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Received: 23 December 2021 | Revised: 10 June 2022 | Accepted: 23 June 2022

DOI: 10.1111/prd.12465

Periodontology 2000 WILEY

REVIEW ARTICLE

Minimal invasiveness in soft tissue augmentation at dental implants: A systematic review and meta-analysis of patient-reported outcome measures

Daniel S. Thoma | Franz J. Strauss | Leonardo Mancini | Thomas J. W. Gasser | Ronald E. Jung

Clinic of Reconstructive Dentistry, Center of Dental Medicine, University of Zurich, Zürich, Switzerland

Correspondence
Daniel S. Thoma, Clinic of Reconstructive Dentistry, Center of Dental Medicine, University of Zurich, Plattenstrasse 11, 8032 Zürich, Switzerland.
Email: daniel.thoma@zzm.uzh.ch

1 | INTRODUCTION

Mucogingival surgery has become a frequent procedure at dental implant sites to enhance the quality and/or quantity of the mucosa. This is based on clinical studies[1,2] and systematic reviews[3-5] demonstrating the benefits of these procedures not only in peri-implant health and aesthetics but also in plaque control by reducing the brushing discomfort in patient with a lack of keratinized tissues around implants.

The efficacy of soft tissue augmentation surgeries has been well documented rendering, depending on the procedure, a gain of keratinized tissue ranging between 1.15 ± 0.81 mm and 2.57 ± 0.50 mm[6] and a gain of mucosal thickness ranging between 1.13 and 0.76 mm.[4] The materials and transplants used for soft tissue augmentation can be mainly classified into three categories: (1) autogenous soft tissue grafts (harvested from the patients' palate or tuberosity), (2) allografts, and (3) xenografts. The clinical decision for a specific material/transplant over the other is often based on the clinician's preference and the scientific documentation available.[7-9]

Traditionally, autogenous grafts have been preferred due to their short-term efficacy as well as long-term stability. These grafts are, however, associated with an increased patient morbidity and psychological and physical discomfort.[10,11] This increased morbidity is predominantly derived from the second surgical site. In order to circumvent the aforementioned disadvantages of autogenous grafts, various soft tissue substitutes have been developed and evaluated in preclinical and clinical studies and often compared to the gold standard, the autogenous soft tissue graft.[12-14]

The efficacy of soft tissue substitutes for the two procedures—gain of keratinized tissue (KTW) and gain of mucosal thickness (GT)—is considered by many clinicians to be slightly less effective than autogenous grafts even though the scientific evidence does hardly demonstrate a substantial inferiority.[7,15,16,17] The best treatment, however, is not necessarily the one that shows the highest efficacy in randomized clinical trials but rather the one that fits a certain set of individual characteristics and is in accordance with the patient's preferences.[18,19] Accordingly, reliance on patients' preferences, the so-called patient reported-outcome measures (PROMs) are becoming more and more important for the selection of the therapy.[20-26]

PROMs are tools to capture the patient´s perception about aspects of their health and how a disease or its treatment influence the quality of life.[23,27,28] PROMs in medicine became particularly critical when oncologists confronted patients whose decision to accept or reject a therapy was based on the quality of life during their final years rather than the predicted length of survival.[29]

Even though PROMs are not individualized measures but rather an average of what patients value the most, they are becoming a decisive factor for the clinical decision making in day-to-day clinical practice.[19] A recent systematic review exploring PROMs related to soft tissue augmentation procedures provided inconclusive results due, in part, to limitations of analytical approaches and the

Daniel Thoma and Franz J. Strauss contributed equally to the manuscript and should be considered as joint first authors.

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heterogeneity of the included studies.[30] Therefore, the PROMs of soft tissue substitutes compared to autogenous grafts following soft tissue augmentation at implant sites remain uncertain. In other words, whether soft tissue substitutes for soft tissue augmentation procedures can outweigh the disadvantages of autogenous graft on PROMs (eg, morbidity) or lead to similar satisfaction levels to autogenous graft at implant sites is still unclear.

Based on the principles of evidence based medicine that requires patients to be actively involved in the decision making,[31] clear information on the expected level of morbidity or satisfaction of soft tissue substitutes over autogenous grafts might not only improve patients' understanding and acceptance of the treatment modality but also support clinicians in the decision making.

The primary aim of this systematic review was, therefore, to compare PROMs of soft tissue substitutes versus autogenous grafts for soft tissue augmentation procedures at implant sites.

2 | MATERIALS AND METHODS

2.1 | Protocol development registration and reporting format

A detailed protocol was developed and followed according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement[32] and the 2021 Cochrane collaboration guidelines.[33] The protocol was registered in PROSPERO, identification number CRD 293509.

2.2 | Eligibility criteria

According to the PICO design a focused question was used to facilitate the inclusion and exclusion of studies.

2.2.1 | Focused question

In patients with dental implants undergoing soft tissue augmentation (P), do soft tissue substitutes (I) compared to autogenous soft tissue graft (C) limit the post-operative morbidity and other patient reported-outcomes measures (O).

Population (P): Patients in need of soft tissue augmentation around single or multiple implants.
Intervention (I): Soft tissue augmentation using soft tissue substitutes (volume stable collagen matrix, acellular dermal matrix, or any soft tissue substitute).
Comparison (C): Autogenous connective tissue graft, free gingival graft, or no graft (repositioned flaps).
Outcome (O): PROMs, including pain, edema, hematoma, painkillers administrated, aesthetic satisfaction, treatment satisfaction, willingness to redo the surgery, oral health impact profile, quality of life, surgery time, and adverse effects.

2.3 | Search strategy

A systematic electronic search was conducted on Medline (PubMed), Embase, Central, Web of Science, and Epistemonikos (for relevant systematic reviews addressing the topic). A systematic search of the gray literature (OpenGrey) and of registered but unpublished trials at ClinicalTrial.gov was also performed. The electronic search was conducted up to November 22, 2021, and designed and adapted to each type of database.

2.4 | Medline

"acellular dermal matrix"[All Fields] OR "dermal matrix allograft"[All Fields] OR "collagen matrix"[All Fields] OR "connective tissue graft"[All Fields] OR "free gingival graft"[All Fields] OR "vestibuloplasty"[All Fields] OR "soft tissue augmentation"[All Fields] OR "apically positioned flap"[All Fields] OR "soft tissue graft"[All Fields] OR "alloderm" [All Fields] OR "keratinized tissue"[All Fields] OR "soft tissue graft"[All Fields] OR "subepithelial connective tissue graft"[All Fields] OR "connective tissue"[All Fields] OR "FGG"[All Fields] OR "human fibroblast-derived dermal substitute"[All Fields] OR "dermagraft"[All Fields] OR "apligraf"[All Fields] OR "extracellular membrane"[All Fields] OR "gingival autograft"[All Fields] OR "attached gingiva"[All Fields] OR "attached mucosa"[All Fields] OR "KM"[All Fields] OR "soft tissue augmentation"[All Fields] OR "soft tissue transplantation"[All Fields] OR "ridge augmentation"[All Fields] OR "soft tissue correction"[All Fields] AND "Dental implants"[MeSH Terms] OR "dental implants, single tooth"[MeSH Terms] OR "dental implants, single tooth"[MeSH Terms] OR "dental implants"[All Fields] OR "dental implant"[All Fields].

2.5 | Embase

("acellular dermal matrix" OR "dermal matrix allograft" OR "collagen matrix" OR "connective tissue graft" OR "free gingival graft" OR "vestibuloplasty" OR "apically positioned flap" OR "alloderm" OR "keratinized tissue" OR "soft tissue graft" OR "subepithelial connective tissue graft" OR 'connective tissue' OR "fgg" OR "human fibroblast-derived dermal substitute" OR "dermagraft" OR "wound matrix" OR "apligraf" OR "extracellular membrane" OR "gingival autograft" OR "attached gingiva" OR "attached mucosa" OR "km" OR "soft tissue augmentation" OR "soft tissue transplantation" OR "ridge augmentation" OR "alveolar ridge augmentation" OR "soft tissue correction") AND "Dental implants"[MeSH Terms] OR "dental implants, single tooth"[MeSH Terms] OR "dental implants, single tooth"[MeSH Terms] OR "dental implants"[All Fields] OR "dental implant"[All Fields].

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2.6 | Central

"soft tissue graft" OR "acellular dermal matrix" OR "keratinized tissue" OR "connective tissue" AND "dental implant".

