

The Effect of Keratinized Mucosa on Peri-Implant Health and Patient-Reported Outcome Measures: A Systematic Review and Meta-Analysis [†]

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Abstract: Objectives: The aim of this systematic review was to analyze the effect of keratinized mucosa (KM) on different peri-implant health-related parameters and on patient-reported outcome measures (PROMs). Material and methods: Randomized controlled trials, cohort, cross-sectional and case-control human studies with a follow-up period of at least 6 months comparing two groups of patients with presence or absence of KM, or with KM < 2 mm or ≥2 mm were included. Primary outcomes were implant failures, PROMs and BoP (BoP/mBI). Additional outcomes were PPD, plaque accumulation (mPI/PI), gingival inflammation (GI/mGI), marginal bone loss (MBL), soft tissue recession (REC) and biological complications. Results: Fifteen studies were included (one RCT, two cohort prospective and twelve cross-sectional). Meta-analysis was performed for cross-sectional studies. Implant failure and complications were not presented as outcome measures, and five studies analyzed PROMs. Results from the meta-analysis reported no evidence of any statistical significant difference between groups in PPD, BoP and MBL, while a statistical significant difference in GI/BI, PI and REC was present in favor of the group with KW ≥ 2 mm. More biological complications were present in the group with no KM/KM < 2 mm but few cases were present to draw any conclusions. Although a meta-analysis could not be performed, a consistent trend toward the worst pain/discomfort in KM < 2 mm was observed. Conclusions: No clear evidence was found supporting the role of KM in peri-implant health and PROMs, even if more plaque and marginal inflammation were present in the KM < 2 mm group. Clinical relevance: KM could have a role in patients with erratic maintenance and patient comfort.

Keywords: keratinized mucosa; PROMs; peri-implant health; implant failure; systematic review; meta-analysis



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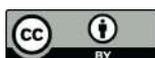
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1. Introduction

The use of dental implants to replace missing teeth has become an increasingly common and predictable clinical practice [1–3]. Nowadays, the long-term maintenance of healthy peri-implant tissues and of the esthetic of implant rehabilitation is considered of primary importance [4,5]. Additionally, patient satisfaction and patient ease in maintaining

good oral hygiene are key factors for the success of the treatment. In this respect, the role of keratinized mucosa (KM) around implants is still controversial [6–8].

The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions stated that a lack of KM is among the principal factors associated with the recession of peri-implant mucosa [9]. Furthermore, it affirmed that the evidence is equivocal regarding the effect of KM on the long-term wellbeing of the peri-implant tissues. The results of the studies on this topic are divergent and without consensus [10–17]. It seems, however, that KM may have advantages regarding patient comfort and the ease of plaque removal [9]. This is in line with the review paper of Wennström & Derks [6] suggesting that although the lack of an “adequate” width of KM per se is not harmful to peri-implant health, it may hamper the performance of proper oral hygiene.

Other systematic reviews have tried to clarify the importance of KM, addressing its ideal width in relation to health and esthetics with controversial results [6–8,18].

The aim of this systematic review was to update the knowledge about the influence of KM on peri-implant health and esthetics, also addressing patient-related variables that were never considered in previous reviews.

2. Material and Methods

2.1. Protocol Registration and Reporting Format

This review was written following the PRISMA Statement for reporting Systematic Reviews and Meta-Analyses [19] and following the Cochrane Collaboration guidelines [20]. The protocol was registered in the PROSPERO database, hosted by the National Institute for Health Research, University of York, Center for Reviews and Dissemination (CRD 42021231674).

2.2. Focused Question

The PICOT format [21] was followed in structuring the research questions.

The focused question was

“In patients having at least one implant-supported restoration under functional loading for at least 6 months does the presence of keratinized mucosa influence soft tissue health, bone levels, esthetics and patient-related variables around implants against the null hypothesis of no influence?”

2.3. Inclusion Criteria

- Randomized controlled trials, cohort, cross-sectional and case–control human studies;
- Studies comparing two groups of patients with a presence or absence of KM, or with $KM < 2\text{ mm}$ or $\geq 2\text{ mm}$;
- At least 6 months of follow-up;
- Reports of correlation with at least one of the outcome measures considered.

2.4. Reasons for Article Exclusion Included

- (i) Retrospective cohort and cross-sectional studies;
- (ii) No full text availability;
- (iii) Inability to use the KM data or analysis provided.

2.5. Primary Outcome Measures

- Implant failures, defined as the removal of a previously osseointegrated implant due to biological or prosthetic complications;
- Patient-related outcomes: pain, patient satisfaction regarding esthetics, and quality of life;
- Bleeding on probing (BoP or mBI), recorded as bleeding at the bottom of the implant sulcus/pocket with the help of a periodontal probe.
- Biological complications: peri-implantitis, and mucositis.

2.6. Secondary Outcome Measures

- Probing pocket depth (PPD) measured with a periodontal probe, as the distance from the gingival margin to the bottom of the pocket;
- Gingival index (GI), modified gingival index (mGI), bleeding index (BI) or modified sulcular bleeding index (msBI), recorded as marginal bleeding on buccal and lingual/palatal surfaces of the study implants with the help of a periodontal probe;
- Plaque index (PI) or modified plaque index (mPI), recorded as the presence of plaque on buccal and lingual/palatal surfaces of the study implants with the help of a periodontal probe;
- Marginal bone loss (MBL) assessed on periapical radiographs;
- Soft tissue recession (REC) measured clinically with a probe or on hard plaster models with a digital caliper or a probe;

2.7. Search Strategy and Study Selection

A systematic literature search was conducted through the following electronic databases: The Cochrane Central Register of Controlled Trials, EMBASE, and the National Library of Medicine via Pubmed. The search technique was initially created with a list of headings for medical issues and free text terms for the MEDLINE database, and then properly modified for other databases. No limitations were placed on the publishing date, the journal, or the language. A bibliographic database was downloaded with the search results to make it easier to remove duplicates and check cross-references. Appendix A contains information on the search method and how the databases' search key phrases were created. In May 2021, the final electronic search was carried out.

2.8. Selection of Studies

The titles and abstracts (if available) of the items found through the search were double-checked and independently reviewed by two examiners (L.G., and P.G.). The examiners were specifically trained and calibrated with the first 10 consecutive publications. The entire text of all studies that might have met the eligibility requirements or for which the title and abstract did not provide enough information to make a judgment call were then collected. The next screening process included any article that at least one reviewer thought might be relevant. The full-text publication was then independently and twice reviewed by the same review examiners. Any discrepancy in the studies' eligibility was settled either through open discussion between the two reviewers until a consensus was established or via arbitration by a third party (M.G.G.). The reasons for the exclusion of any article that did not adhere to the eligibility requirements were highlighted. Any disagreements regarding the studies' inclusion were settled in the same way as described above.

