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SYSTEMATIC REVIEW

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The influence of thin as compared to thick peri-implant soft tissues on aesthetic outcomes: A systematic review and meta-analysis

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Abstract

Objectives: In systematically healthy patients with an implant-supported fixed restoration (P), what is the influence of thin (E) as compared to thick (C) peri-implant soft tissues on aesthetic outcomes (O)?

Methods: Following an a priori protocol, a literature search of six databases was conducted up to August 2020 to identify prospective/retrospective clinical studies on healthy patients with an implant-supported fixed reconstruction. Measurement of the buccal soft tissue thickness and an aesthetic outcome was a prerequisite, and sites presenting with a buccal soft tissue thickness of <2 mm or shimmering of a periodontal probe were categorized as a thin phenotype. After study selection, data extraction, and risk of bias assessment, random-effects meta-analysis of Mean Differences (MD) or Odds Ratios (OR) with their corresponding 95% Confidence Intervals (CI) were conducted, followed by sensitivity analyses and assessment of the quality of evidence.

Results: Thirty-four unique studies reporting on 1508 patients with 1606 sites were included (9 randomized controlled trials, one controlled trial, 10 prospective cohort studies, 8 cross-sectional studies, and 6 retrospective cohort studies). The mean difference of the pink aesthetic score (PES) after the follow-up was not significantly different between thin (<2.0 mm) or thick soft tissues (≥2.0 mm) or phenotypes (12 studies; MD = 0.15; [95% CI = −0.24, 0.53]; $p = .46$). PES changes during the follow-up, however, were significantly in favour of thick soft tissues (≥2.0 mm) or phenotypes ($p = .05$). An increased mean mucosal thickness was associated with an increased papilla index (5 studies; MD = 0.5; [95% CI = 0.1, 0.3]; $p = .002$) and an increase in papilla presence (5 studies; OR = 1.6; [95% CI = 1.0, 2.3]; $p = .03$). Thin soft tissues were associated with more recession, −0.62 mm (4 studies; [95% CI = −1.06, −0.18]; $p = .006$). Patient-reported outcome measures (patient satisfaction) were in favour of thick soft tissues −2.33 (6 studies; [95% CI = −4.70, 0.04]; $p = .05$). However, the quality of evidence was very low in all instances due to the inclusion of non-randomized studies, high risk of bias and residual confounding.

Conclusion: Within the limitations of the present study (weak study designs and various soft tissue measurements or time-points), it can be concluded that increased soft tissue thickness at implant sites was associated with more favourable aesthetic outcomes.

KEYWORDS
aesthetic outcomes, colour measurement, dental implants, dentistry, meta-analysis, patient-reported outcomes, soft tissue thickness, systematic review

1 | INTRODUCTION

The replacement of missing teeth with implant-supported crowns or fixed dental prostheses is a predictable and well-documented treatment modality in order to restore function and chewing comfort of patients (Adler et al., 2016; Bonde et al., 2013; Cochran et al., 2011). These goals are achieved even in more complex clinical situations, where hard and soft tissue regeneration is necessary prior to or after implant placement (Maiorana et al., 2005; Nevins & Mellonig, 1994; Sanz-Sánchez et al., 2015). Simultaneously with an evolution of surgical techniques and prosthodontic options, the patient's wishes and expectations have evolved concurrently (Testori et al., 2018). This transition towards more efforts in meeting patients' aesthetic expectations, led to an increased reporting of aesthetic outcomes. Moreover, aesthetic assessments became a criterion to rate treatment success (Pjetursson et al., 2014).

Objective factors define the importance of aesthetic outcomes in every case, including the location of the prosthetic replacement as well as the lip line, which defines the exposition of the regenerated area. Additional subjective factors are based on the patient's and the clinician's expectation (Cosyn et al., 2017; Stefanini et al., 2018). A clinically challenging situation is usually based on a combination of these factors. An aesthetic result is therefore not only defined by the shape and colour of the prosthetic reconstruction. The soft tissue architecture, texture and colour can be of paramount importance for treatment success (Thoma et al., 2014).

The reporting of the soft tissue status is diverse in the literature and is currently done through the use of various indices with varying reproducibility and reliability (Tettamanti et al., 2016). Outcomes encompass objective scores such as the pink aesthetic score (Fürhauser et al., 2005), the papilla index (Jemt, 1999), colour measurements (Jung et al., 2008), marginal mucosal level as well as subjective patient-reported outcome measures (Chang et al., 1999). The buccal soft tissue thickness is considered an important factor potentially influencing most aesthetic parameters. In vitro, a tissue thickness of at least 2mm has been demonstrated to diminish discoloration caused by restorative abutment materials (Jung et al., 2007). Moreover, the buccal tissue thickness indicates the phenotype of the patient, thereby serving as a reference for the overall tissue status of the patient. In this context, patients with a thick phenotype were associated with a more favourable papilla fill (Garabetyan et al., 2019).

No attempts have been made so far to summarize variety of the results evaluated in various study designs with the intention to associate soft tissue thickness and/or phenotype with aesthetic outcomes. Therefore, it is the aim of the present systematic review to assess in systemically healthy patients with an implant-supported restoration, what is the influence of thin as compared to thick peri-implant soft tissues (<2.0 mm = thin; ≥2.0 mm = thick; or determined by shimmering of a periodontal probe) on aesthetic outcomes, based on prospective and retrospective clinical study designs.

2 | MATERIAL AND METHODS

2.1 | Protocol and registration

This systematic review was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (Moher et al., 2009). A protocol was developed and registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42020197503) and all post hoc changes were noted (Appendix S1). The review aimed to answer the following focused question: "In systematically healthy patients with an implant-supported fixed restoration (P), what is the influence of thin (E) as compared to thick (C) peri-implant soft tissues on aesthetic outcomes (O)?"

2.2 | Participants-Exposure-Comparison-Outcome-Study design (PECOS)

- *Population:* Systemically healthy patients of any sex, age over 18 years and with presence of at least one dental implant with a fixed reconstruction.
- *Exposure (for the primary analysis)*: sites presenting with a buccal soft tissue thickness of <2 mm or categorized as a thin phenotype (Müller et al., 2000; Olsson & Lindhe, 1991) through transparency of a periodontal probe (De Rouck et al., 2009; Kan et al., 2003).
- *Comparison (for the primary analysis):* Sites presenting with a buccal soft tissue thickness of ≥2 mm or categorized as a thick phenotype (Müller et al., 2000; Olsson & Lindhe, 1991) as no transparency of a periodontal probe (De Rouck, Eghbali, et al., 2009; Kan et al., 2003).
- *Outcomes:* Aesthetic analysis based on the pink aesthetic score (PES) (Fürhauser et al., 2005) was the primary outcome. Any kind of further aesthetic evaluation scores, papilla indices, presence

of papilla, papilla height, colour measurements, marginal mucosal level (MML), patient-reported outcome measures (PROMs) was included.

- *Study design:* Observational as well as experimental clinical studies were eligible, including randomized clinical trials, controlled clinical trials, case-control studies, cross-sectional and prospective cohort studies or case series as well as retrospective case-control studies, cohort studies or case series.