2.7 | Web of science

TS = ("acellular dermal matrix" OR "dermal matrix allograft" OR "collagen matrix" OR "connective tissue graft" OR "free gingival graft" OR "vestibuloplasty" OR "soft tissue augmentation" OR "apically positioned flap" OR "soft tissue graft" OR "alloderm" OR "keratinized tissue" OR "soft tissue graft" OR "subepithelial connective tissue graft" OR "connective tissue" OR "FGG" OR "human fibroblast-derived dermal substitute" OR "dermagraft" OR "apligraf" OR "extracellular membrane" OR "gingival autograft" OR "attached gingiva") AND TS = "dental implant*".

2.8 | Epistemonikos

("acellular dermal matrix" OR "dermal matrix allograft" OR "collagen matrix" OR "connective tissue graft" OR "free gingival graft" OR "vestibuloplasty" OR "soft tissue augmentation" OR "apically positioned flap" OR "soft tissue graft" OR "alloderm" OR "keratinized tissue" OR "soft tissue graft" OR "subepithelial connective tissue graft" OR "connective tissue" OR "FGG" OR "human fibroblast-derived dermal substitute" OR "dermagraft" OR "apligraf" OR "extracellular membrane" OR "gingival autograft" OR "attached gingiva" OR "attached mucosa" OR "KM" OR "soft tissue augmentation" OR "soft tissue transplantation" OR "ridge augmentation" OR "soft tissue correction" AND "dental implant*") OR abstract:("acellular dermal matrix" OR "dermal matrix allograft" OR "collagen matrix" OR "connective tissue graft" OR "free gingival graft" OR "vestibuloplasty" OR "soft tissue augmentation" OR "apically positioned flap" OR "soft tissue graft" OR "alloderm" OR "keratinized tissue" OR "soft tissue graft" OR "subepithelial connective tissue graft" OR "connective tissue" OR "FGG" OR "human fibroblast-derived dermal substitute" OR "dermagraft" OR "apligraf" OR "extracellular membrane" OR "gingival autograft" OR "attached gingiva" OR "attached mucosa" OR "KM" OR "soft tissue augmentation" OR "soft tissue transplantation" OR "ridge augmentation" OR "soft tissue correction") AND "dental implant".

2.9 | Inclusion criteria

- Randomized clinical trials (RCT), prospective-, retrospective-, and case-series studies performing soft tissue augmentation around implants.
- Evaluation and reporting patient-reported outcomes measures over a minimum follow-up period of 1 week.

2.10 | Exclusion criteria

- In vitro studies and preclinical studies
- Soft tissue augmentation around teeth

2.11 | Study selection

Based on the inclusion/exclusion criteria, two calibrated authors (F.J.S., T.G.) screened independently the titles, abstracts, and full text to check for eligibility. The inter-agreement among the authors was based on a Cohen's Kappa score. Any disagreements were resolved by discussion with a third author (D.T.). All articles that did not meet the eligibility criteria were excluded and the reasons for exclusion were noted.

2.12 | Data extraction

Data were independently extracted by two reviewers (L.M., F.J.S.) using data extraction tables (Excel Microsoft corporation). In case of missing data, the authors of the included studies were contacted via email to provide the missing or additional data.

2.13 | Quality assessment

Risk assessment and quality of the included studies was performed independently by two reviewers (L.M., F.J.S.) using the following tools and according to the type of study: (a) Cochrane Risk of Bias Tool for Randomized Controlled Trials, (b) ROBINS-I tools[34] for non-randomized cohort studies and (c) The Joanna Briggs Institute Critical Appraisal tool[35] for case series.

2.14 | Data synthesis

Descriptive and qualitative aspects of the included studies were summarized (study design, population, primary outcome, morbidity, patient's satisfaction, aesthetic satisfaction, surgery time, and pain medication taken).

2.15 | Statistical analysis

To summarize and compare the studies, mean values of PROMs were pooled and analyzed with weighted mean differences (WMDs) and 95% confidence intervals (CIs). To investigate possible differences in the mean values of PROMs between soft tissue substitutes and autogenous grafts, meta-analyses for the different outcomes were conducted with a software (RevMan 5.4.; The Cochrane Collaboration 2020). For all meta-analysis, the DerSimonian-Laird method with

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random effect models were used since they are conservative and consider both within- and between-study variability.[36] The I^2 statistic was used to examine statistical heterogeneity of pooled effect estimates.

3 | RESULTS

3.1 | Search

A total of 9880 articles were identified through the electronic search (Figure 1). After removal of 3570 duplicates, 6310 titles were screened, and 520 articles were evaluated on the basis of their abstract. Based on the inclusion criteria 29 studies were finally included. The inter-rater agreement at the abstract selection and full text review stage was almost perfect between reviewers ($\kappa = 0.81$).

3.2 | Description of included studies

Nineteen articles were randomized clinical trials (RCTs),[37-49] seven non-randomized[1,50,51,52,53,54,55] and three case series.[56-58] Characteristics of the included RCTs are summarized in Table 1. Characteristics of the remaining studies (non-randomized studies and case series) are summarized in Table S1.

Sixteen RCTs were two-arm studies[37,39,40,41,42,43,44,45,46,47,48,59,60,61,62,63,64] and three were three-arm studies.[38,49,65]

From the seven non-randomized studies, three had a two-arm design,[51,53,65] one had a three-arm design[50] and three lacked of control groups.[54,66]

Out of the three cases series, two had a conventional[56,57] design and one had a split-mouth design.[58]

The minimum follow up was of 1 week and the maximum ranged between 1 and 3 years. The total number of patients treated was 911.

3.3 | Study samples

Sample size per study varied from 10 to 60 while the age ranged between 18 to 72 years. From the total of 911 patients treated, 290 (31.8%) were females and 224 (24.5%) were males. The gender of the remaining population (397 patients) was not reported.

Smokers were included in 18 studies.[37,38,39,42,43,45,46,52,53,54,55,56,58,60,62,64,65,66]

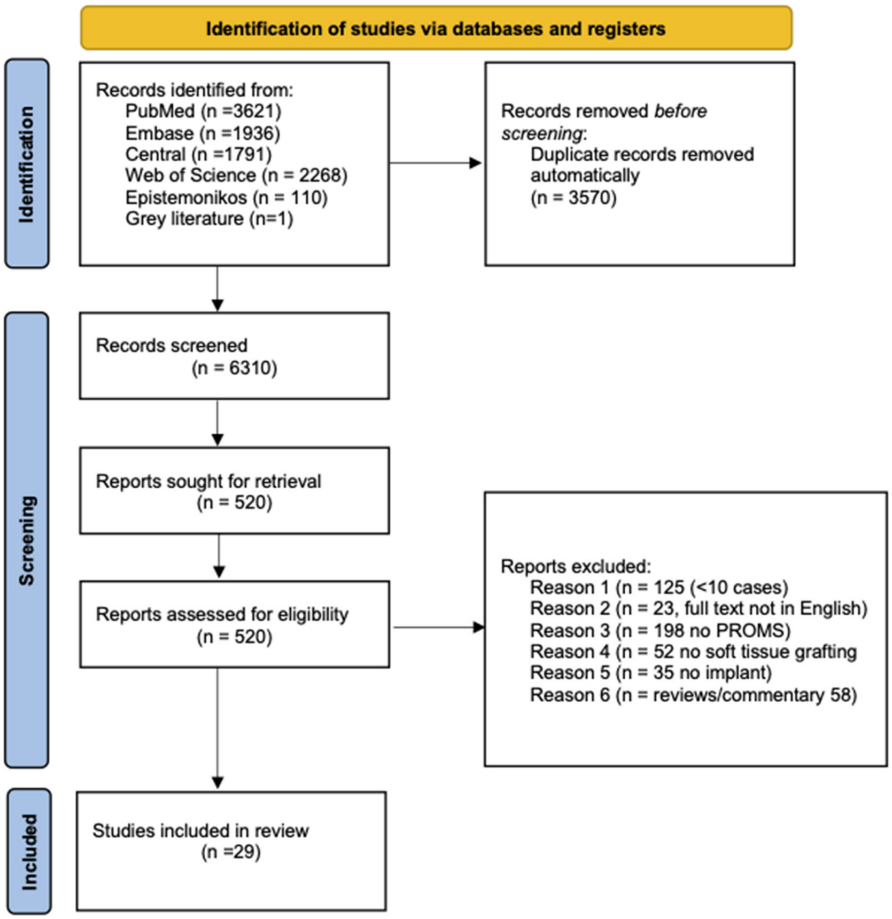

FIGURE 1 Flowchart of the study according to the 2020 PRISMA Checklist

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TABLE 1 Randomized clinical trials included in the review