2.9. Data Extraction and Management

Using a data extraction sheet created especially for this review, two examiners (M.S., and A.P.) independently retrieved all pertinent information from the included publications. The data extraction form including a quality assessment and risk of bias assessment were piloted for 5 papers and modified as required. Calibration of the examiners was conducted on the same papers. Disagreements between the reviewers were always settled via a consensus and open debate. If a dispute persisted, a neutral third party (M.G.G.) resolved it.

2.10. Quality Assessment, Risk of Bias and Data Analysis

Risk of bias for the included studies was evaluated independently by two authors (M.S., and A.P.). The appropriate Joanna Briggs Appraisal Checklist was used for cross-sectional and cohort prospective studies [22]. Possible disagreements were discussed between the same authors. The third author (M.G.G.) was consulted if no agreement was reached. The risk of bias of the study was judged as follows:

- High risk if at least two domains were considered at high risk (no);

- Moderate risk if one domain was considered at high risk or if two or more domains were considered unclear;
- Low risk if no domains were considered at high risk (yes).

For RCTs, it was performed in accordance with the method suggested by the Cochrane collaboration group [20].

2.11. Strategy for Data Synthesis

The analysis was performed by comparing data according to the cutoff used to define the adequate width of keratinized mucosa (KM) (≥ 2 mm of KM is currently the cut-off value most frequently adopted in the literature). Studies providing data on the presence or absence of KM were analyzed separately for each outcome. If the results were not significantly different from those of studies using 2 mm as a cut-off, all studies were aggregated. Data on GI, mGI/BI, msBI and mPI/PI were aggregated and to be able to compare them the data were normalized.

The following confounding factors were considered: smoking habits, history or the actual presence of periodontal disease, the type of implant surface (rough or machined), the type of implant-supported reconstruction, implant position and the maintenance protocol (Table description).

Whenever possible, the patient was used as the statistical analysis unit, unless all of the comparative studies reported their findings using implants as the statistical analysis unit. Each outcome variable underwent meta-analysis, and the I^2 statistic was used to evaluate heterogeneity. To summarize the data for the continuous primary outcomes, weighted mean difference (WMD) or standardized mean difference (MD) with 95% confidence intervals (CI) were chosen. If no substantial heterogeneity was found ($i^2 = 60\%$; $p > 0.05$), mean differences for continuous data were integrated using fixed-effects models; otherwise ($i^2 > 60\%$; $p < 0.05$), a random-effect model was used. The analysis was undertaken using Review Manager software (RevMan 5.4, Version 5.4.1 Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020).

2.12. Sensitivity Analysis

In order to investigate if study quality was a factor affecting the results, two sensitivity analyses were performed, one excluding the studies that were judged at high risk of bias and one including only low-risk-of-bias studies. Moreover, a sensitivity analysis was performed excluding a study [23] presenting data of patients with erratic maintenance which were different from those of all the other patients examined in the other included studies.

3. Results

3.1. Search Results and Study Selection

Figure 1 shows the process for performing a literature search. Briefly, 1427 records were left after duplicates were removed for title and abstract screening, 74 studies' full-text evaluations were completed, and 15 papers were included in the analysis (Table 1) based on preset inclusion criteria. Table 2 lists excluded studies and the explanations for exclusion.

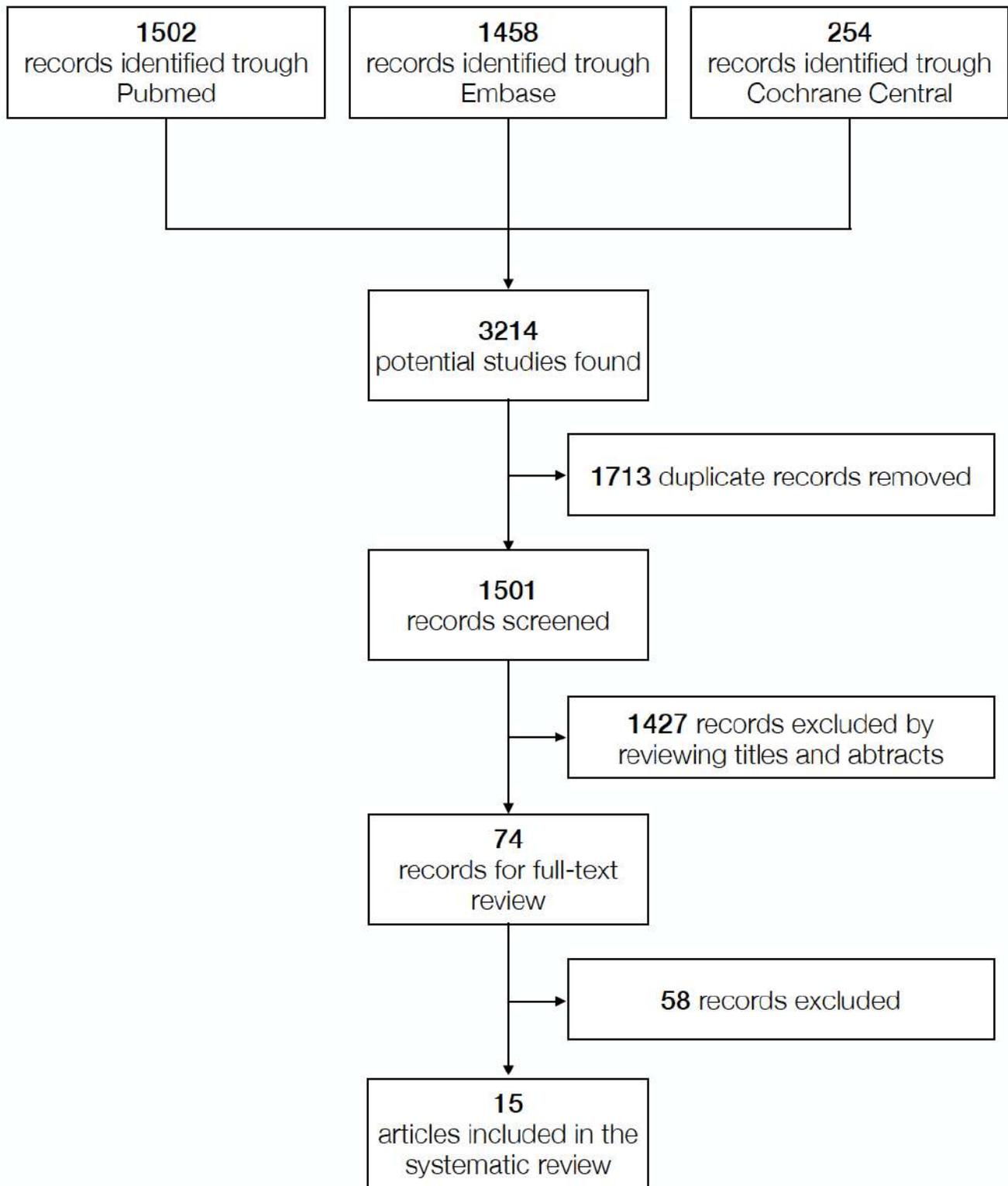


Figure 1. Literature research process.