2.3 | Exclusion criteria

This review aimed to investigate an association of soft tissue thickness and aesthetic outcomes. Hence, data of soft tissue thickness or a determination of the phenotype as well as aesthetic outcomes were prerequisites. No restrictions were made in terms of study duration. The following exclusion criteria were set: (a) studies addressing vertical but not horizontal soft tissue dimension; (b) studies with phenotype determination via photographs; (c) case reports or case series (<10 patients); (d) animal studies and non-clinical studies; (e) reports on patients with any systemic disease or syndrome; (f) articles presenting data without standard deviations; (g) articles with <3 patients in group thin or in group thick.

2.4 | Search strategy

The following electronic general, open access, regional and grey literature bibliographic databases were searched up to August 20, 2020 without any limitations for date, language, or type: MEDLINE (searched via PubMed), The Cochrane Central Register of Controlled Trials, Scopus, Web of Science, Virtual Health Library (including BBO), and Embase (Appendix S2). No search filters were applied other than humans, where available. The electronic search was supplemented by a hand search of the reference/citation lists of all eligible full-text articles and related systematic reviews. In addition, all articles having cited the eligible full-text articles were screened.

2.5 | Outcome measures

The pink aesthetic score (PES) (Fürhauser et al., 2005) was the primary outcome of this review. Secondary outcomes included the separate PES components and other aesthetic measures including papilla indices, presence of papilla, papilla height, colour differences (ΔE) evaluated by means of a spectrophotometer, marginal mucosal level (MML), and patient-reported outcome measures (PROMs). The analysis was conducted with the earliest available time-point of soft tissue thickness or phenotype, combined with measurements of the latest possible follow-up for the aesthetic outcome. However, all available time-points after delivery of the prosthetic restoration were included. In case of several reports on the same population, the longest follow-up was included and analysed separately either as post-treatment value and/or treatment-induced changes (according to the availability of studies).

2.6 | Study selection

Two authors (SB and MP) independently screened all titles, while the first 100 titles were discussed for calibration purposes prior to formal selection. Any disagreements between the two reviewers were discussed and settled by involving a third author (DT). The same process was repeated for abstract screening. Full-text screening was performed by one author also giving the reason of exclusion, while a second author independently checked the decision for all papers in a cross-over procedure. The lists of references and citations of all eligible studies and relevant systematic reviews were checked for additional studies.

2.7 | Data extraction

Corresponding authors of articles which measured aesthetic outcomes but did not provide data stratified according to soft tissue thickness/phenotype were contacted by e-mail. They were kindly asked to provide a table with the data stratified according to soft tissue thickness/phenotype or to provide the raw data. A second e-mail was sent after 10 days. Data extraction was conducted using pre-defined data sheets by one author (SB), while a second author (MP) independently checked all extracted data. Again, disagreements were solved by consensus after discussion with including a third author (DT). At this stage, studies with less than 3 patients in group thin or in group thick were excluded.

2.8 | Assessment of internal validity/risk of bias

The risk of bias assessment was performed with a customized 15-item tool which is based on the critical appraisal tools of Joana Briggs Institute for cohort studies, case-control studies, and case series (https://joannabriggs.org/critical-appraisal-tools). The items were customized in order to ideally address the large heterogeneity of study designs and also to take the stratification of the original data into account, now focusing on the comparison of thin and thick soft tissues. Two authors performed independently the assessment (SB and MP) and disagreements were again discussed to reach consensus.

2.9 | Strategy for data synthesis

Any study was included, independently of reporting-completeness. Authors of studies that measured soft tissue thickness and aesthetics but did not associate those two were contacted with a request to provide the raw data. Multiple arms from a trial were pooled to avoid

arm-clustering. Non-parametric summary data was converted into parametric data and in case of missing data, data were calculated or requested from the authors. Clustering of implants within patients was taken into account with robust standard errors during the re-analysis of raw data.

Two analytic strategies were employed. Initially, comparisons were made between the usual categorization of thin (<2.0 mm) versus thick phenotypes (≥2.0 mm) within- and then across-trials with Mean Differences (MDs) for continuous outcomes and Odds Ratios (ORs) for binary outcomes and their corresponding 95% confidence intervals (CIs). The number needed to treat (NNT) was calculated for statistically significant ORs. Additionally, for studies with available raw data of actual soft tissue thickness, generalized linear or logistic regression models against the average soft tissue thickness were run to better describe any existing relationship. Then the coefficients from the regression models were similarly meta-analysed across-trials. A random-effects model was chosen a priori supported by both clinical and statistical reasoning (Papageorgiou, 2014) and using a restricted maximum likelihood estimator (Veroniki et al., 2016), 95% predictions were calculated for meta-analyses of ≥3 studies to incorporate observed heterogeneity and give a range of plausible effects in a future clinical setting.

The extent and impact of between-study heterogeneity were assessed by inspecting the forest plots and by calculating the τ^2 and the I^2 statistics, respectively. Conventional I^2 thresholds were considered as well as localization/direction of studies, further incorporating uncertainty intervals around τ^2/I^2 (Ioannidis et al., 2007).

For meta-analyses with ≥10 studies, hints of reporting biases were investigated with contour-enhanced funnel plots and the Egger test (Egger et al., 1997).

Robustness of the results was checked for meta-analyses with ≥5 studies with sensitivity analyses based on (a) inclusion/exclusion of trials with methodological shortcomings, (b) inclusion/exclusion of studies with inadequate sample size, and (c) inclusion of the most/least precise studies to assess the impact of small-study effects.

All P values were two sided with α set at 5%, except for heterogeneity tests (αlpha of 10%). All analyses were conducted in Stata 14.0 (StataCorp), and the dataset is available through Zenodo (Bienz et al., 2021).

3 | RESULTS

3.1 | Search

The initial search yielded 2,522 publications. Finally, 39 articles reporting on 34 unique patient populations were included, all reporting on at least 3 patients in group thin and in group thick. All details on the search strategy are given in Figure 1. Included studies and the respective characteristics are displayed in Table 1. The list of excluded full-text articles with the reason of exclusion is given in Appendix S3. Out of the included unique studies, nine were randomized controlled trials, one was a controlled clinical trial, 10 were prospective cohort studies, eight were cross-sectional studies, and six were retrospective cohort studies. Overall, 1,508 patients and 1606 sites were analyzed.

3.2 | Description of soft tissue assessment

3.2.1 | Linear soft tissue measurements (mm)

Seventeen unique studies reported on the soft tissue thickness in mm. Nine studies measured the thickness with an endodontic file 1mm below the buccal mucosal margin (Asgeirsson et al., 2019; Benic et al., 2017; Bösch et al., 2018; Büchi et al., 2014; Hosseini et al., 2020; Jung et al., 2008; Sailer et al., 2009; Siqueira et al., 2013; Thoma et al., 2017). Two studies measured with an ultrasound device at 1–2 mm below the buccal mucosal margin (Chang & Wennström, 2013; Chang et al., 1999).

