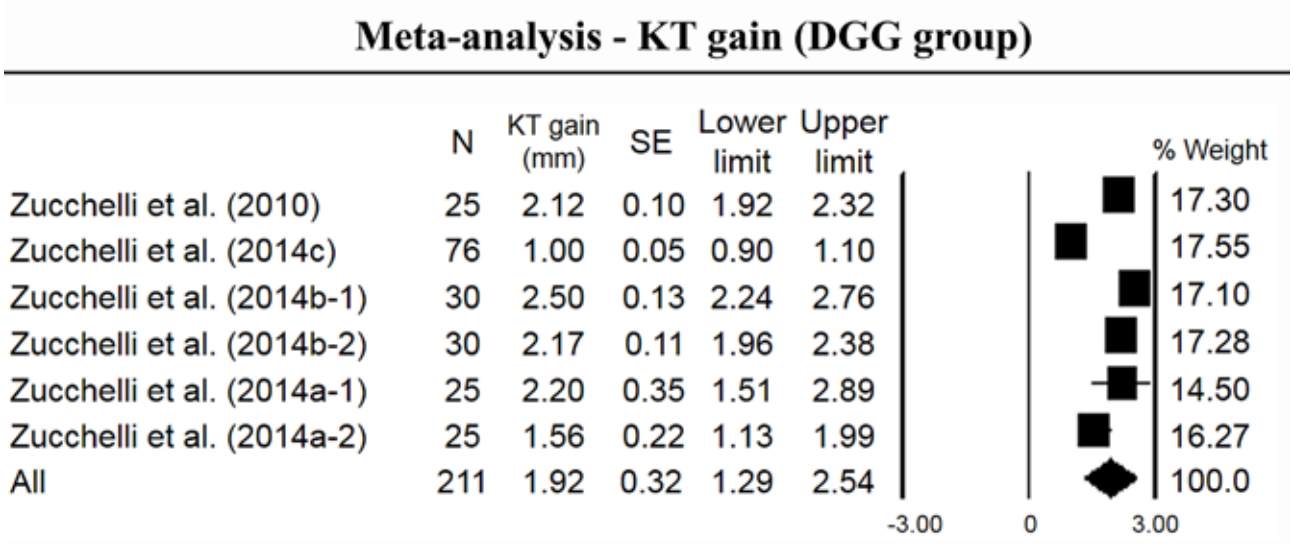


Figure 3. Meta-analysis comparing the mRC and KT gain SCTG and DGG groups

Table 5. Comparison between CAF + SCTG and CAF + SCTG at 5 year of follow-up

Group	N. of articles	Sites	Rec Red	mRC	KT gain	PD gain	CAL gain
SCTG	1	57	2.44 (0.56)	92.30 (NA)	1.37 (0.88)	NA	NA
DGG	1	76	3.06 (0.60)	97.14 (NA)	1.71 (10.51)	0.11 (0.32)	2.87 (0.64)
Tot.		133					

Note: SCTG: Subepithelial Connective Tissue Graft; DGG: De-epithelialized Gingival Graft; Rec Red: Recession Reduction; mRC: mean Root Coverage; KT gain: Keratinized Tissue gain; PD gain: probing depth gain; CAL gain: Clinical Attachment Loss gain

PD reduction

The WM of the PD reduction was -0.03mm (95% CI= -0.23mm to 0.14mm, Fig. 4) and -0.39mm (95% CI= -0.78mm to -0.01mm, Fig. 4) for CTG and DGG technique, respectively. In addition, the I^2 test was 0% and 68.53% with a p value for the chi-square test of 0.504 and 0.007 for CTG and DGG technique, respectively, representing a low heterogeneity in CTG group but a high heterogeneity in DGG group among the pooled studies.