Table 1. Included studies in the analysis.

Publication	Design/Follow-Up/Analysis/Country	Population	Case Definition	Objectives	Mean Age	Smoke	Outcomes	Implant Type	Type Reconstruction	Mandibular/Maxillary Implants	History of Periodontitis
Ladwein et al., 2015 [24]	cross-sectional/4–15 years/implant level/Germany	211 patients, 967 implants	no KM = 0 mm, yes KM >0 mm	existence of KM and peri-implant health	at implant insertion: 54.63 ± 13.58	not excluded, but not reported	mAPI, mSBI, PD (mm, 4 sites), BoP, width of KM, implant mobility, X-ray at bone level Rec, PPD (4 sites), X-ray bone level, implant loss, plaque score, BoP, FMPS	Tissue-level Standard Plus/Standard Straumann	all	418 (275 posterior)/549 (374 posterior)	
Rocuzzo et al., 2016 [25]	prospective comparative study with no baseline data (cross-sectional)/10 years/patient level/Italy	98 patients, 98 implants	no KM = 0 mm, yes KM >0 mm	to investigate long-term clinical conditions around dental implants in relation to presence or absence of KM	51.2 ± 10.6 (KM group), 42 ± 9.2 (AM group)	smokers included (13 smokers in KM group and 8 smokers in AM group)	smoking habits, n. of sites requiring during SPT additional treatment, presence of soreness/discomfort during oral hygiene practices	Straumann SLA	single or fixed dental prosthesis	posterior mandible	patients with history of moderate periodontitis (54 patients in KM group and 20 in AM group)
Esfahanizadeh et al., 2016 [26]	cross-sectional/more than 6 months/implant-level/Germany	36 patients, 110 implants	KM ≥ 2 mm adequate n = 48, KM < 2 mm inadequate n = 62	to assess the correlation of KM width with peri-implant soft tissue health and related factors	nr	28 patients smokers and 82 non smokers	KM width, PPD, mBI, mPI, mGI, GR, method of brushing	Bone-level implant submerged and 2-stage procedure	single crown or fixed cemented porcelain fused to metal partial denture	molar or premolar site in jaw	nr
Kabir et al., 2020 [27]	cross-sectional/mean loading time, 10.15 ± 6.31 years/analysis on patient and implant level/Germany	130 patients, 612 implants	KM ≥ 2 mm, KM < 2 mm	influence of KM on the severity of peri-implant mucositis	69.85 ± 10.32	11 smokers	PPD (6 sites), BoP, and mPI,mGI	Straumann and Astra	nr	all	71 patient with history of periodontitis

Table 1. Cont.

Publication	Design/Follow-Up/Analysis/Country	Population	Case Definition	Objectives	Mean Age	Smoke	Outcomes	Implant Type	Type Reconstruction	Mandibular/Maxillary Implants	History of Periodontitis
Monje et al., 2019 [23]	cross-sectional/more than 3 years (mean 5.7 ± 2.79 years)/implant level/Spain	37 patients, 66 implants	KM ≥ 2 mm, KM < 2 mm	assess the significance of KM in erratic compliers	49.9 ± 12.9	past or present heavy smokers excluded	PPD, mBI, PI, KM, vestibule depth (VD), suppuration, brushing comfort, X-ray at bone level	nr	nr	all	8 out of 37 patients with active periodontal disease, 16 with history of chronic disease and 13 not diagnosed with history of periodontal disease
Kungsadalpipob et al., 2020 [28]	cross-sectional/at least 12 months (mean 4.4 years)/implant level/Thailand	200 patients, 412 implants	KM ≥ 1 mm, no KM = 0 mm	to determine association between absence of KM and peri-implant tissue health to determine whether or not the width of the keratinized gingiva around dental implants has an effect on the health of the surrounding soft and hard tissues	57.3 (18–79)	4 current smokers	PPD, REC, mPI, mSBI, X-ray at bone level	nr	nr	all	36% history of periodontal disease
Bouri et al., 2008 [29]	cross-sectional/(4.91 ± 2.76 years vs. 4.10 ± 2.48 years)/implant level/USA	76 patients, 200 implants	KM ≥ 2 mm, KM < 2 mm	to determine long-term maintenance of implants with different surfaces in relation to KM clinical and radiographic outcome following FGG compared to KM < 2 mm	nr	smokers included	PPD, PI, GI, X-ray of bone loss	nr	nr	nr	nr
Chung et al., 2006 [11]	cross-sectional/mean loading period 8.1 ± 0.23 years/implant level/USA	69 patients, 339 implants	KM ≥ 2 mm, KM < 2 mm	to determine long-term maintenance of implants with different surfaces in relation to KM clinical and radiographic outcome following FGG compared to KM < 2 mm	61.3 ± 13.6	2 smokers out of 69	PPD, X-ray of bone loss, mPI, GI, mBI	Branemark, ITI, BioHorizons, 3i Osteotite, Steri-Oss Nobel Biocare machined 235; rough 104	nr	all	nr
Oh et al., 2017 [30]	RCT/18 months/implant level/USA	30 patients, 45 implants	KM ≥ 2 mm, KM < 2 mm	to determine long-term maintenance of implants with different surfaces in relation to KM clinical and radiographic outcome following FGG compared to KM < 2 mm	65 ± 5 y (FGG), 63 ± 9 (control)	smokers excluded	PPD, bone level, BoP, GI, PI, complications	rough surface implant	single unit	all	all included patients with chronic moderate generalized periodontitis

Table 1. Cont.