Publication/ year	Study design	total number of patients/ analyzed	Follow up	Soft tissue timing	Time point PROMs	Primary outcome (Mean SD) mm	Morbidity VAS (Mean SD)	Satisfaction VAS (Mean SD)	Pain killers (Mean SD)	Surgery time (min)	Quality of life/ OHIP	Other PROMs
Anderson et al 2014	Two arms	13/13	6 mo	Delayed	2, 6 wk, 3, 6 mo	Mucosal thickness gain 6 mo **ADM** 1.25 **SCTG** 0.93	VAS (0-10) 2 wk **ADM** 4.17 ± 2.22 **SCTG** 3.43 ± 3.99	NR	**ADM** 1.00 ± 0.84 **SCTG** 1.86 ± 0.90	NR	QoL 5 points scale **ADM** 2 wk 1.83 ± 0.76 6 mo 1.32 ± 0.57 **SCTG** 2 wk 2.06 ± 1.4 6 mo 1.60 ± 1.28	Wound healing index 2 wk **ADM** 2.50 ± 0.54 **SCTG** 1.57 ± 0.53
Baldi et al 2020	Three arms	36/31	6 mo	2° stage	6 mo	KTW increase 6 mo **XCM** 1.05 ± 0.76 **SCTG** 0.80 ± 1.73 **No graft** 0.16 ± 1.01	NR	VAS (0-100) **XCM** 93.8 ± 7.7 **SCTG** 97.2 ± 3.0 **No graft** 92.2 ± 8.4	NR	NR	NR	Aesthetic evaluation (VAS 0-100) **XCM** 92.1 ± 8.3. **SCTG** 94.1 ± 34 **No graft** 92.9 ± 7
Cairo et al 2017	Two arms	60/58	6 mo	2° stage	1, 2 wk 1, 3, 6 mo	Mucosal thickness gain 6 mo **XCM** 0.9 ± 0.2 **SCTG** 1.2 ± 0.3	VAS (0-100) 1 wk **XCM** 13 ± 10 **SCTG** 37 ± 15	VAS (0-100) **XCM** 95.5 ± 5 **SCTG** 91 ± 9	**XCM** 2.2 ± 0.8 **SCTG** 3.9 ± 0.7	**XCM** 35.5 ± 9.4 **SCTG** 51.7 ± 7.0	NR	Aesthetic evaluation VAS (0-100) **XCM** 90 ± 8 **SCTG** 90 ± 9
Cosyn et al 2021	Two arms	60/59	3 mo	Implant placement	1 wk 3 mo	Mucosal thickness gain 3 mo **XCM** **0.85** **SCTG** **1.15**	VAS (0-100) 1 wk **XCM** 20.5 ± 21.3 **SCTG** 25.94 ± 23.5	NR	**XCM** 4.47 ± 4.1 **SCTG** 5.24 ± 7.8	**XCM** 13 ± 6.7 **SCTG** 22.03 ± 6.7	NR	Aesthetic evaluation VAS (0-100) **XCM** 82 ± 13.28 **SCTG** 81.36 ± 21.68
De Bruyckere et al 2020	Two arms	42/40	1 y	Implant placement	1, 2, 3 d 2 wk 1 y	PES **GBR** 10.11 ± 1.83 **SCTG** 10.48 ± 2.25	VAS (0-100) 2 wk **GBR** 5.05 ± 0.21 **SCTG** 2.05 ± 3.61	VAS (0-100) **GBR** 84 ± 14 **SCTG** 87 ± 15	**GBR** 7.1 **SCTG** 4.8	NR	OHIP14 **GBR** 18.6 ± 5.5 **SCTG** 15.7 ± 2.3	Willingness to redo the intervention (n. of Pt.) **GBR** 19/21 **SCTG** 17/21

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TABLE 1 (Continued)

Publication/ year	Study design	total number of patients/ analyzed	Follow up	Soft tissue timing	Time point PROMs	Primary outcome (Mean SD) mm	Morbidity VAS (Mean SD)	Satisfaction VAS (Mean SD)	Pain killers (Mean SD)	Surgery time (min)	Quality of life/ OHIP	Other PROMs
Froum et al 2015	Two arms	32/31	3 mo	Implant placement	1, 2 wk 1, 2, 3 mo	Mucosal thickness gain 3 mo **XCM** 0.74±0.78 **No graft** 0.09±0.40	VAS (0-100) 2 wk **XCM** 12.1 ±20.3 **No graft** 5.5 ±7.9	VAS (0-100) **XCM** 97.7 ±5.0; **No graft** 96.7 ±4.9	NR	NR	NR	NR
Hämmerle et al (raw data)	Two arms	88/79	1 y	2° stage	Baseline, 1-10 d and 1 mo	Mucosal thickness gain 4 mo **XCM** 0.9 ±2.0 **SCTG** 1.2 ±1.4	VAS (0-100) 1 wk **XCM** 2.6 ±4.9 **SCTG** 15.5 ±24.2	**NR**	**XCM 5.6 ±6.5; SCTG 9.5 ±21**	**XCM** 42.3 ±18 **SCTG** 48.7 ±15.9	OHIP14 4 mo **XCM** 5.7 ±7.3 **SCTG** 6.8 ±9.9	NR
Huang et al 2021	Two arms	33/26	6 mo	Delayed	Post-op 2, 6 mo	KTW increase 6 mo **XCM** 1.8 ±1.0 **FGG** 4.1 ±1.6	VAS (0-10) 1-wk **XCM** 2.6 ±2.3 **FGG** 3.4 ±1.8	VAS (0-10) **XCM** 9.7 ±0.6 **FGG** 9.6 ±0.6	**XCM** 2.0 ±1.6 **FGG** 3.7 ±3.1	**XCM** 39±8 **FGG** 60±9	NR	NR
Huber et al 2018	Two arms	20/19	12 mo	Before implant placement	1 y	Mucosal thickness gain 1 y **XCM** −0.4 ±0.9 **SCTG** 0.4 ±1.4	Reported elsewhere (Thoma et al 2016)	NR	NR	NR	OHIP 14 1 y **XCM** 0.5 ±1.6 **SCTG** 1.0 ±2.6	NR
Hutton et al 2018	Two arms	20/20	4 mo	implant placement	2 wk 1, 2, 4 mo	mucosal thickness gain 4 mo **ADM** 0.05±1.57 **SCTG** 0.44±2.04	VAS (0-100) 2 wk **ADM** 10.10±7.78 **SCTG** 23.60±24.7	VAS (0-100) **ADM** 94.80±7.31 **SCTG** 98.30±2.26	NR	NR	NR	Adverse effects dehiscence at the recipient site **ADM** 7/10 SCTG 3/10
Lorenzo et al 2012	Two arms	24/22	6 mo	Delayed	10 d, 1 mo	KTW increase 6 mo **XCM** 2.3 mm **SCTG** 2.33 mm	VAS (0-10) 10 d **XCM** <3 **SCTG** <3	NR	**XCM** 4 tablets **SCTG** 8 tablets	**XCM** 32.50 **SCTG** 46.25	NR	NR

(Continues)

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TABLE 1 (Continued)