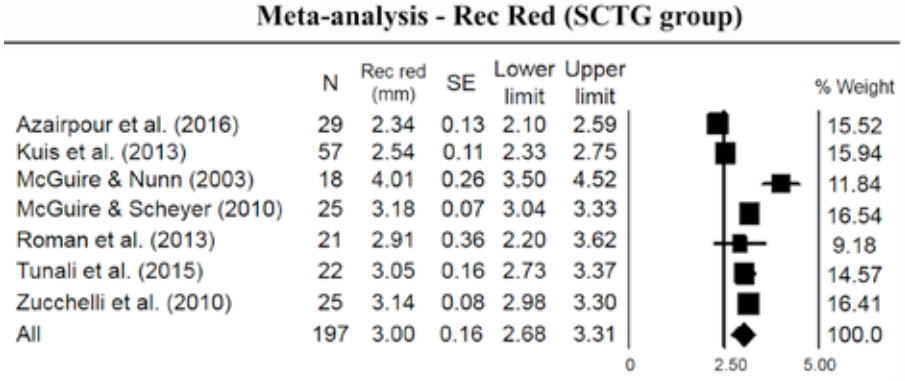
CAL gain

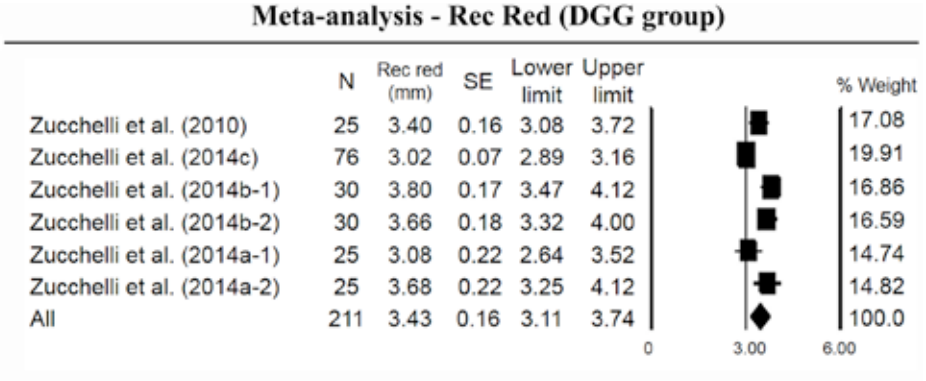
The WM of the CAL gain was 3.00mm (95% CI= 2.68mm to 3.32mm, Fig. 4) and 3.74mm (95% CI= 3.25mm to 4.24mm, Fig. 4) for the CTG and DGG techniques, respectively. In addition, the I^2 test was 24.19% and 48.35% with a p value for the chi-square test of 0.253 and 0.085 for the CTG and DGG study groups, respectively, representing a low heterogeneity in the CTG group but a moderate heterogeneity in the DGG group among the pooled studies.