Publication	Design/Follow-Up/Analysis/Country	Population	Case Definition	Objectives	Mean Age	Smoke	Outcomes	Implant Type	Type Reconstruction	Mandibular/Maxillary Implants	History of Periodontitis
Buyukozdemir Askin et al., 2015 [31]	longitudinal/6 months/implant level/Turkey	18 patients, 60 implants	KM \leq 2 mm, KM $>$ 2 mm	effect of KM width on peri-implant tissue health	47.5 \pm 11.26	smokers excluded	PPD, bone loss, BOP, GI, PI, rec	nr	nr	nr	nr
Perussolo et al., 2018 [32]	longitudinal prospective/4 years/implant level/Brazil	54 patients, 206 implants	KM \geq 2 mm, KM $<$ 2 mm	influence of KM on marginal bone loss, peri-implant tissue health and brushing discomfort	55.7 \pm 10.7	heavy smokers ($>$ 10) excluded	Bone level, mPI, PPD, CAL, BoP, KM, brushing discomfort (VAS)	nr	all	all	patient with periodontal disease excluded
Crespi et al., 2010 [33]	longitudinal cross-sectional/4 years/implant level/Italy	29 patients, 164 implants	KM \geq 2 mm, KM $<$ 2 mm	influence of KM on peri-implant health in the long-term maintenance of immediately placed and loaded implants to evaluate the role	49.52 (25–67)	heavy smokers excluded	Bone level, mBI, PI, REC, PPD, KM	Sweden & Martina external exagon	partially or total bridge fixed reconstruction	all	nr
Esper et al., 2012 [12]	cross-sectional/1 year/implant level/Brazil	109 patients, 202 implants	KM \geq 2 mm, KM $<$ 2 mm	of keratinized mucosa around dental implants in the maintenance of peri-implant health	16 to 50 years	smokers excluded	PPD, GI, PI	nr	fixed implant supported crown	maxilla	nr

Table 1. Cont.

Publication	Design/Follow-Up/Analysis/Country	Population	Case Definition	Objectives	Mean Age	Smoke	Outcomes	Implant Type	Type Reconstruction	Mandibular/Maxillary Implants	History of Periodontitis
Gharpure et al., 2021 [34]	longitudinal-cross-sectional/mean follow-up, 6.9 ± 3.7 years/implant level/USA	63 patients, 193 implants	KM ≥ 2 mm, KM < 2 mm	to determine KMW is a risk indicators for the development of peri-implant mucositis and peri-implantitis	66.87 ± 12.42 years	current or former smokers with <3 months of cessation before implant placement excluded	Tissue phenotype, KM,PPD, Gi, PI, BoP, bone level; questionnaire for PROMs	platform switching (94); tissue level (38)	either single crowns adjacent to a natural tooth, implant crown, or splinted implants adjacent to a natural tooth or implant crown; cemented or screw-retained restorations	all	13 with intact periodontium, 10 with healthy but reduced periodontium, 5 with gingivitis on intact periodontium, 10 with gingivitis on reduced periodontium. Periodontitis: 4 IIA, 2 IIB, 3 IIIA, 12 IIIB, 1 IIIC, 2 IV B, 1 IV C
Manopattanasoontorn et al., 2021 [35]	longitudinal-cross-sectional/implant level/mean loading period, 53.91 ± 39.55 months (range 12–191)/implant and patient level/Thailand	165 patients; 331 implants	KM ≥ 2 mm, KM < 2 mm	to investigate the association between the keratinized mucosa (KM) width and peri-implant diagnostic parameters in implant maintenance	58.95 ± 11.58 (range 18–79)	144 (87.3) non-smokers and 21 (12.7) current or former smokers	KM width, mPI, mBI, REC, PPD, bone level	Straumann (123), Astratech (105); Zimmer (40); Nobel replace (17); Intralock (16); other (30) Implant type: bone level 205, tissue level 226	Screw-retained crown (88); cemented retained crown (243)	posterior maxilla and mandible	101 (61.2) patients without history of chronic periodontitis, 64 (38.8) with history of chronic periodontitis

Table 2. Excluded studies and reasons for exclusion.

Reason for Exclusion	Reference
KM data or analysis not suitable for the study	Garaicoa-Pazmino C. 2020, Gurgel B.C.V. 2020, Shimomoto T. 2020, Wuang D. 2020, Sanz-Marrtin 2020, Se-lim Oh 2020, Lombardi T. 2019, Spinato S. 2019, Grischke J. 2019, Todisco M. 2019, Isler S.C. 2019, Mailoa J. 2018, Bonino F. 2018, Crespi R. 2018, Arora H. 2017, Schwarz F. 2017, Fuchigami K. 2017, Ueno D. 2016, Ferreira C.F. 2015, Baht P.R. 2015, Parpaiola A. 2015, Reddy V.K. 2013, Boynuegri D. 2013, Suphanantachat S. 2012, Finne K. 2012, Jeong S m 2011, Buser D. 2011, Van Brakel R. 2011, Chang M. 2010, Van de Velde T. 2010, Gallucci G. 2009, Schrot A.R. 2009, Siciliano VI 2009, Zembic A. 2009, Botticelli D. 2008, Garcia R.V. 2006, Roos Jansaker A.M. 2006, Weber H.P. 2006, Bianchi A.E. 2004, Bragger U. 1997, Bengazi F. 1996, Wenstrom J. 1994, Merickse-stern R. 1994
The design of the study does not match the inclusion criteria	Monje A. 2020, Wuang Q. 2020, Ravidà A. 2020, Schwarz F. 2016, Schwarz F. 2016, Atsuta I. 2016, Romanos G. 2015, Sawalha N. 2015, Figuero E. 2014, Lee K.H. 2010, Kim B.S. 2009, Adibrad M. 2009, Zigdon and Machtei 2008, Souza A.B. 2015
No full text retrieved	Agrawal H. 2020, Potocsky K. 2013

3.2. Description of Studies

One study was a randomized controlled clinical trial [30] (Supplementary Table S1), two studies were cohort prospective studies [30–32] (Supplementary Table S1), ten were cross-sectional studies [11,12,23,24,26–29,34,35] and two studies presented cross-sectional data on patients followed for 10 years [25] and 4 years [33] (Supplementary Table S2).

The total sample population consisted of 1325 patients and 4005 implants. The follow-up of the included cohort prospective studies ranged from 6 months to 4 years.

Two studies [24,25] analyzed the presence or absence of KM, while one study analyzed $KM \geq 1$ and no KM [28]. Eleven studies [11,12,23,26,27,29,30,32–35] were stratified into two groups $KM \geq 2$ and $KM < 2$ mm, while one study included both $KM > 2$ and $KM \leq 2$ [31].