Publication/ year	Study design	total number of patients/ analyzed	Follow up	Soft tissue timing	Time point PROMs	Primary outcome (Mean SD) mm	Morbidity VAS (Mean SD)	Satisfaction VAS (Mean SD)	Pain killers (Mean SD)	Surgery time (min)	Quality of life/ OHIP	Other PROMs
Sanz et al 2009	Two arms	20/20	6 mo	Delayed	10 d, 1 mo	KTW increase 6 mo **XCM** 2.1 mm **FGG** 2.4 mm	VAS (0-10) 10 d **XCM** 2.30 ± 2.39 **FGG** 4.01 ± 8.5	NR	**XCM** 1.8 ± 2.15 **FGG** 12.8 ± 13.3	**XCM** 30.80 ± 7 **FGG** 47.20 ± 10	NR	NR
Tarasenko et al 2020	Three arms	63/58	6 mo	Delayed	Post-op, 1, 3, 5 d 1 wk	KTW increase 6 mo **XCM** 2.51 ± 0.60 **FGG** 4.47 ± 1.10 **No graft** 1.38 ± 0.79	VAS (0-10) 5 dn **XCM** 1.06 ± 1.43 **FGG** 4.48 ± 2.0 **No graft** 0.50 ± 0.82	NR	NR	NR	NR	NR
Thoma et al 2016	Two arms	20/20	3 moths	Before implant placement	1 wk, 1, 3 mo	Mucosal thickness gain 3 mo **XCM** 1.00 **SCTG** 1.5	VAS (0-10) 1-wk **XCM** 1.5 ± 1.7 **SCTG** 2.6 ± 1.6	NR	**XCM** 4.0 ± 3.4 **SCTG** 4.8 ± 3.4	**XCM** 44.8 ± 19.6 **SCTG** 37.3 ± 12.1	OHIP 14 3 mo **XCM** 4.6 ± 5.9 **SCTG** 4.4 ± 5.6	Adverse effects dehiscence at the recipient site **XCM** 7 **SCTG** 13
Thoma et al 2020	Two arms	20/19	3 y	Before implant placement	3 y	Mucosal thickness gain 3 y **XCM** 0.4 ± 1.1 **SCTG** 1.1 ± 1.5	Reported elsewhere (Thoma et al 2016)	NR	Reported elsewhere (Thoma et al 2016)	Reported elsewhere (Thoma et al 2016)	OHIP 14 3 y **XCM** 1.0 ± 1.3 **SCTG** 0.0 ± 0.0	NR
Vellis et al 2019	Two arms	30/30	6 mo	Delayed	1, 2 wk	KTW increase 6 mo **XCM** 3.23 ± 1.51 **FGG** 3.73 ± 1.92	VAS (0-10) 2 wk **XCM** 1.9 ± 2.6 **FGG** 2.97 ± 2.9	NR	NR	NR	NR	NR
Wiesner et al 2010	Two arms	20/20	1 y	Implant placement	1 y	Mucosal thickness gain 1 y **CTG** 1.20 ± 0.63 **No graft** 0.15 ± 0.34	NR	Number of patients satisfied **SCTG** 10; **No grafts** 9	NR	NR	NR	NR

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TABLE 1 (Continued)

Publication/ year	Study design	total number of patients/ analyzed	Follow up	Soft tissue timing	Time point PROMs	Primary outcome (Mean SD) mm	Morbidity VAS (Mean SD)	Satisfaction VAS (Mean SD)	Pain killers (Mean SD)	Surgery time (min)	Quality of life/ OHIP	Other PROMs
Zuiderveld et al 2018A	Two arms	60/60	1 y	Implant placement	Post-op 1 mo 1 y	Mid-buccal mucosal level changes 1 y **SCTG** 0.1 ±0.8 **No graft** −0.5 ±1.1	NR		NR	NR	OHIP14 1 y **SCTG 2.0** **No graft 2.0**	Willingness to redo the intervention VAS (0-10) **SCTG** 9.8 **No graft** 9.6
Zuiderveld et al 2018B	Three arms	60/60	1 y	Implant placement	Post-op 1 mo 1 y	Mid-buccal mucosal level changes 1 y **XCM** −0.17 ±1.3 **SCTG** −0.04±1.1 **No graft** −0.48±1.5	NR	VAS (0-10) **XCM** 9 ±1.2 **SCTG** 7.8 ±1.9 **No graft** 8.6 ±1.08	NR	NR	OHIP70 1 y **XCM** 16.9 ±4.7 **SCTG** 19.3 ±7.6 **No graft** 17.9 ±6.3	Willingness to redo the intervention VAS (0-10) **XCM 9.9** **SCTG 9.6** **No graft 9.8**

Abbreviations: ADM, acellular dermal matrix; APF, apically positioned flap; FGG, free gingival graft; KTW, keratinized tissue width; NR, not reported; OHIP, oral health impact profile; PROMs, patient related outcomes; QoL, quality of life; SCTG, subepithelial connective tissue graft; SD, standard deviation; VAS, visual analogue scale; XCM, xenogeneic collagen matrix.

Bold values indicates the idea is to differentiate the material from the scale (VAS).

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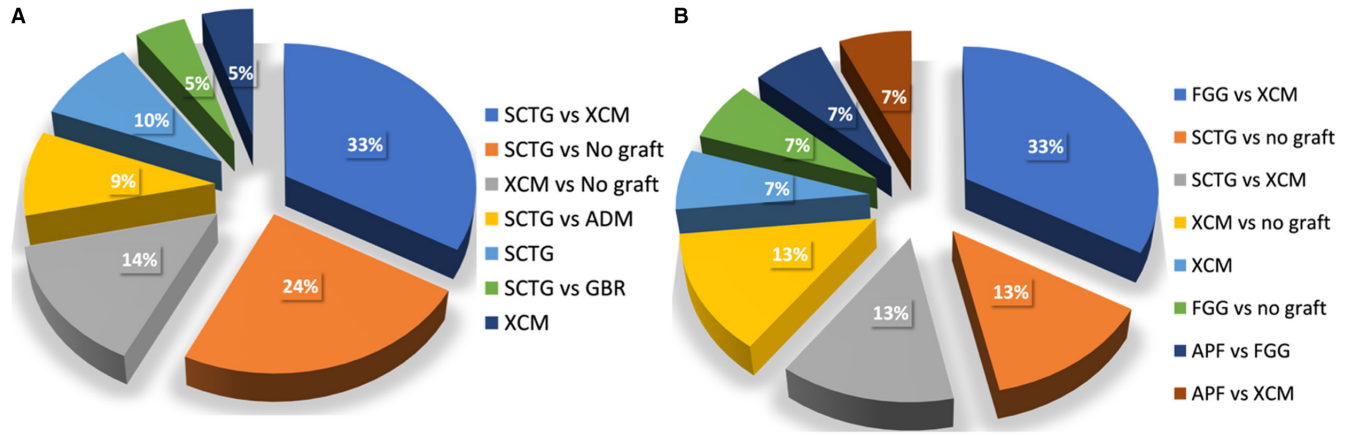

FIGURE 2 Type of biomaterial for the intervention and the corresponding comparison in the included studies. (A) Pie chart displaying the biomaterials used for *gain of mucosal thickness* and the corresponding comparison. (B) Pie chart displaying the biomaterials used for *keratinized tissue augmentation* and the corresponding comparison. ADM, acellular dermal-matrix; APF, apically positioned flap; FGG, free gingival graft; SCTG, subepithelial connective tissue graft; SGG, strip gingival graft; XCM, xenogeneic collagen-matrix

3.4 | Intervention comparison

Gain of mucosal thickness as the primary outcome was evaluated in 13 studies.[37,39,40,42,43,44,45,47,50,51,53,56,60] The type of soft tissue substitute and the corresponding comparisons are summarized in Figure 2A.

Keratinized tissue augmentation as primary outcome was assessed in 12 studies[38,41,46,48,49,57,58,59,61,62,64,65] (Figure 2B).

Three studies used peri-implant recession coverage[54,55,66] as the primary outcome and one study[41] used PROMs as the primary outcome.

3.5 | PROMs

3.5.1 | Pain

Pain was reported in 15 studies using Visual Analog Scale (VAS) scales. A VAS scale 0-10 was applied in nine studies and a VAS scale 0-100 in six studies. Meta-analysis was attempted for all soft tissue augmentation procedures with both VAS scales (0-10 and 0-100).

3.5.2 | Pain: gain of mucosal thickness

Based on the 0-100 VAS scale, meta-analysis revealed that soft tissue substitutes significantly reduced the pain perception compared to subepithelial connective tissue graft (SCTG) following the surgical intervention (n = 4; WMD = 14.91 VAS units; 95% CI 6.42-23.40; $P < .0006$) (Figure 3A). Likewise, based on a 0-10 VAS scale the meta-analysis revealed a similar trend and a borderline significance of pain reduction when soft tissue substitutes were applied (n = 4; WMD = 1.62 VAS units; 95% CI 0.01-3.23; $P = .05$) (Figure 3B).

3.5.3 | Pain: gain of keratinized tissue

According to the 0-100 VAS scale meta-analysis revealed, that compared to SCTG, soft tissue substitutes significantly reduced the pain perception after keratinized tissue augmentation (n = 2; WMD = 21.43 VAS units; 95% CI 12.58-30.28; $P < .0001$) (Figure 4A). Consistently, based on the 0-10 VAS scale, the meta-analysis showed that soft tissue substitutes significantly reduced the pain as compared to SCTG following keratinized tissue width augmentation (n = 4; WMD = 1.65 VAS units; 95% CI 0.66-2.64; $P = .001$) (Figure 4B).