Five studies measured on the cast model, which was used for the production of the final implant crown. Three out of these studies measured the soft tissue thickness at the level of the implant shoulder (Bressan et al., 2011; Ferrari et al., 2017; Kim et al., 2016). One study measured 1mm below (Martínez-Rus et al., 2017) and one study measured 2mm below the buccal mucosal margin (Chu et al., 2018). A further study measured the thickness at 1mm below the buccal margin based on surface scans and a cone beam computed tomography (Sanz-Martín et al., 2019).

These studies were combined for analysis, except for the ones that measured the thickness at the level of the implant shoulder (Bressan et al., 2011; Ferrari et al., 2017; Kim et al., 2016).

3.3 | Categorical soft tissue assessments (phenotype)

Twelve unique studies evaluated the tissue phenotype according to the shimmering of a probe (De Rouck, Eghbali, et al., 2009; Kan et al., 2003). Five studies assessed the phenotype before tooth extraction or during immediate implant placement (IIP). These studies evaluated aesthetic outcomes at a later time-point. Seven studies assessed the phenotype and the aesthetic outcomes at the same time-point (during the follow-up).

Three studies evaluated the tissue phenotype according to the shape of the natural teeth and the keratinized mucosa (Müller et al., 2000; Olsson & Lindhe, 1991). Thereof, two studies evaluated at IIP (Chen et al., 2009; Evans & Chen, 2008), and one study performed the evaluation at crown insertion (Gu et al., 2015).

Finally, two studies did not describe in detail how the phenotype was determined (Hof et al., 2015; Noelken et al., 2014). One study used 3 categories (thin, normal, thick) (Noelken et al., 2014). For the present analysis, only the thin and the thick arm of the study were extracted.

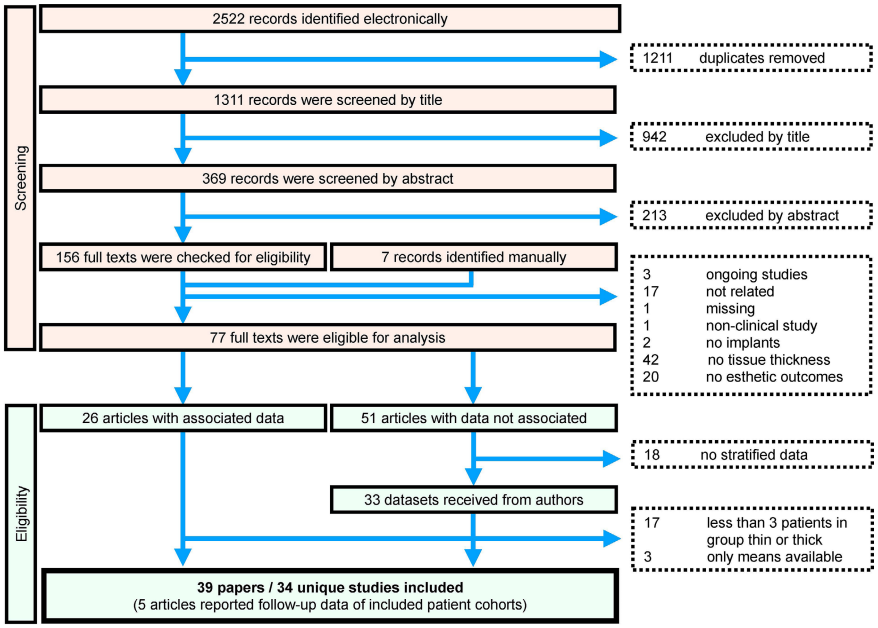

FIGURE 1 Flowchart depicting the search strategy. A list with all excluded full-text articles is given in Table 2. Related systematic reviews that have been screened are listed in Appendix 4

3.4 | Risk of bias assessment

Table 2 displays a summary of the risk of bias assessment. The full risk of bias assessment is available in Appendix S6. In summary, 12/34 (35%) studies were of retrospective nature. A balanced recruitment of patients with thin and thick soft tissues as well as independence of the outcome from inclusion criteria was present in the majority of the studies. Whether or not the distribution of gender, smoking and age were similar in both groups could not be verified in the majority of the studies, because of the data stratification for the present review, which was usually done on the basis of soft tissue thickness and the outcome of interest only. The distribution of the sites according to maxilla/mandible and anterior/posterior was unclear or not applicable for the majority of the studies. Many studies included the aesthetic area for teeth in the location 15–25 only. The reconstruction as a confounding factor remained unclear in 19/34 (56%) studies. The measurements of the soft tissue thickness and of the aesthetic outcomes were described in detail in 30/34 (88%) studies. Only 8/34 studies evaluated the aesthetic outcome blindly, however blinding is here associated with the original purpose of the study. In regards to tissue thickness, assessors could be considered blinded in the majority of the studies. Whether or not the follow-up time was similar for patients with thin and thick soft tissues remained unclear in 12/34 (35%) studies. In 27/34 (79%) studies, the analysis was based on the patient level and thereby ignored issues with within-patient clustering.

3.5 | Outcomes

For all analyses, the statistical unit was the patient and not the site.

3.5.1 | Pink aesthetic score (PES)

Twelve studies reported on the pink aesthetic score or a modified pink aesthetic score (Fürhauser et al., 2005). Eleven studies evaluated the phenotype, one study measured the soft tissue thickness (Sanz-Martín et al., 2019). The follow-up time ranged between 1 and 8.9 years. The mean difference (MD) and 95% confidence intervals (CI) of the score amounted to 0.15 [95% CI: −0.24, 0.53] (I^2: 45%/τ^2: 0.19) and was not statistically significantly different between thin (<2.0 mm) or thick soft tissues (≥2.0 mm) or phenotypes ($p = .46$).

Three studies reported several time-points (Gu et al., 2015; Sanz-Martín et al., 2019; Zhao et al., 2016). The increase of the score over time was marginally statistically significantly greater for patients with a thick phenotype, amounting to 0.72 [95% CI: 0.00, 1.43] (I^2: 15%/τ^2: 0.07) ($p = .05$).

Five studies reported each item of the PES separately (Chen et al., 2009; Cosyn et al., 2012; Cosyn, Eghbali, et al., 2013; Zuiderveld et al., 2018, 2019). The mean differences between patient with a thin versus a thick phenotype amounted to 0.21 [95% CI: −0.02, 0.43] for the mesial papilla, 0.04 [95% CI: −0.17, 0.25] for the distal papilla, 0.08 [95% CI: −0.08, 0.23] for the midfacial mucosa level, 0.04 [95% CI: −0.09, 0.17] for the midfacial contour, −0.13 [95% CI: −0.28, 0.03] for the alveolar process and −0.10 [95% CI: −0.22, 0.03] for the colour and texture, with no statistically significant differences according to phenotype ($p > .05$).

Three studies reported aesthetic outcomes based on a subjective aesthetic score (Evans & Chen, 2008; Hof et al., 2015; Paniz et al., 2014). No statistically significant difference was found between thin/thick phenotypes (MD: 0.11; [95% CI: −0.13, 0.36]; $p = .37$; I^2: 20%/τ^2: 0.01).