Implant failure and complications were not presented as outcome measures.

Only four studies analyzed patient-reported outcomes [23,25,32,34].

All the included studies reported the values of parameters related to peri-implant soft tissue health. PPD and PI (or mPI) were reported in all studies. BoP was reported in seven studies [24,25,27,30–32,34], while mBI was reported in seven studies [11,23,24,26,28,33,35], GI in was reported in seven studies [11,12,29–31,33,34], and mGI was reported in one study [26].

Radiographic bone level was reported in all included studies except one [26].

Mucosal recession was reported in six studies [25,26,28,31,33,35].

Smoking habits were reported in all included studies except one [24]. Smokers were excluded in three studies [12,30,31], and heavy smokers were excluded in other three studies [23,32,33].

History of periodontal disease was reported in eight studies [23,25,27,28,30,32,34,35].

In the cross-sectional studies, time point assessment ranged from more than 6 months after loading to 15 years. The cohort prospective studies of Buyukozdemir et al. [31] had a follow-up of six months, while those of Perussolo et al. [32] had a follow-up of 4 years. In the RCT study [30], the reported follow-ups were at 6, 12 and 18 months after the free gingival graft.

3.3. Risk of Bias Assessment

Table 3 presents the findings of the risk of bias assessment (The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional studies (last amended in 2017), Table 4 (The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cohort studies (last amended in 2017) and Table 5 (The Cochrane Risk of bias for RCTs)). Among the cross-sectional group, a study was deemed to be at high risk [24], and two were deemed to be at low risk [25,27]. In the cohort prospective group, one study was judged to be at high risk [32]; the RCT [30] was judged to be at high risk too. The risk of bias for each of the other studies was considered to be moderate.

Table 3. The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional studies (last amended in 2017).

Publication	Criteria for Inclusion Defined	Detailed Description of Subjects and Setting	Measurement of Exposure Valid and Reliable	Measurement of a Condition Done Using Objective and Standard Criteria	Confounding Factors Identified	Statement of Strategies to Deal with Confounding Factors	Measurements of Outcomes Valid and Reliable	Appropriate Statistical Analysis	Overall Risk of Bias
Chung 2006 [11]	YES	YES	YES	YES	YES	YES	YES	NO	MODERATE
Bouri 2008 [29]	YES	YES	YES	YES	YES	YES	YES	NO	MODERATE
Crespi 2010 [33]	YES	YES	YES	YES	YES	NO	YES	YES	MODERATE
Esper 2012 [12]	YES	YES	YES	YES	YES	YES	YES	NO	MODERATE
Ladwein 2015 [24]	YES	YES	YES	YES	NO	NO	YES	NO	HIGH
Esfahanizadeh 2016 [26]	YES	YES	YES	YES	YES	YES	YES	NO	MODERATE
Rocuzzo 2016 [25]	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Monje 2019 [23]	YES	YES	YES	YES	YES	YES	YES	NO	MODERATE
Kabir 2020 [27]	YES	YES	YES	YES	YES	YES	YES	YES	LOW
Kungsadalpipob 2020 [28]	YES	YES	YES	YES	YES	YES	YES	NO	MODERATE
Gharpure 2021 [34]	YES	YES	YES	YES	YES	YES	YES	NO	MODERATE
Manopattanasoontorn 2021 [35]	YES	YES	YES	YES	YES	YES	YES	NO	MODERATE

Table 4. The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cohort study (last amended in 2017).

Publication	Similar and from the Same Population Groups	Measure of Exposures Similar to Assign People	Measurement of Exposure Valid and Reliable	Confounding Factors Identified	Statement of Strategies to Deal with Confounding Factors	Participants Free of the Outcome at the Start of the Study	Measurements of Outcomes Valid and Reliable	Sufficient and Long Enough Follow-up Time	Drop out Clearly Explained and Detailed	Strategies to Address Complete Follow-up	Appropriate Statistical Analysis	Overall Risk of Bias
Perussolo (2018) [32]	YES	YES	YES	YES	YES	UNCLEAR	YES	YES	NO	UNCLEAR	NO	HIGH
Buyukozdemir (2013) [31]	YES	YES	YES	YES	YES	YES	YES	YES	YES	UNCLEAR	NO	MODERATE

Table 5. The Cochrane Risk of bias for RCT.

Publication	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data Addresses	Selective Reporting	Other bias (Appropriate Statistical Analysis)	Overall Risk of Bias
(Oh S-L 2016) [30]	low	high	n.a	low	low	low	high	high

3.4. Description of Results and Meta-Analysis

Meta-analysis could be conducted only for cross-sectional studies. For the cohort prospective studies, a meta-analysis could be not performed due to the limited number of included studies, the different time points of the follow-up evaluations and the different outcome measures. Confounding factors could not be analyzed since only a few papers reported all this information [25,35], and data could not be used.

3.4.1. Implant Failures

Implant failure was not presented as an outcome measure; only in one study, four implants were lost (two to infection and one to fracture in the no KM group; one to fracture in the KM group) and presented as drop outs [32].

3.4.2. Patient-Related Outcomes

Three cross-sectional studies reported on pain. Rocuzzo et al. [25] reported the presence of soreness/discomfort dichotomously as present in 0 patients in the KM group and 5 patients in the no KM group; Monje and Blasi [23] reported V0AS discomfort (VAS = 0 extreme discomfort; VAS = 100 maximum comfort) in the KM ≥ 2 group as 97.0 ± 8.5 while in the KM < 2 mm group it was 53.8 ± 30. Gharpure et al. [34] reported awareness of food impaction and pain/discomfort. They reported that implants with inadequate KM had greater food impaction (53% versus 40%, *p* = 0.193) and pain/discomfort during oral hygiene practices (28% versus 10%, *p* = 0.027) than those with adequate KM.

Perussolo et al. [32] reported at 18 months of discomfort during brushing measured on a VAS (VAS = 0 no discomfort, VAS = 100 extreme discomfort) in the KM < 2 group as 12.28 ± 17.59 while that in the KM ≥ 2 group was 4.25 ± 8.39. Although a meta-analysis could not be performed, a consistent trend toward the worst pain/discomfort in the KM < 2 mm group was observed.

None of the included studies reported on patient satisfaction and quality of life.

3.4.3. BoP (Figures 2 and 3)

Four cross-sectional studies presented data on BoP. Three studies [25–27] were included in the meta-analysis (Figure 2). The study of Ladwein et al. [24] was excluded because S.D. was not given.