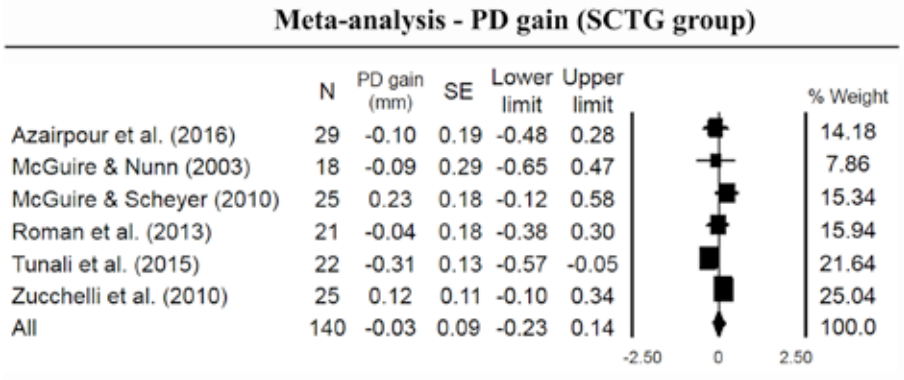
Discussion

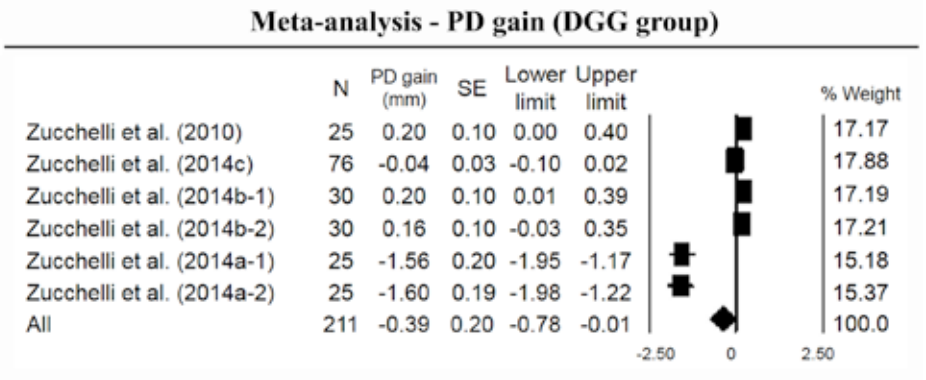
While successful mucogingival therapy primarily relied on the complete resolution of a recession defect (Wennstrom *et al.*, 1996), De Sanctis & Zucchelli (2007) hinged gingival recession treatment on complete root coverage, minimal probing depths, KT gain and an aesthetic outcome as the main factors of success. Later, Cairo *et al.* (2009) introduced the Root Coverage Esthetic Score (RES), which represented an objective evaluation of the recession defect correction results. This score is based on assessment of the gingival margin level, marginal tissue contour, soft tissue texture, mucogingival alignment, and gingival color. More recently, patient satisfaction was proposed as an additional factor for success (Roman *et al.*, 2012; Stefanini *et al.*, 2016). Within patient satisfaction and perception of the treatment, post-operative discomfort plays a major role (Roman *et al.*, 2012).

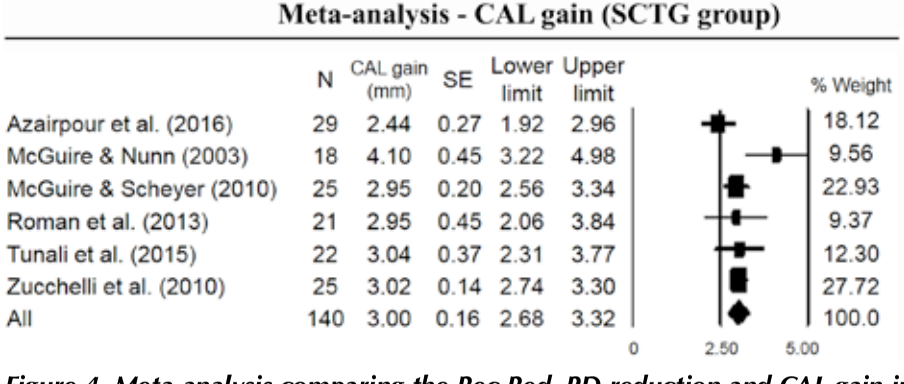
Due to CTG substitutes' incapability to provide comparable or superior results to autologous CTG (Cairo *et al.*, 2014), effort has been directed towards minimizing patient morbidity following palatal harvesting (Zucchelli *et al.*, 2010; Femminella *et al.*, 2016). Many authors preferred the use of SCTG as opposed to DGG merely due to its healing by primary intention, which is believed to decrease morbidity as contrasted with open wound healing (Del Pizzo *et al.*, 2002; Wessel *et al.*, 2008). However, Zucchelli *et al.* (2010) verified that when the palate was properly managed and protected, both DGG and SCTG harvesting techniques demonstrate similar post-operative discomfort.











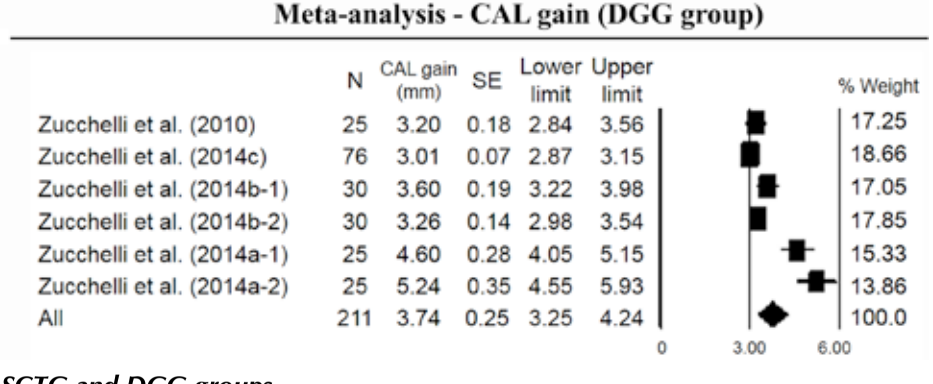


Figure 4. Meta-analysis comparing the Rec Red, PD reduction and CAL gain in the SCTG and DGG groups