3.5.2 | Papilla index

The average papilla index (Jemt, 1999) was reported in 11 studies. Seven studies evaluated the soft tissue thickness (Asgeirsson et al., 2019; Bösch et al., 2018; Büchi et al., 2014; Chang & Wennström, 2013; Chang et al., 1999; Jung et al., 2008; Sailer et al., 2009), while four determined the phenotype (Evans & Chen, 2008; Guarnieri, Savio, et al., 2016; Hof et al., 2015; Nisapakultorn et al., 2010) with follow-up periods ranging between 1 and 7.2 years. The mean difference of the score amounted to −0.19 [95% CI: −0.50, 0.13] (I^2: 83%/τ^2: 0.22) and was not statistically significantly different (p = .25) (Figure 2a).

A second evaluation was performed using average soft tissue thickness as a continuous variable, depicting the improvement of the score per additional mm of soft tissue thickness (Figure 2b). Here, a significant association was found (p = .002), where each additional mm of soft tissue thickness was associated with an increase in score by 0.21 points [95% CI: 0.08, 0.34] (I^2: 0%/τ^2: 0).

3.5.3 | Presence of a papilla

Two studies reported the presence of a papilla at mesial and distal sites (Romeo et al., 2008; Siqueira et al., 2013). In addition, eight studies providing the raw data of the papilla index according to Jemt were added to the analysis. A score 0 or 1 was considered as no papilla, a score 2,3 or 4 was considered as presence of a papilla. Five studies measured soft tissue thickness and 4 studies determined the phenotype, while the mean follow-up time ranged between 6 months and 7.2 years. The analysis using the traditional categorization (Figure 3) for thin/thick phenotype (<2.0 mm/≥2.0 mm, respectively) found no significant difference in papilla presence prevalence (OR = 0.59; 95% CI = 0.27, 1.29; p = .18; I^2 = 46%/τ^2: 0.71). However, investigating a linear relation between the mean soft tissue thickness and the presence of a papilla indicated that each additional mm of soft tissue thickness was associated with higher odds of a papilla being present (OR = 1.55; 95% CI = 1.03, 2.31; p = .03; I^2=1%/τ^2: 0). Assuming a papilla prevalence of 66.7% for soft tissue thickness of 2.0 mm (from available data), this is translated to a number needed to treat of 11, which indicates that every 11th implant placed in a site with an increased soft tissue thickness will have a papilla that would not be present in a site with a reduced thickness.

3.5.4 | Papilla height

Four studies reported on the height of the papilla. Three studies measured soft tissue thickness (Bösch et al., 2018; Chang & Wennström, 2013; Chang et al., 1999) and one determined the phenotype (Kniha et al., 2019). The mean follow-up time ranged between 18 months and 8.9 years. As different reference levels (incisal or MML) were taken from the included studies, the Standardized Mean Difference was chosen post hoc (after changing the sign as necessary) to combine all trials and found no statistically significant difference (SMD: 0.27; [95% CI: −0.10, 0.63]; p = .47; I^2: 0%/τ^2: 0).

3.5.5 | Colour differences

Nine studies reported differences in colour as compared to the neighbouring or contralateral tooth assessed with a spectrophotometer. Eight studies measured the soft tissue thickness (Benic et al., 2017; Büchi et al., 2014; Chu et al., 2018; Hosseini et al., 2020; Jung et al., 2008; Martínez-Rus et al., 2017; Sailer et al., 2009; Thoma et al., 2017) and one determined the phenotype (Paniz et al., 2014). The mean follow-up time ranged between the time-point of the insertion of the fixed dental prosthesis and 5.1 years. No significant difference in ΔE was seen either between thin (<2.0 mm) and thick (≥2.0 mm) soft tissues (MD: 0.66; [95% CI: −0.16, 1.47]; p = .11; I^2: 0%/τ^2: 0) or according to the average soft tissue thickness (MD: 0.21; [95% CI: −0.17, 0.60]; p = .27; I^2: 0%/τ^2: 0).

For the studies measuring the soft tissue thickness at the level of the implant shoulder (Bressan et al., 2011; Ferrari et al., 2017; Kim et al., 2016), similarly no significant difference was observed between thin and thick soft tissues (MD: 0.83; [95% CI: −3.52, 5.18]; p = .71; I^2: 98%/τ^2: 14.31).

3.5.6 | Marginal mucosal level

Four studies reported changes of the marginal mucosal level (MML) over time. Two studies measured soft tissue thickness (Bösch et al., 2018; Sanz-Martín et al., 2019) and the remaining two studies determined the phenotype (Evans & Chen, 2008). The mean follow-up time ranged between 12 months and 8 years. A significantly greater reduction in MML (more recession) was found for thin phenotype patients −0.62 [95% CI: −1.06, −0.18] (I^2: 43%/τ^2: 0.08) (p = .006) compared to thick phenotype patients.

3.5.7 | Patient-reported outcome measures (PROMs)

Patient-reported satisfaction based on data obtained by means of a visual analogue scale (VAS) was reported in six studies. Three out of these studies determined the phenotype at the same visit (Chang & Wennström, 2013; Chang et al., 1999; Cosyn et al., 2012), two studies determined the phenotype at tooth extraction before therapy (Cosyn, Eghbali, et al., 2013; Zuiderveld et al., 2018), and one study measured the soft tissue thickness after crown insertion (Sanz-Martín et al., 2019). The mean follow-up time ranged between 12 months and 8.9 years. The mean difference of the score amounted to −2.33 [95% CI: −4.70, 0.04] (I^2: 0%/τ^2: 0) in favour of thick soft tissues or phenotype (p = .05).