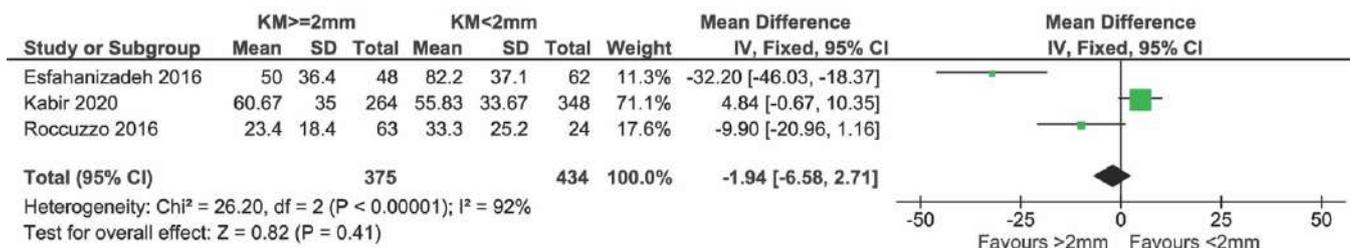


Figure 2. Cross-sectional studies reporting on BoP included in the meta-analysis [25–27].

In total, 375 and 434 implants with KM ≥ 2 mm and KM < 2 mm, respectively, were compared. There was no evidence of a difference in BoP% between groups (mean difference = -1.94%; 95% CI = -6.58; -92.71, *p* = 0.41). High heterogeneity in effects was detected among the studies (I² = 92%; *p* < 0.00001).

Sensitivity analysis including only low-risk studies showed no evidence of any effect and did not change the results substantially (mean difference = 1.91%; CI = -3.02; -6.84, *p* = 0.45). Heterogeneity decreased but not significantly (I² = 82% *p* = 0.02) (Figure 3).

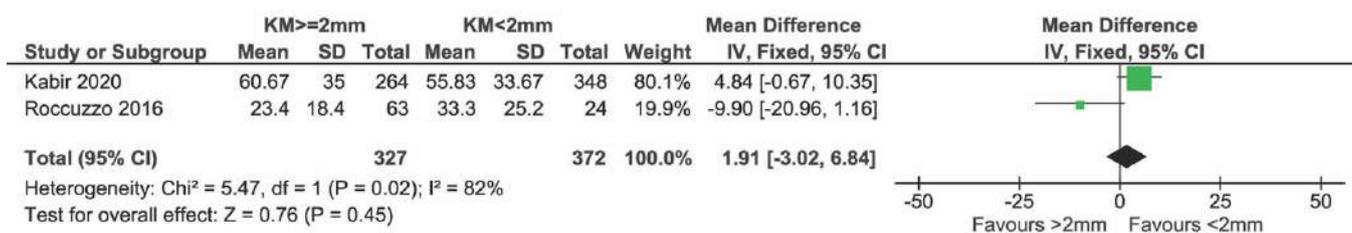


Figure 3. Sensitivity analysis including only low risk studies reporting on BoP [25,27].

Both cohort prospective clinical studies [31,32] reported data on BoP and found a statistical significant difference in favor of KM ≥ 2 mm (p < 0.05). In the RCT of Oh et al. [30], a statistical significant difference in favor of KM ≥ 2 mm was reported.

3.4.4. Biological Complications

Roccuzzo et al. [25] described, over ten years of follow-up, the percentage of biological complications (51.4% in the no KM group and 12.7% in the KM group) that required additional treatment (antibiotics or surgical therapy). Crespi et al. [33] reported, at 2 years after placement, two implants with a peri-implantitis process with 2 mm of bone loss in the group with KM < 2 mm. Oh et al. [30] reported two subjects with one implant each in the KM < 2 mm group who were excluded from the study due to complications that required additional treatments (curettage with antibiotic prescription). In the KM ≥ 2 mm group, one subject with one implant was excluded due to curettage for biological complication performed before the free gingival graft.

3.4.5. PPD (Figures 4–7)

All the twelve cross-sectional studies reported on PPD and were included in the meta-analysis (Figure 4). In total, 2402 and 1281 implants with KW ≥ 2 mm and KW < 2 mm, respectively, were compared (Figure 4). There was a non-significant trend of a lower PPD in favor of the group with KM < 2 mm/absence, with a mean difference (MD) of 0.03 mm (95% CI = -0.02; 0.09 mm, p = 0.23).

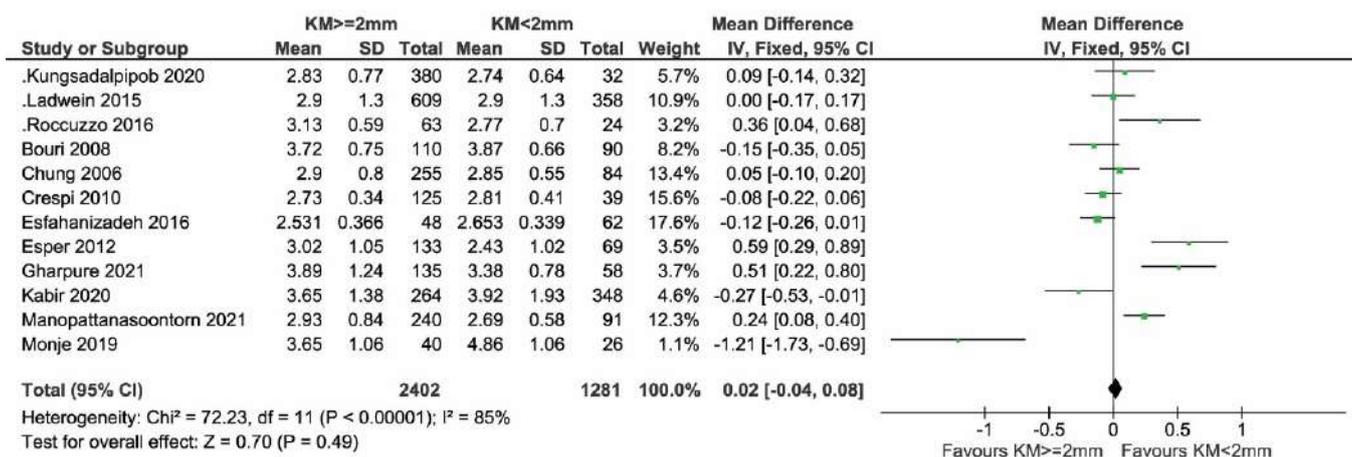


Figure 4. Cross-sectional studies reporting on PPD included in the meta-analysis [11,12,23–29,33–35].