3.6 | Satisfaction

Patient satisfaction was reported in 15 studies: 9 RCTs[38,39,40,41,42,47,48,49,59]; 4 non-randomized studies,[50,52,53,66] and 2 case series.[56,57] All but one study[56] reported satisfaction using VAS scales either 0-100 or 0-10. In one clinical study[56] a VAS scale 0-5 was used to assess patient satisfaction. Furthermore, one study reported the number of satisfied patients.[47] Meta-analysis in terms of satisfaction was attempted for all studies that used VAS scales 0-10 or 0-100.

Based on the 0-100 VAS scale, meta-analysis showed no significant differences between soft tissue substitutes and autogenous grafts (n = 4; WMD = 0.40 VAS units; 95% CI −4.22 to 5.02; $P = .86$). Similarly, based on a 0-10 VAS scale, meta-analysis revealed no significant differences between substitutes and autogenous grafts in terms of satisfaction (n = 2; WMD = −0.56 VAS units; 95% CI −1.62 to 0.50; $P = .30$) (Figure 5).

3.7 | Aesthetic perception

The overall aesthetics perceived by the patient was reported in 10 studies: 6 RCTs,[38,39,40,41,48,49] 3 non-randomized studies[50,54,55] and 1 case series.[56] Pooled data analyses revealed no significant

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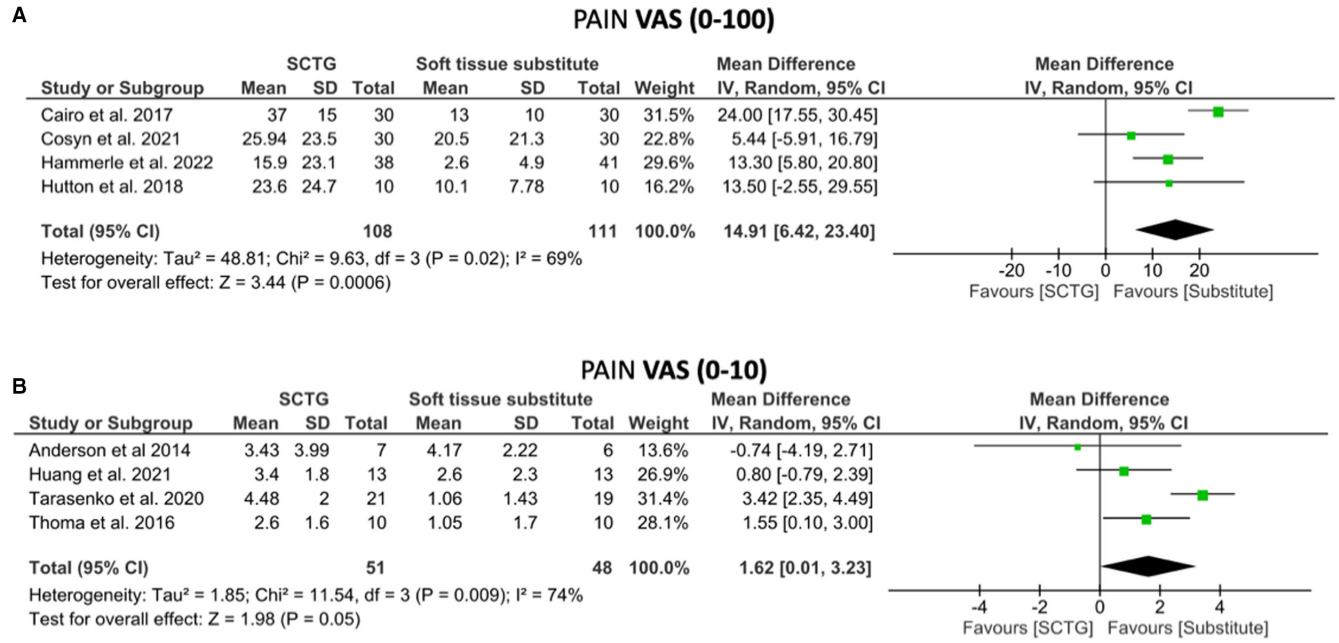

FIGURE 3 Forest plots of pooled pain perception comparing autogenous grafts (SCTG) versus soft tissue substitutes after mucosal thickness augmentation based on a VAS scale 0-100 (A) and 0-10 (B)

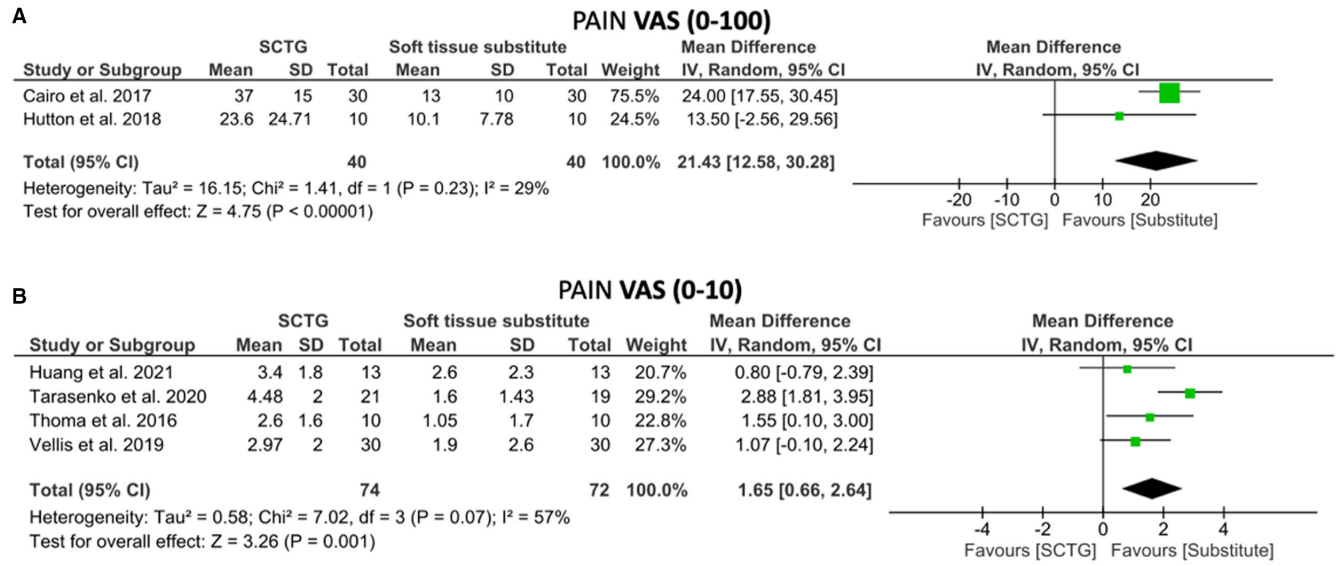

FIGURE 4 Forest plots of pooled pain perception comparing autogenous grafts (SCTG) versus soft tissue substitutes after keratinized tissue augmentation based on a VAS scale 0-100 (A) and 0-10 (B)

differences between autogenous soft tissue grafts and soft tissue substitutes in terms of aesthetics as rated by the patient (n = 3; WMD = −0.04 VAS units; 95% CI −3.86 to 3.78; $P = .98$) (Figure 6).

3.8 | Pain medication

The intake of medication for pain management was reported in nine studies; seven RCTs[37,39,40,41,45,59,62] and one non-randomized study.[64] Painkillers were often administrated for 2 weeks after surgery and Ibuprofen was the most used. The posology ranged between 250 mg and 600 mg. In addition, Thoma et al 2016 indicated mefenamic acid 250 mg.[45] Pooled data analysis revealed a significant reduction in painkiller intake when soft tissue substitute was used during the 2 weeks post-op (n = 6; WMD = 1.56 tablets; 95% CI 1.22-1.91; $P < .00001$) after soft tissue augmentation (mucosal-thickness/keratinized-tissue augmentation) (Figure 7).