TABLE 1 Study characteristics

	Design			Patients			Implants	
Study	Design	Setting	Country	Patients (M/F)	Age[b]	Smokers	IMPs	Brand
Asgeirsson 2019	PCS	Uni	CH	24 (13/11)	49.1	NR	24	ST
Benic 2017	CSS	Uni	CH	40 (22/18)	36.6;	NR	40	NR
Bösch 2018	RCTpa	Uni	CH	29 (13/16)	43.7	NR	29	ST
Bressan 2011	PCS	Uni	IT	20 (NR)	NR	NR	20	A
Büchi 2014; Eisner 2018; Laass 2019	RCTpa	Uni	CH	20 (13/7); 18 (12/6); 16 (NR)	46 50.3 53	NR NR NR	20 18 16	A A A
Chang 1999	PCS	Pract	SE	20 (13/7)	34 (18–49)	NR	21	NB
Chang 2013; Veltri 2016	CSS	Uni	SE	32 (17/15); 12 (NR)	50 NR	NR NR	32 12	A A
Chen 2009	RCS	Pract	AU	85 (32/53)	43.2	11	85	ST
Chu 2018	RCS	Uni	US	23 (NR)	NR	NR	23	NR
Cosyn 2012	CSS	Uni	BE	44 (19/25)	52	NR	44	NB
Cosyn 2013	RCS	Uni	BE	104 (43/61)	51	18	112	NB
Evans 2008	RCS	Pract	AU	42 (17/25)	47.9	NR	42	ST (25) /3i (17)
Ferrari 2017	RCTpa	Uni	IT	90 (NR)	NR	NR	90	A
Gu 2015	PCS	Uni	CN	40 (22/18)	31.3	NR	40	ST
Guarneri 2016	CSS	NR	IT	39 (21/18)	NR	NR	39	BH
Hof 2015	CSS	Uni	AT	153 (73/80)	37	15	153	NB
Hosseini 2020	CCTpa	Uni	DJ	19 (8/11)	22	NR	33	A
Jung 2008; Fenner 2016	RCTpa	Uni	CH	30 (16/14); 28 (15/13);	61.5 48	NR 6	30 28	ST ST
Kan 2011	PCS	Uni	US	35 (NR)	36.8	NR	35	NB
Kim 2016	CSS	Uni	US	30 (NR)	NR	NR	30	A
Kniha 2019	PCS	Uni	DE	39 (21/18);	45	Non-smokers	40	ST
Martínez-Rus 2017	RCTwp	Uni	ES	20 (9/11)	53.4	NR	20	AV
Nisapakultorn 2010	CSS	Uni	TH	40 (18/22)	45.2	NR	40	A/Fr/NB/ST/Z
Noelken 2014	PCS	Pract	DE	20 (4/16)	47.3	3	37	A
Paniz 2014	CSS	Uni	IT	39 (14/25)	49	NR	39	A
Romeo 2008	PCS	Uni	IT	48 (22/26)	46	NR	48	ST
Sailer 2009; Zembic 2009	RCTpa	Uni	CH	22 (8/14); 18 (8/10)	41.3 NR	NR NR	40 28	NB NB
Sanz-Martín 2019	PCS	Uni	ES	12 (3/9)	53	3	12	NB
Siqueira 2013	RCS	Uni	BR	18 (10/8)	19–72;	NR	18	NR
Thoma 2017	RCTwp	Uni	CH	24(NR); NR; NR	NR	NR	24	ST

Treatment details	FU	Measurement level	Thickness measure	Outcome[c]
Use of non-original titanium bases	12 m	PAT	In mm with endofile (after FDPi)	JEMT (12 m)
Peri-implant soft tissue colour	61 m	PAT	In mm with endofile (61 m)	ΔE (61 m)
Customized zirconia or titanium AB	18 m	PAT	In mm with endofile (after FDPi)	JEMT, ΔE, PH, MML (18 m)
Gold, titanium and zirconia AB (same crown)	0 m	PAT	In mm on the model (at IS)	ΔE (FDPi)
Zirconia versus pink veneered AB	60 m	PAT	In mm with endofile (after FDPi)	ΔE, JEMT (60 m)
Tissue dimensions compared to teeth	38 m	IMP	USD in mm (38 m)	PH, JEMT, PROMS (38 m)
Tissue dimensions around implants	106 m	PAT	USD in mm (90 m)	PH, JEMT (90 m) PES (FDPi and 106 m)
IIP aesthetic results	18.8 m	PAT	Müller (at IIP)	PES (at 18.8 m)
Soft tissue colour changes	>5 m	PAT	In mm on the model, at 2 mm below margin	ΔE (>5 m)
Early versus conventional IP	30 m	PAT	DeRouck (30 m)	PES (30 m)
Four IP modalities	12 m	IMP	DeRouck (at IP)	PES, PROMS (12 m)
IIP aesthetic results	18.9 m	PAT	Müller (at IIP)	MML, JEMT, SES (18.9 m)
Influence of AB colour	0 m	PAT	In mm with calliper (at IS)	ΔE
Single implant aesthetics	24 m	PAT	Müller (at FDPi)	PES (FDPi, 12 m, 24 m)
Factors influencing soft tissue changes	>60 m	PAT	DeRouck (at >60 m)	JEMT (at >60 m)
Timing of IP on aesthetic outcomes	54 m	PAT	Visual inspection thin or thick (54 m)	PES, JEMT (54 m)
Tissue changes following CTG	60 m	IMP	In mm with endofile (after FDPi)	ΔE (FDPi, 12 m, 36 m, 60 m)
Ceramic versus titanium AB	86 m	PAT	In mm with endofile (at FDPi)	ΔE (1–2wk) JEMT; VAS (86 m)
IIP and tissue stability	48 m	PAT	DeRouck at tooth extraction	PH, MML (pre-extraction, 12 m, 48 m)
Soft tissue colour with different AB	NR	PAT	In mm on the model at IS (same time as ΔE)	ΔE (same time as thickness)
Papilla-crown height dimensions	36 m	IMP	DeRouck (after FDPi)	PH (at 3 m, 12 m, 36 m)
AB material, tissue thickness, optical outcomes	0 m	PAT	In mm on the model (final impression at 1 mm below the mucosal margin)	ΔE (at FDPi)
Soft tissue levels around implants	>6 m	PAT	DeRouck (at FU)	JEMT (FU)
Soft tissue aesthetics following immediate loading	24 m	IMP	Thin/medium/thick Only thin and thick arm included	PES (2y)
Subjective and objective soft tissue colour	>6 m	PAT	DeRouck (at FU)	ΔE and subjective score (at >6 m)
Interproximal tissue dimensions with single implants	12 m	PAT	DeRouck (Pre-extraction)	Presence of papilla (at 12 m)
Customized zirconia and titanium AB	36 m	IMP	In mm with endofile (12 m)	ΔE (12 m) JEMT (36 m)
Soft tissue augmentation with substitute	12 m	PAT	In mm at 1 mm (diff STL/DICOM, after FDPi)	MML, PES; PROMS (0,6,12 m)
Influence of bone dimensions on inter-implant papilla dimensions	6–60 m	PAT	In mm with endofile (at FU)	Presence of papilla, black space height (at FU)
Fluorescent versus conventional zirconia AB	0 m	PAT	In mm with endofile (after FDPi)	ΔE (after FDPi)

(Continues)

TABLE 1 (Continued)

	Design			Patients			Implants	
Study	Design	Setting	Country	Patients (M/F)	Age[b]	Smokers	IMPs	Brand
Zhao 2016	RCS	Uni	CN	45 (25/20)	38.6	NR	45	ST
Zuiderveld 2018a	RCTpa	Uni	NL	60 (25/35)	41.9	Non-smokers	60	NB
Zuiderveld 2018b	RCTpa	Uni	NL	60 (28/32)	46.7	Non-smokers	60	NB
Zuiderveld 2019	PCS	Uni	NL	40 (11/29)	38.55	Non-smokers	40	NB

Abbreviations: ΔE, difference in colour assessed with spectrophotometer; 3i, 3i implant system; A, Astra Tech implant system; AB, abutment; AV, Avinent implant system; BH, BioHorizons implant system; CCTpa, Controlled clinical trial(parallel design); CSS, cross-sectional study; CTG, connective tissue graft; DeRouck, biotype according to De Rouck 2009 or Kan 2003, shimmering of a probe (De Rouck, Eghbali, et al., 2009); DICOM, cone beam computed tomography file; FDPi, fixed dental prosthesis insertion; Fr, Friadent implant system; FU, follow-up after crown insertion; IIP, immediate implant placement; IMP, implant; IP, implant placement; IS, implant shoulder; JEMT, papilla index according to Jemt; m, month; Müller, biotype classification according to Müller (Müller et al., 2000); NB, Nobel Biocare or Branemark implant system; NR, not reported PAT, patient; PCS, prospective case series/prospective cohort study; PES, pink aesthetic score (Fürhauser et al., 2005); PH, papilla height; Pract, private practice/clinic; PROMs, patient-reported outcome measures, RCTpa, randomized clinical trial (parallel design); RCS, retrospective cohort study; RCTwp, randomized clinical trial (within-person design); ST, Straumann implant system; STL, standard tesselation language file (surface scan); Uni, university clinic; USD, ultrasound device; wk, week; y, year; Z, Zimmer dental implant system.