Once the harvesting approach was demonstrated to be a non-influencing factor of patient morbidity (Zucchelli *et al.*, 2010), the question then becomes whether the clinical outcomes of periodontal plastic surgery are influenced by a DGG or SCTG approach. The present systematic review shows slightly superior results in terms of Rec Red, mRC, KT gain, PD reduction and CAL gain favoring CAF + DGG compared to CAF + SCTG. To the best of our knowledge, this is the first instance where a clinical difference between autologous CTG harvested via two different approaches was demonstrated. In a RCT comparing the outcome of CAF + SCTG versus CAF + DGG (Zucchelli *et al.*, 2010), the differences between the two groups were not statistically significant. However, the KT gain together with the Rec Red, gingival thickness and CAL gain were found to be greater in the CAF + DGG group. It can be speculated that the lack of a statistically significant difference in this article is due to the clinician's ability and expertise, probably having harvested a SCTG from the superficial layer of the palate and not from the deeper part. This variation would be expressed in the composition, specifically the less amount of fatty and glandular tissue, minimizing the difference between the two grafts. As a matter of fact, the KT gain found by Zucchelli *et al.*, (2010) in the two groups (1.92 ± 0.49 and 2.12 ± 0.52 for CAF + SCTG and CAF + DGG, respectively) is similar to the average KT gain in CAF + DGG group (1.92 mm) shown in this systematic review.

Having an adequate amount of KT around teeth and implants is essential for maintaining oral hygiene, minimizing the risk of gingival recession, and improving aesthetics (Ericsson *et al.*, 1984; Lang *et al.*, 1972; Chung *et al.*, 2006). Soft tissue augmentation using autologous CTG has also been introduced at pontic sites (Gonzalez-Martin *et al.*, 2014); in periodontal regenerative surgery (Zucchelli *et al.*, 2017); guided bone regeneration (Urban *et al.*, 2017); in the treatment of peri-implantitis (Schwarz *et al.*, 2014); and in cases of soft tissue dehiscence around implants (Zucchelli *et al.*, 2013), among others. The results of the present study suggest that soft tissue augmentation with DGG can provide better KT gain compared to the traditional SCTG.

The present systematic review was based on RCT's with a follow-up period no less than 1 year. The reason behind this criterion is that clinical parameters such as mRC and the amount of KT should only be evaluated medium to long-term (Agudio *et al.*, 2009; Pini-Prato *et al.*, 2010). In fact, Pini-Prato *et al.*, (Pini-Prato *et al.*, 2010) compared the results of CAF alone versus CAF + CTG at 6 months, where a greater percentage of complete root coverage with the former was observed; however, this result gradually diminished after 12 months, and even more after 5 years (where CAF + CTG demonstrated a greater percentage of complete root coverage). The addition of a CTG caused coronal displacement of the gingival margin over time, while patients treated with CAF alone showed an apical relapse of the gingival margin (Pini-Prato *et al.*, 2010). The authors attributed the apical relapse, of the CAF alone, to the lower amount of KT attained, which may, in turn, negatively affect the stability of the gingival margin during the maintenance phase. In a systematic review, Cairo *et al.*, demonstrated that CAF + CTG was the most effective technique in correcting the recession defects (mRC) and in augmenting the KT gain. However, the present study suggests that if the CTG is achieved by DGG, the magnitude of the former statement may be further reinforced and refined.

It is also believed that the phenomenon of "creeping attachment" benefits from a thick and wide keratinized mucosa, leading to an eventual improvement of complete root coverage, together with a stable gingival margin (Agudio *et al.*, 2009; Pini-Prato *et al.*, 2010). Agudio *et al.* (2009) demonstrated that the increased KT achieved at the treated sites as contrasted with untreated sites, maintained their stability over a period of 10-27 years. Also, thin gingival biotype is reportedly at a greater risk of gingival recession than thick biotype, especially in cases of plaque-associated inflammation (Olsson *et al.*, 1991; Zweers *et al.*, 2014). Therefore, another advantage of increased KT is the local change of the biotype from thin to thick (Jung *et al.*, 2008), which reduces the likelihood of GR recurrence (Ericsson and Lindhe, 1984).