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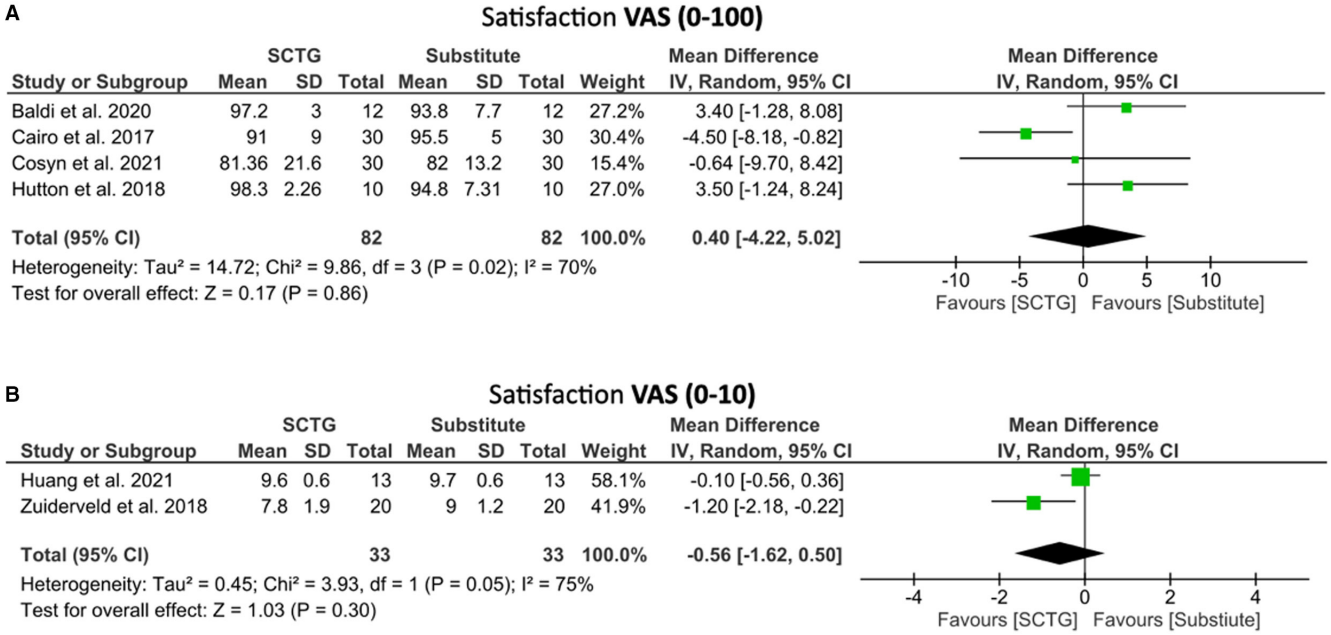

FIGURE 5 Forest plots of pooled patient satisfaction comparing autogenous grafts (SCTG) versus soft tissue substitutes based on a VAS scale 0-100 (A) and 0-10 (B)

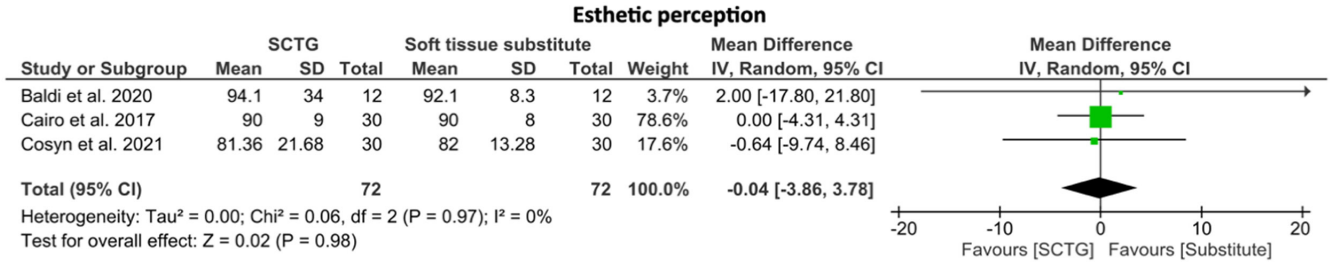

FIGURE 6 Forest plots of pooled aesthetics perceived by the patients comparing autogenous grafts (SCTG) versus soft tissue substitutes based on a VAS scale 0-100

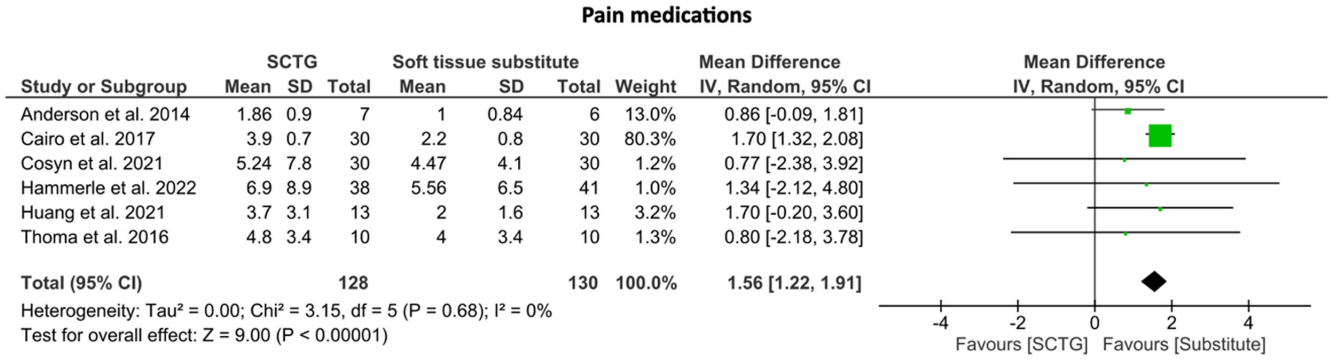

FIGURE 7 Forest plots of pooled pain killers used after soft tissue augmentation (mucosal-thickness/keratinized-tissue augmentation) during the 2 wk post-op

3.9 | Surgery time

Time spent for completing the surgery was reported in eight studies: seven RCTs[39,40,43,45,59,62,64] and one non-randomized study.[50] All but one study[45] showed a reduction in surgery time with soft tissue substitutes compared to autogenous grafts. The meta-analysis revealed a significant reduction in the surgery time with soft tissue substitutes after soft tissue augmentation when compared to autogenous

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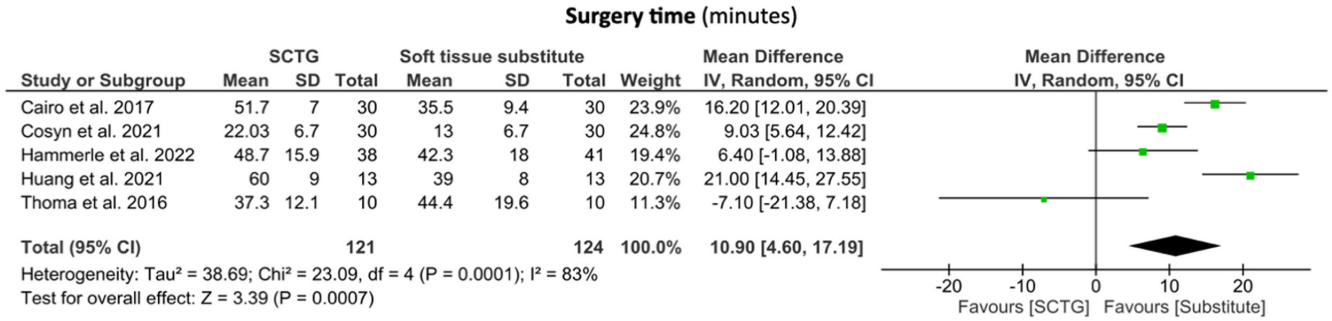

FIGURE 8 Forest plots of pooled surgery time in minutes comparing autogenous grafts (SCTG) versus soft tissue substitutes