[a]Countries given with their alpha-2 codes.

[b]Age is given as mean (one value) or range (in parenthesis).

[c]Only outcomes relevant to aesthetics.

3.6 | Additional analyses

As considerable discrepancies were seen between meta-analyses using the thin/thick mucosa categorization (with a traditional 2.0 mm cut-off) and meta-analyses of linear effects using individual patient data (Table 3), post hoc exploratory analyses from studies providing individual participant data were performed to investigate the influence on papilla presence of different cut-off values: 1.5, 2.0, 2.5, 3.0, and 3.5 mm (Appendix S7). A cut-off of 3.0 mm was found to be more appropriate for this particular outcome as compared to a 2.0 mm cut-off, since then all studies shifted to the right side of the forest plot (i.e. indicated that papillae were more often present with thick sites). This was retained for the cut-off of 3.5 mm.

Several subgroup and meta-regression analyses were performed to investigate the effect of several methodological characteristics on the meta-analyses' results (sensitivity analyses; Appendix S8). This indicated possible differences between prospective and retrospective studies (for the meta-analysis of PES component for mesial papilla) and between blinded and non-blinded studies (for the meta-analysis of PES component for root/contour/texture). Stratified analyses (Appendix S9) for solely prospective studies indicated that sites with thin soft tissues were associated with greater PES scores for the mesial papilla than sites with thick soft tissues (MD = 0.41; [95% CI = 0.08, 0.74]; $p = .02$). This comparison was not statistically significant ($p = .07$) in the original analysis. In the stratified analysis including blinded studies only, the results remained statistically non-significant ($p < .05$).

Hints of reporting bias (including the possibility of publication bias) could be assessed only for 3 meta-analyses that included at least 10 studies (Appendix S10), but found no evidence of bias (Egger test $p > .05$). Assessment of the quality of evidence using the GRADE framework indicated in all instances very low quality due to the inclusion of non-randomized studies, increased risk of bias due to methodological limitations, and the risk of residual confounding that could not be completely ruled out.

4 | DISCUSSION

The present systematic review revealed (a) overall more favourable aesthetic outcomes for thick soft tissues or thick phenotypes (b) no differences in terms of the PES (c) a higher increase of the PES over time for thick soft tissues (c) more favourable papilla scores per additional mm in soft tissue thickness (d) a higher chance for the presence of a papilla for thick phenotypes or thick soft tissues (e) less recession over time and a higher patient satisfaction scores for thick soft tissues or thick phenotypes.

The pink aesthetic score was not significantly different comparing sites with thin and thick soft tissues. Six studies reported each single item, and the comparisons of single items revealed only minor, clinically negligible differences, except for the mesial papilla. The difference in terms of the mesial papilla (which was significant in the analysis with prospective studies only) remains difficult to put into context, as the distal papilla did not show any difference. Whether or not there is truly no difference or whether or not a difference

Treatment details	FU	Measurement level	Thickness measure	Outcome[c]
Aesthetic outcomes of non-augmented sites	74 m	PAT	Müller (at FU)	PES (after FDPi, at 6–10 m, at 5–8 years)
IP in preserved sockets, additional CTG, XCM or no graft at IP	12 m	PAT	DeRouck (Pre-extraction)	PES (12 m)
IIP with or without CTG	12 m	PAT	DeRouck (Pre-extraction)	PES, PROMS (12 m)
IP in preserved versus. Non-preserved extraction sockets	12 m	PAT	DeRouck (after FDPi)	PES (12 m)

could not be detected remains speculation. Important to notice is that except for one study (Sanz-Martín et al., 2019), all other included studies determined the phenotype. Overall, it appears that phenotype determination was a weaker predictor than the soft tissue thickness measurements in mm. Even though there is no direct comparison between the two methods in a single study, the majority of the data revealing differences was based on measurements in mm. Furthermore, various time-points were used for phenotype determination, from pre-extraction to follow-up visits, which is surely a confounding factor.

The higher increase of the score for thick soft tissues was mainly supported by two studies (Gu et al., 2015; Zhao et al., 2016). Both investigations reported an overall increase of the score during the first year. This is in line with other studies reporting an improvement during the first year following crown insertion (Groenendijk et al., 2020; Raes et al., 2011).

The papilla index was associated with the buccal soft tissue thickness, based on the linear regression model. From a clinical point of view, an increase of the score by 0.21 per additional mm in soft tissue thickness is difficult to interpret and might not be of a high clinical relevance. However, the association of the buccal thickness with the proximal area was further supported by the number needed to treat to obtain the presence of a papilla. An additional mm in soft tissue thickness will lead to the presence of a papilla in every 11th papilla.

Recession or the change in marginal mucosal levels was significantly greater in patients with thin soft tissues. This finding is not a novelty and was reported earlier around teeth and around implants (Kim et al., 2020; Mailoa et al., 2018). Several studies already applied this finding as an inclusion/exclusion criterion, often excluding thin phenotypes in case of immediate implant placement (Cosyn et al., 2013; De Rouck, et al., 2009; Guarnieri et al., 2016). The number of studies included in the present analysis appears rather low. Several studies were excluded because they provided data for thick phenotypes only. In addition, the broad search for various aesthetic outcomes might not have ideally addressed this particular outcome during the selection process.

Surprisingly, there was no difference in terms of colour differences. Several preclinical and clinical studies reported thick soft tissues to mask the shimmering of restorative materials (van Brakel et al., 2011; Jung et al., ,,,2007, 2008). A soft tissue thickness of 2mm was defined as a cut-off value in order to cover the colour of any restorative material. The present meta-analysis was based on a relatively homogenous material, using similar time-points and measurement techniques for the tissue thickness, and using similar methodology for the colour assessment with a neighbouring or contralateral tooth as a reference. It can only be speculated that the considerable number of ceramic abutments is a reason for non-increased differences in case of thin soft tissues (Pitta et al., 2020). However, the analysis based on a linear regression model did not reveal differences either.

Patient-reported outcome measures resulted in significantly higher patient satisfaction in case of thick soft tissues, based on six evaluated studies. This aspect underlines the importance of the soft tissue conditions around the implant. Even though these patients reported on the overall treatment outcome, the soft tissue status seems to be a substantial part of their judgement.