Sensitivity analysis after removing the study by Ladwein et al. [24], judged to be at high risk, showed no evidence of any effect due to KM (mean difference = 0.02 mm; 95% CI = -0.04, 0.08 mm; p = 0.08). Significant heterogeneity in effects was observed among the studies (I² = 86%; p < 0.001) (Figure 5).

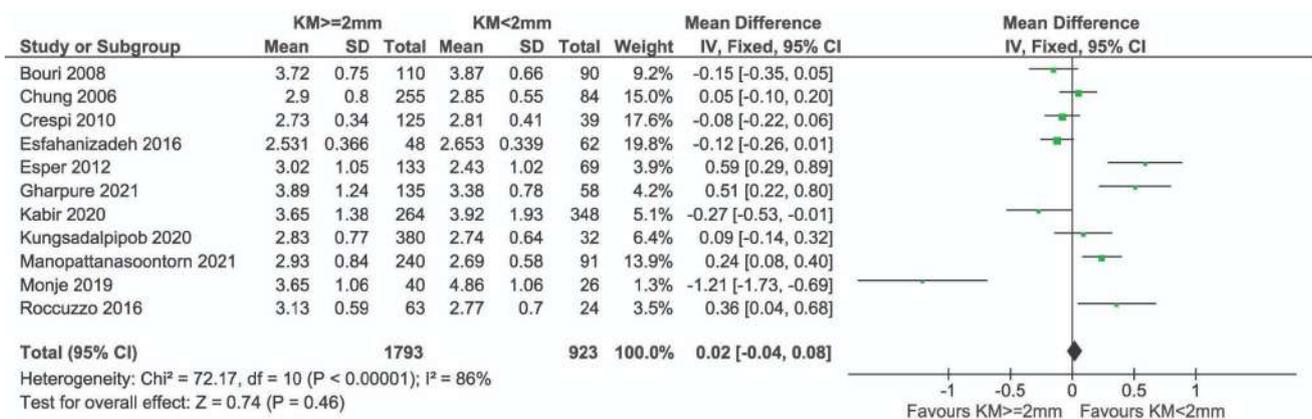


Figure 5. Sensitivity analysis excluding high-risk studies reporting on PPD (Ladwein et al. [24] and [11,12,23,25–29,33–35]).

Sensitivity analysis after removing the study by Monje et al. [23] (Figure 6) and with only low-risk-of-bias studies did not change the results substantially (Figure 7).

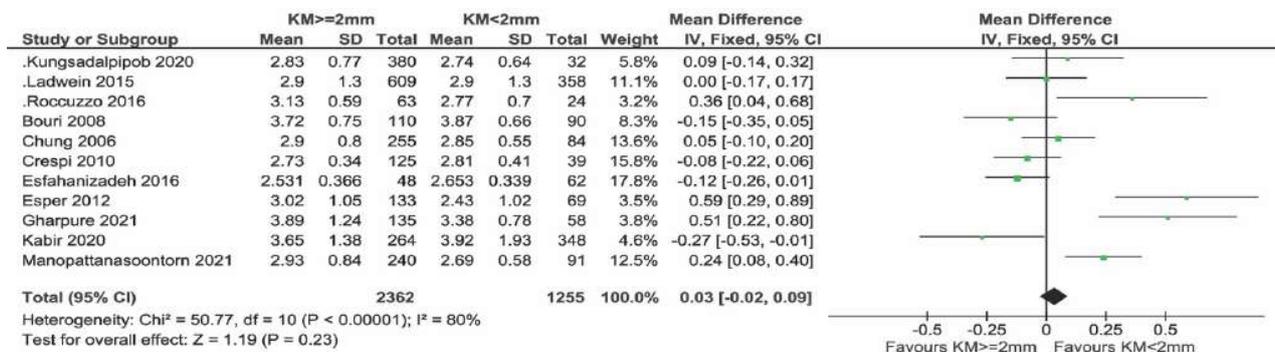


Figure 6. Sensitivity analysis of PPD excluding the study of Monje & Blasi [11,12,24–29,33–35].

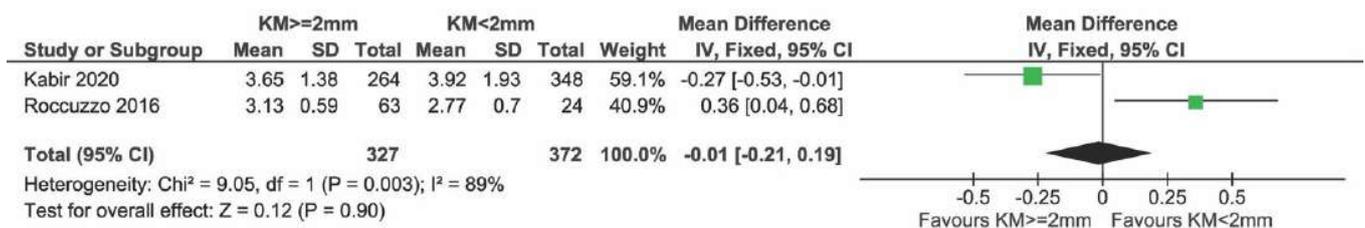


Figure 7. Sensitivity analysis including only low-risk studies reporting on PPD [25,27].

In the two cohort prospective studies and in the RCT, no significant differences between groups in PPD were reported.

3.4.6. GI, mGI/BI, and msBi (Figures 8 and 9)

Briefly, 9 out of 12 gave data on GI, mGI/BI, and msBI, and were included in the meta-analysis (Figure 8). The data taken on a 0–3 scale were normalized to a 0–4 scale to be able to compare all the data. In total, 1595 and 841 implants with KM ≥ 2 mm and KM < 2 mm, respectively, were compared. There was evidence of a difference in GI, mGI/BI, and msBI in favor of the group with KM ≥ 2 mm (mean difference = −0.26; 95% CI = −0.47, −0.05; p = 0.01). Highly significant heterogeneity in effects was detected among the studies (I² = 97%, p < 0.0001).