The difference in KT gain between CAF + DGG and CAF + SCTG is probably due to the dissimilar nature of the grafts, DGG being mainly composed of lamina propria, and thus characterized by a greater amount of fibrous connective tissue (Bertl *et al.*, 2015). These properties make DGG firmer, more stable and easier to manage than SCTG (Zucchelli and Mounssif, 2015). Moreover, the composition of the connective tissue can influence the differentiation of the overlying epithelial layer (Karring *et al.*, 1975) and deeper palatal connective tissue may be less capable of inducing keratinization of the epithelium (Ouhayoun *et al.*, 1988). On the other hand, due to a deeper harvesting site, SCTG is essentially composed of submucosa, which consists of a large amount of fatty and glandular tissue (Bertl *et al.*, 2015). Sullivan & Atkins (1968) have suggested that fatty tissue should be completely removed from the graft, due to its inclination to act as a barrier to diffusion and vascularization. Similarly, Miller (1985b) speculated that submucosa can prevent a direct interface between connective tissue and the root. Based on this assumption, two studies investigated the effect of the CTG orientation on gingival augmentation

without observing significant differences (Al-Zahrani *et al.*, 2004; Lafzi *et al.*, 2007). The absence of difference between groups in these investigations can be explained by the fact that graft composition, rather than orientation, is what plays a role in stimulating the differentiation of the epithelial layer. These findings are in agreement with Cordioli *et al.* (2001) who reported a lack of transformation of the mucosa into KT when bilaminar techniques involved SCTG. Moreover, a recent systematic review from Sculean *et al.* (2014) concluded that CTG from the deep palate seems to not have the same potential of inducing keratinization in comparison to a more superficial CTG.

Furthermore, the composition of the CTG is also responsible for graft shrinkage which, in turn, can alter the amount of KT. Zucchelli *et al.* (2010) found less post-operative shrinkage with DGG compared to SCTG (Zucchelli *et al.*, 2010). According to Bertl (2015) the fatty and glandular tissue, which characterizes SCTG, is the main cause for the greater shrinkage. It can be speculated that the slightly enhanced Rec Red and mRC associated with the DGG group is also due to the minimal shrinkage of the underlying DGG compared to SCTG.

Another primary goal of mucogingival surgery is PD reduction and, thus, increased CAL. The present study showed that CAF + DGG was able to slightly reduce PD, whereas CAF + SCTG did not show any PD improvement following treatment (-0.03 mm on average). As a consequence of the superior Rec Red and PD reduction, CAL gain pertaining to the CAF + DGG group was found to be greater than that of the CAF + SCTG group, with 3.74 mm and 3.0 mm respectively. It can be assumed that a larger amount of connective tissue fibers as well as the absence of fatty and glandular tissue leads to enhanced attachment between DGG and the tooth surface versus SCTG, as suggested by Miller (1985b). However, it is important to highlight that the non-complete de-epithelialization of the graft that may result in cyst formation (Harris, 2002).

Within the limitations of the present study, several factors can be described. Firstly, many of the included investigations were performed by the same group. Secondly, the palatal thickness was only provided in a single study; this parameter can indeed play a major role in the choice of the harvesting approach and also in the graft composition. Lastly, the harvested graft size was reported in only 2 studies. Although, Zucchelli *et al.* (2014b) have demonstrated that reduced DGG size is associated with a comparable outcome to a larger DGG. To the best of our knowledge, the present systematic review is the first study that suggests that the CTG harvesting approach may affect the clinical outcomes of CAF. Thus, autologous CTG involving both DGG and SCTG, each with varying characteristics and potential, should be considered a non-specific term. The ease of harvesting along with the enhanced stability and consistency of the graft are the intra-operative advantages initially attributed to DGG. Despite the mean difference of the clinical parameters between the two techniques was within 1 mm, the present study further highlights that DGG is associated with greater mRC, KT gain and CAL gain when compared with SCTG, and should accordingly may be considered as the new technique of choice for autologous CTG harvesting.

Conclusion

Limited evidence are available in literature when comparing CAF + DGG to CAF + CTG. However, taking into account the limitations of the present review, it can be concluded that CAF + DGG seems to provide superior mRC, KT gain and CAL gain than CAF + SCTG and therefore, the DGG approach may be considered as the preferred choice for obtaining autologous CTG.

Indication for further research

- Increase the number of RCTs with at least 1 year of follow-up, as well as the number of RCTs with longer follow-up
- Further RCTs that compare the two different palatal harvesting techniques
- RCTs reporting the palatal harvesting technique
- RCTs that specify the average dimension of the harvested CTG together with the palatal thickness
- RCTs based on the CONSORT guidelines

Clinical relevance

Despite limited evidence is available in the literature when comparing CAF + CTG to CAF + DGG, it can be suggested that DGG may be considered as the preferred harvesting technique when incorporated with a CAF.

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Conflict of interest and source of funding

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