There was a tendency that the actual measurements in mm were associated with the aesthetic outcome and the phenotype determinations were not. This needs to be interpreted with caution, as the

TABLE 2 Risk of bias summary for the included studies

Question	Yes	No	Unclear	Not applicable
Was the study prospective?	24 (67%)	12 (33%)	0 (0%)	0 (0%)
Were patients with thin/thick soft tissue recruited at the same place/time?	25 (69%)	0 (0%)	11 (31%)	0 (0%)
Had the inclusion criteria for patient selection nothing to do with the outcome of interest (aesthetics)?	33 (92%)	0 (0%)	3 (8%)	0 (0%)
Were patients with thin/thick soft tissue similar in age?	8 (22%)	0 (0%)	28 (78%)	0 (0%)
Was the distribution of gender similar for patients with thin/thick soft tissue?	4 (11%)	3 (8%)	29 (81%)	0 (0%)
Was the distribution of smokers similar for patients with thin/thick soft tissue?		0 (0%)	33 (92%)	3 (8%)
Was the distribution of maxillary and mandibular sites similar for patients with thin/thick soft tissue?	2 (6%)	4 (11%)	6 (17%)	24 (67%)
Was the distribution of anterior and posterior sites similar for patients with thin/thick soft tissue?	2 (6%)	1 (3%)	5 (14%)	28 (78%)
Was the confounding factor of reconstruction similar between patients with thin/thick soft tissue (or controlled for)?	16 (44%)	0 (0%)	20 (56%)	0 (0%)
Was soft tissue thickness measured in a valid and reliable way?	31 (86%)	0 (0%)	5 (14%)	0 (0%)
Were the outcomes (aesthetics) measured in a valid and reliable way?	36 (100%)	0 (0%)	0 (0%)	0 (0%)
Were the outcomes (aesthetics) measured blindly?	8 (22%)	2 (6%)	26 (72%)	0 (0%)
Was the follow-up time sufficient for outcomes to occur (1 yr following crown insertion)?	27 (75%)	8 (22%)	1 (3%)	0 (0%)
Was the follow-up time similar for patients with thin/thick soft tissue?	19 (53%)	0 (0%)	16 (44%)	1 (3%)
Was clustering of implants within patients absent (or appropriately analysed)?	30 (83%)	0 (0%)	6 (17%)	0 (0%)

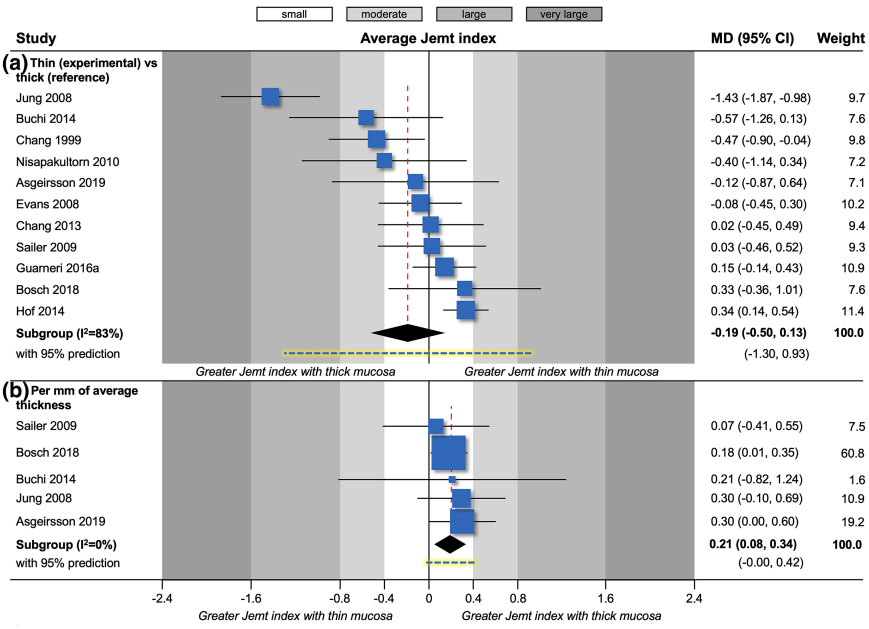

FIGURE 2 Forest plot illustrating the results of the papilla index. CI, confidence interval; MD, mean difference

present review did not directly compare the two types of soft tissue assessment. The linear regression analyses rendered the most distinct answers, revealing improvements of the aesthetic outcome with an increasing soft tissue thickness. The buccal soft tissue thickness is obviously a continuous biological variable and might have been addressed in a more appropriate way as compared to the attempts with a categorization. Therefore, it is also recommended for future studies to apply a measurement of the thickness rather than a phenotype determination.

The present review included 34 unique studies and was designed to be rather inclusive, as it was expected that the reporting in the field of aesthetic outcomes is substantially diverse. The review encompasses several study designs. Vice versa, the main limitation is the heterogeneity of the included material. This is represented with eight different aesthetic outcomes on the one hand. On the other hand, various definitions were used to determine the phenotype and different methodologies were applied to measure the soft tissue thickness, at different heights. Moreover,

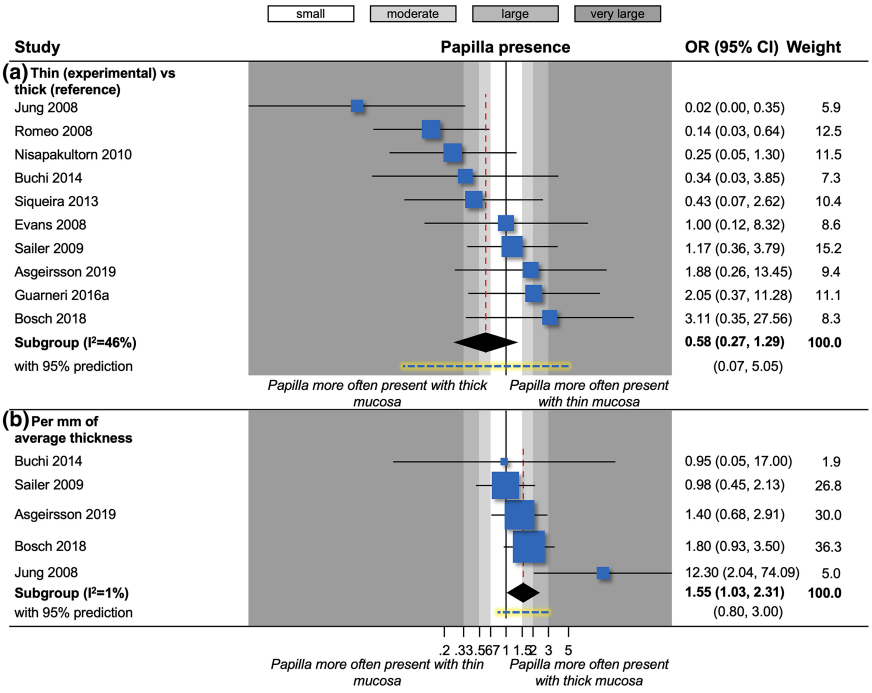

FIGURE 3 Forest plot illustrating the results for the presence of a papilla. CI, confidence interval; OR, Odds ratio

the time-points of the assessment varied as well. It has to be considered that the present review did condense the data of different time-points and different evaluation methods for the buccal soft tissue thickness.