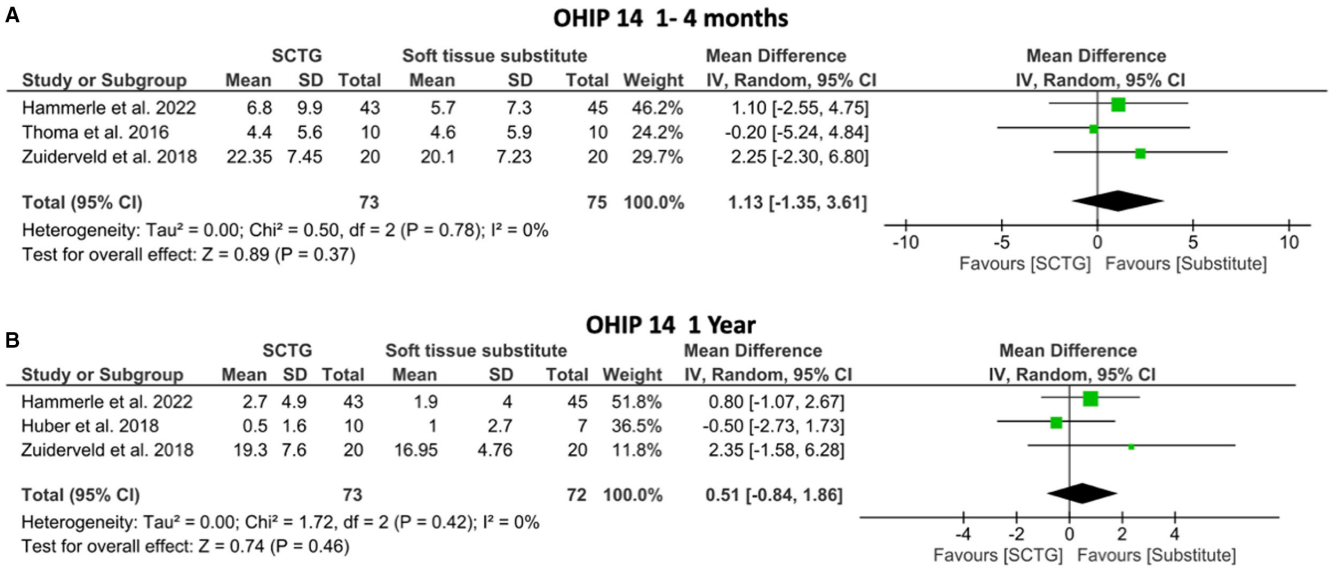

FIGURE 9 Forest plots of pooled quality of life in the short (A) and the longer (B) term, based on OHIP-14 scale

grafts (mucosal-thickness/keratinized-tissue augmentation) (n = 5; WMD = 10.9 minutes; 95% CI 4.60-17.19; $P < .00001$) (Figure 8).

3.10 | Quality of life

The influence of the surgery on the quality of life was reported in eight RCTs. Two different questionnaires were used to evaluate the quality of life either The Oral Health Impact Profile-14 (OHIP-14)[41,43,45,48,49] or the Kiyak Post-Surgical Patient Questionnaire.[37] Pooled data analyses revealed no significant differences between autogenous soft tissue grafts and soft tissue substitutes in terms of impact on the quality of life, neither in the short (1-4 months) nor in the long term (1 year; n = 3; WMD = 1.13; 95% CI −1.35 to 3.61; $P < .37$) (Figure 9).

3.11 | Clinical outcomes

3.11.1 | Mucosal thickness

The gain in mucosal thickness as primary outcome was clearly reported in 9 RCTs,[37,39,40,42,43,44,45,60,61] whereas in one study it was unclear whether mucosal thickness was the primary outcome.[47] The reported gains in mucosal thickness with SCTG ranged from 0.44 to 1.5 mm[37,39,40,43,44,45,47,60,61] while with xenogeneic collagen matrix (XCM) these gains ranged from 0 to 1.25 mm.[37,39,40,42,43,44,45,60,61]

3.11.2 | Keratinized tissue

The gain in keratinized tissue was assessed as primary outcome in six RCTs. The reported gains in keratinized tissue with FGG ranged from 3.73 to 4.47 mm,[46,59,64,65] while with SCTG these gains ranged from 0.8 to 2.33 mm.[38,62] The keratinized tissue gain with XCM ranged from 1.05 to 3.23 mm,[38,46,59,62,64,65] while the lack of grafting led to a gain of 0.16 mm[37].

3.11.3 | Marginal mucosal level

Two studies reported the mid-facial mucosal changes as primary outcome.[48,49] The changes in mid-facial mucosal margin ranged from −0.04 to 0.1 mm when SCTG was applied, while these changes amounted to −0.17 mm when XCM was applied. The lack of grafting led to an apical displacement of the mid-facial mucosal margin that ranged from −0.48 to 0.5 mm.[48,49]

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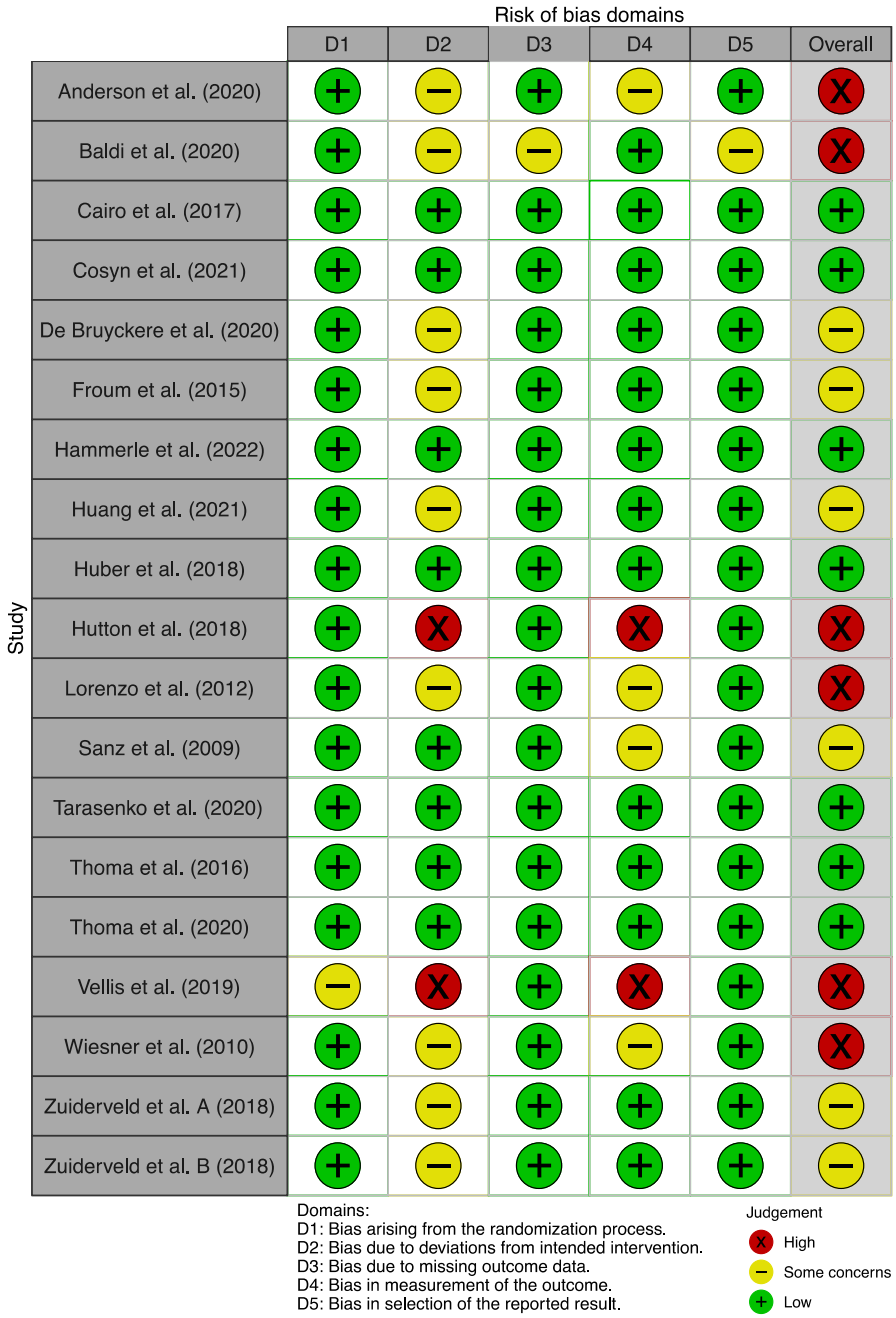

FIGURE 10 Risk of bias assessment for RCTs

3.12 | Risk of bias of included studies

The overall risk of bias of the included studies ranged from low to high. Figure 10 shows the ROB2 risk of bias assessment of the included RCTs with the five key domains. Seven articles showed a low risk of bias, six showed some concerns, and six studies showed a high risk of bias.