A positive feature in that respect was that the research groups mainly repeated their type of soft tissue assessment and aesthetic evaluation. Fortunately, studies which have determined the phenotype according to De Rouck reported the PES mainly. Studies that measured the soft tissue thickness with an endodontic file mainly reported the papilla index and colour differences (ΔE).

Another relevant limitation is the interrelationship of horizontal and vertical soft tissue dimensions. The current review focused on horizontal measurements. However, the height of the horizontal measurement is directly dependent on the vertical aspect. As the marginal mucosal levels are less stable in case of thin soft tissues (Kim et al., 2020; Mailoa et al., 2018), the vertical reference undergoes higher changes over time. The time-point of the evaluation is therefore crucial as well, i.e. whether vertical changes are happening before or after the measurement or not at all.

5 | CONCLUSIONS

Within the limitations of the present study (various study designs with decreased internal validity, various soft tissue measurements and time-points), it can be concluded that increased soft tissue thickness at implant sites was associated with:

- A significantly greater increase of the PES score following treatment in the presence of thick soft tissues
- An increasing papilla score with increased soft tissue thickness per additional mm
- A higher chance for the presence of a papilla for thick soft tissues
- Less recession over time for thick soft tissues
- Higher patient satisfaction scores in the presence of thick soft tissues

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CONFLICT OF INTEREST

This systematic review was conducted on behalf of a consensus workshop organized by the Osteology Foundation, the Spanish Society of Periodontology and the German Society of Implantology. The project was self-funded by the Clinic of Reconstructive Dentistry and the Clinic of Orthodontics and Pediatric Dentistry from the University of Zurich. The authors declare no conflicts of interest related to the study. Some individual patient datasets included in this study belonged to publications co-authored by some of the review's authors but were re-analysed by a third person not involved in the original studies.

AUTHOR CONTRIBUTION

Stefan Bienz: Conceptualization (equal); Data curation (equal); Investigation (equal); Project administration (equal); Supervision

TABLE 3 Performed meta-analyses for all outcomes

Outcome	Comparison	*N*	Effect (95% CI)	*p* value	I^2 (95% CI)	τ^2 (95% CI)	95% prediction
Jemt index	Average thickness (per mm)	5	MD = 0.21 (0.08, 0.34)	.002	0% (0%, 73%)	0 (0, 0.09)	0, 0.42
Jemt index	Thin versus thick (reference)	11	MD = −0.19 (−0.50, 0.13)	.25	83% (62%, 94%)	0.22 (0.07, 0.70)	−1.30, 0.93
Papilla presence[a]	Average thickness (per mm)	5	OR = 1.55 (1.03, 2.31)	.03	1% (0%, 94%)	0 (0, 3.68)	0.80, 3.00
Papilla presence[a]	Thin versus thick (reference)	10	OR = 0.59 (0.27, 1.29)	.18	46% (0%, 84%)	0.71 (0, 4.36)	0.07, 5.05
PES (post)	Thin versus thick (reference)	12	MD = 0.15 (−0.24, 0.53)	.46	45% (0%, 80%)	0.19 (0, 0.94)	−0.93, 1.22
PES (post)	Average thickness (per mm)	2	MD = 0.09 (−1.52, 1.70)	.91	0% (0%, 98%)	0 (0, 68.39)	–
PES (delta)	Thin versus thick (reference)	3	MD = −0.72 (−1.43, 0)	.05	15% (0%, 96%)	0.07 (0, 9.34)	−6.43, 5.00
Papilla height (post)	Thin versus thick (reference)	4	SMD[b] = 0.27 (−0.10, 0.63)	.15	0% (0%, 80%)	0 (0, 0.56)	−0.54, 1.07
Papilla height (delta)	Thin versus thick (reference)	2	SMD[b] = −0.21 (−0.78, 0.36)	.47	0% (0%, 98%)	0 (0, 9.82)	–
SES	Thin versus thick (reference)	3	MD = 0.11 (−0.13, 0.36)	.37	20% (0%, 95%)	0.01 (0, 0.73)	−1.94, 2.16
VAS (post)	Thin versus thick (reference)	6	MD = −2.33 (−4.70, 0.04)	.05	0% (0%, 63%)	0 (0, 16.46)	−5.68, 1.03
PES: mesial papilla	Thin versus thick (reference)	5	MD = 0.21 (−0.02, 0.43)	.07	73% (26%, 95%)	0.05 (0.01, 0.35)	−0.56, 0.97
PES: distal papilla	Thin versus thick (reference)	5	MD = 0.04 (−0.17, 0.25)	.70	59% (0%, 94%)	0.03 (0, 0.33)	−0.62, 0.70
PES: midfacial level	Thin versus thick (reference)	5	MD = 0.08 (−0.08, 0.23)	.33	0% (0%, 66%)	0 (0, 0.07)	−0.17, 0.33
PES: midfacial contour	Thin versus thick (reference)	5	MD = 0.04 (−0.09, 0.17)	.58	0% (0%, 88%)	0 (0, 0.17)	−0.18, 0.25
PES: root/colour/texture	Thin versus thick (reference)	5	MD = −0.10 (−0.22, 0.03)	.14	0% (0%, 65%)	0 (0, 0.04)	−0.30, 0.11
PES: alveolar process	Thin versus thick (reference)	3	MD = −0.13 (−0.28, 0.03)	.12	0% (0%, 92%)	0 (0, 0.58)	−1.15, 0.90
DE	Thin versus thick (reference)	9	MD = 0.66 (−0.16, 1.47)	.11	0% (0%, 64%)	0 (0, 3.04)	−0.32, 1.64
DE	Average thickness (per mm)	7	MD = 0.21 (−0.17, 0.60)	.27	0% (0%, 66%)	0 (0, 0.82)	−0.29, 0.72
DE (2nd)	Thin versus thick (reference)	3	MD = 0.83 (−3.52, 5.18)	.71	98% (91%, 100%)	14.31 (3.05, 255.03)	−54.87, 56.53
Recession	Thin versus thick (reference)	4	MD = −0.62 (−1.06, −0.18)	.006	43% (0%, 94%)	0.08 (0, 1.81)	−2.18, 0.94
Recession	Average thickness (per mm)	2	MD = 0.34 (−0.18, 0.86)	.21	24% (0%, 99%)	0.06 (0, 30.51)	–

Abbreviations: CI, confidence interval; MD, mean difference; OR, odds ratio; PES, pink aesthetic score; SES, subjective aesthetic score; SMD, standardized mean difference; VAS, visual analogue scale.

[a]Including re-formed categories of the Jemt index.

[b]Using SMD instead of MD and appropriate sign reversal, due to different papilla height reference lines

(equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Miha Pirc:** Data curation (equal); Investigation (equal); Methodology (equal); Project administration (equal); Validation (equal); Writing-review & editing (equal). **Spyridon N. Papageorgiou:** Conceptualization; Data curation; Formal analysis (equal); Methodology (equal); Software (equal);

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