4 | DISCUSSION

4.1 | Main findings

The current systematic review with meta-analysis compared PROMs following surgical interventions (gain of mucosal thickness or gain of keratinized tissue) applying autogenous soft tissue grafts and soft tissue substitutes at implant sites. The present study revealed that, compared to autografts, soft tissue substitutes:

(i) Reduce the pain perception
(ii) Decrease the amount of painkillers
(iii) Show similar levels of patient satisfaction and aesthetics
(iv) Shorten the surgery time

Over the past few years, there has been a paradigm shift in implant dentistry, from the assessment of standard clinical parameters toward the inclusion and more frequent reporting of PROMs.[12,19,23,67] The main value of PROMs is that they consider patients' preferences and perceptions, which may allow to determine the patients' own needs and whether the treatment approach addressed these needs. While the soft tissue gain in millimeters is

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critical for the professional's assessment, these values are often not communicated to the patient because they are irrelevant for them.[19,48,68] Furthermore, these values are difficult to understand by the patient and do not pertain to the patient's chief complaint. Therefore, patients tend to focus on the level of pain produced by the surgical procedure, length of the procedure, and certainly the aesthetic results.[19]

Pain is beyond any doubt a key concern, having the potential to inform the consequences of soft tissue management for dental implants.[69] The present meta-analysis revealed significant less pain perception following soft tissue augmentation when soft tissue substitutes were used. This is most likely explained by the lack of a donor site (palate/tuberosity). It is well known that harvesting a soft tissue graft from the palate may lead to excessive bleeding, numbness, and other complications such as tissue necrosis resulting in increased postoperative pain.[70] In this context, the present findings seem to be in line with a recent systematic review focusing on PROMs following soft tissue grafting at implants sites.[30] Although the aforementioned authors were unable to perform a meta-analysis, the included studies showed a consistent trend toward less pain with soft tissue substitutes. It is worth noting that most of the RCTs comparing soft tissue substitutes and autografts did not use PROMs as a primary outcome, thus limiting the power to find significant differences between the two treatment modalities. This limitation was overcome in the present review by being able to conduct a meta-analysis and thus increasing the power to find significant differences. Moreover, these findings are further supported by the reduced consumption of painkillers in those patients who received a soft tissue substitute. It is reasonable to assume that patients requiring an additional surgical site—and facing eventually further complications—will require more pain medication after soft tissue augmentation. Collectively, this indicates that soft tissue substitutes can significantly reduce the pain perception requiring less pain medication after soft tissue augmentation at implant sites. In patients with high levels of anxiety, the use of soft tissue substitute might be considered the therapy of choice.

In general, there is a consensus among clinicians that a prolonged surgery time may cause increased postoperative inflammation and pain.[8,70,71] This is based on the biologic principle that an extended procedure increases the injury of the operation, leading to prolonged vasodilation and resulting in increased release of pro-inflammatory cytokines.[70] The current meta-analysis revealed that the surgery time was significantly reduced when soft tissue substitutes were used. This reduction in surgery time is most likely attributed to the lack of a second surgical site. Nevertheless, it should be noted that any new soft tissue substitute requires a learning curve; in order to obtain a benefit in time, an adequate training with the biomaterial is needed. This was clearly shown by one clinical study, where the surgery time with soft tissue substitutes tended to be longer than that with autogenous grafts.[45] Together, these results indicate that soft tissue substitutes can shorten the surgery time during soft-augmentation procedures.

Satisfaction has become an important parameter when assessing implant related outcomes including soft tissue augmentation. Often patients have little experience and understanding of this type of procedure prior to receiving implants. It is thus crucial to provide the patient with reliable information for the decision-making as the lack of information may lead to unrealistic expectations. The present study revealed similar high-levels of satisfaction between soft tissue substitutes and autografts. Likewise, the pooled analysis showed that the aesthetic perception—rated by the patients—was not influenced by the treatment modality. These findings indicate that high levels of patients' satisfaction and aesthetics can be achieved regardless of treatment modality. It should be noted, however, that previous clinical reports have revealed better aesthetic outcomes—based on dentists' perception—with soft tissue substitutes following soft tissue augmentation. This discrepancy in perception is not unexpected as recent clinical data indicate a lack of correlation between the clinical assessment and patient's perception of the aesthetics.[72] Compared to dentists, patients tend to be less critical regarding the aesthetics, which in this case may account for the lack of differences in the meta-analysis. Clinically, these findings may imply that the decision on the treatment modality for soft tissue augmentation—using either soft tissue substitutes or autogenous grafts—should not be based solely on satisfaction and aesthetics, but also on other PROMs.

Another important aspect of PROMs is that they aim to capture how the treatment affects the patient's quality of life related to oral health.[23,27,28] The meta-analysis revealed no significant differences in quality of life between autogenous soft tissue grafts and graft substitutes; neither in the short (1-4 months) nor in the longer-term (1 year). The lack of differences between both surgical approaches might be related to the high *flooring effect* (eg, score 0) of the instrument (OHIP-14) in these particular procedures. OHIP-14 is a validated and standardized questionnaire,[73] but since many of its questions are not related to the intervention itself, it might not be sensitive enough to distinguish between autogenous and substitutes grafts. In fact, it has been reported that not all dental interventions do correlate with patients' self-reported quality of life.[29] Likewise, a recent consensus report concluded that the type of graft for soft tissue augmentation had an inconsistent influence on patient's perception of quality of life.[7] Moreover, some questions may be unduly influenced by the mood of the patient at the time of assessment.[67,74] Nevertheless, and despite the aforementioned shortcomings, it seems fair to conclude that both procedures are well accepted by the patient.

4.2 | Clinical efficacy relative to PROMs

The present systematic review revealed the clinical efficacy of autogenous soft tissue grafts and soft tissue substitutes for soft tissue augmentation at implant sites. Autogenous soft tissue grafts showed a mean gain of mucosal thickness up to 1.5 mm (range: 0.4-1.5 mm). Soft tissue substitutes showed a slight lower gain, which amounted to 1.25 mm (range: 0-1.25 mm). Concerning keratinized tissue gains,

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these were clearly in favor of FGG showing a mean gain up to 4.4 mm (range; 3.7-4.4 mm), followed by SCTG and soft tissue substitutes which showed similar gains. With SCTG these keratinized tissue gains ranged from 0.8 to 2.33 mm, while with XCM, these ranged from 1.05 to 3.23 mm. These positive outcomes are not surprising and are largely consistent with previous systematic reviews[4,75] showing that soft augmentation procedures at implant sites tend to be more predictable when autogenous soft tissue grafts are used.

What is interesting to note is that this greater predictability and eventually efficacy of autogenous soft tissue grafts implies higher morbidity for the patient. While from a scientific aspect, this millimeter-outcome might be important, this value is likely irrelevant for the patient.[19] Arguably, the best treatment is not necessarily the one that shows the highest efficacy, but the one that suits the patient´s preferences. In this sense, when opting for soft tissue augmentation procedures at implant sites, clinicians often face the dilemma of choosing between autogenous soft tissue grafts (gold standard) with the inherent higher morbidity and soft tissue substitutes, which tend to show statistically lower efficacy. However, a statistically significant difference does not necessarily equate to a clinical important difference.[76,77] Surprisingly, and despite the growing interest in PROMs, the minimal clinical important difference[76,77] in implant-related outcomes has not yet been determined.[19] Therefore, in the meantime, what decision-makers should ask themselves in daily clinical practice is how much are they willing to give up in terms of clinical efficacy relative to autogenous soft (the gold standard) for the morbidity benefits—minimal invasiveness—of soft tissue substitutes.

4.3 | Quality of the evidence and limitations

The overall risk of bias of the included studies ranged from low to high. These observations suggest a plausible bias raising some doubts about the results. Therefore, the information presented here should be interpreted with caution.

5 | CONCLUSION

Soft tissue substitutes, compared to autogenous grafts, significantly improve PROMs following soft tissue augmentation at implant sites. Soft tissue substitutes can reduce pain perception, amounts of painkillers, and surgery time while achieving similar levels of patient´s satisfaction as autogenous grafts without impairing the clinical outcomes. The current evidence indicates that they constitute a valid and reliable alternative to minimize the invasiveness in soft tissue augmentation procedures at implant sites.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ACKNOWLEDGMENT

The authors would like to thank all authors of the included studies for kindly providing the raw data and thereby allowing the performance of the different meta-analyses. Open access funding provided by the University of Zurich.

ORCID

Daniel S. Thoma https://orcid.org/0000-0002-1764-7447
Franz J. Strauss https://orcid.org/0000-0002-5832-7327
Leonardo Mancini https://orcid.org/0000-0002-7030-155X
Thomas J. W. Gasser https://orcid.org/0000-0002-3161-6065
Ronald E. Jung https://orcid.org/0000-0003-2055-1320

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Thoma DS, Strauss FJ, Mancini L, Gasser Thomas JW, Jung RE. Minimal invasiveness in soft tissue augmentation at dental implants: A systematic review and meta-analysis of patient-reported outcome measures. *Periodontol 2000*. 2023;91:182-198. doi: 10.1111/prd.12465

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