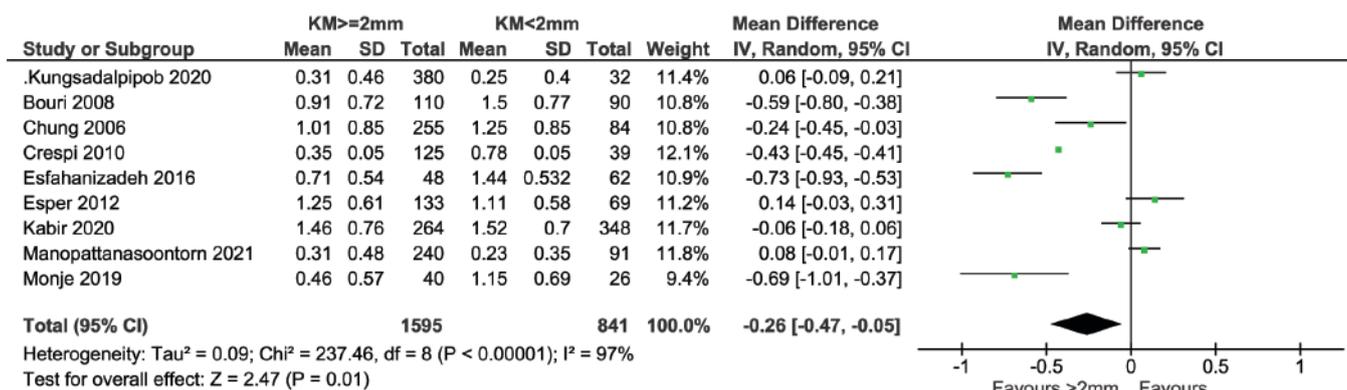


Figure 8. Cross-sectional studies reporting on GI, mGI/BI, and msBi included in the meta-analysis [11, 12,23,26–29,33,35].

Sensitivity analysis after removing the study by Monje et al. [23] showed weak evidence of a difference in GI, mGI/BI, and msBi between the two groups (In Figure 9 p = 0.05). Heterogeneity in effects among the studies was unchanged (I² = 97%; p < 0.0001) (Figure 9).

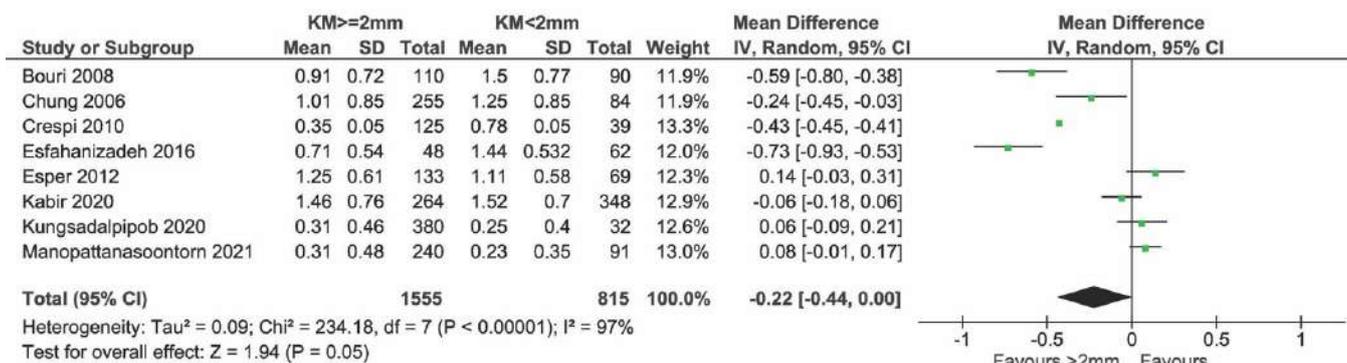


Figure 9. Sensitivity analysis of GI, mGI/BI, msBi excluding the study of Monje & Blasi [11,12,26–29,33,35].

Both Oh et al. [30] and Buyukozdemir et al. [31] reported on GI with statistically significant differences in favor of the presence of KM.

3.4.7. PI and mPI (Figures 10 and 11)

All cross-sectional studies reported on PI, but only nine were included in the meta-analysis because Gharpure et al. [34], Ladwein et al. [24] and Roccuzzo et al. [25] provided data in a non-usable/comparable manner (Figure 10). In total, 1595 and 841 implants with KM ≥ 2 mm and KM < 2 mm, respectively, were compared. There was evidence of a difference in PI in favor of the group with KM ≥ 2 mm (mean difference = -0.25; 95% CI = -0.47, -0.04; p = 0.02). Highly significant heterogeneity in effects was detected among the studies (I² = 98%; p < 0.0001). The sensitivity analysis performed after removing the study of Monje et al. [23] showed no statistical difference between groups (p = 0.08) (Figure 11).

In the cohort studies, only Buyukozdemir et al. [31] reported a statistically significant difference in PI in favor of the presence of KM.

The RCT of Oh et al. [30] reported no significant differences between groups.

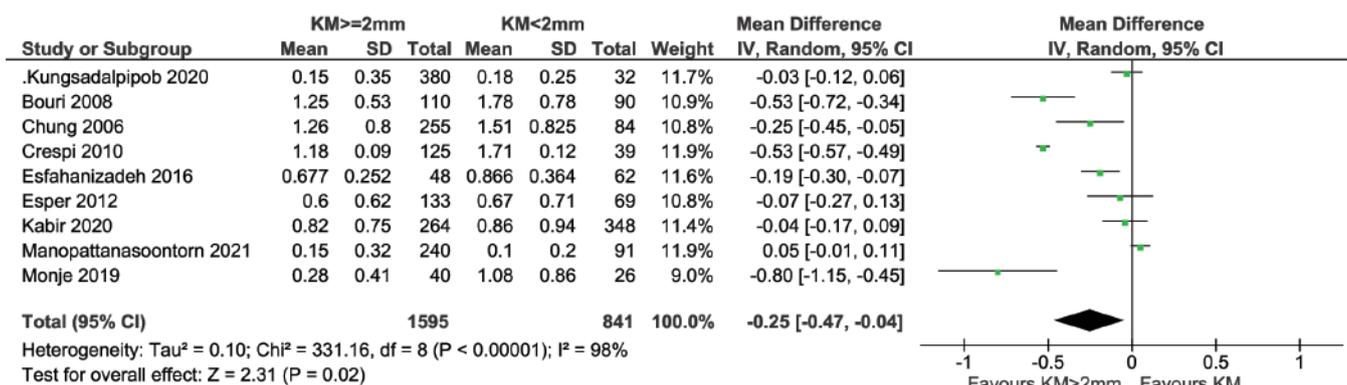


Figure 10. Cross-sectional studies reporting on PI/mPI included in the meta-analysis [11,12,23,26–29,33,35].

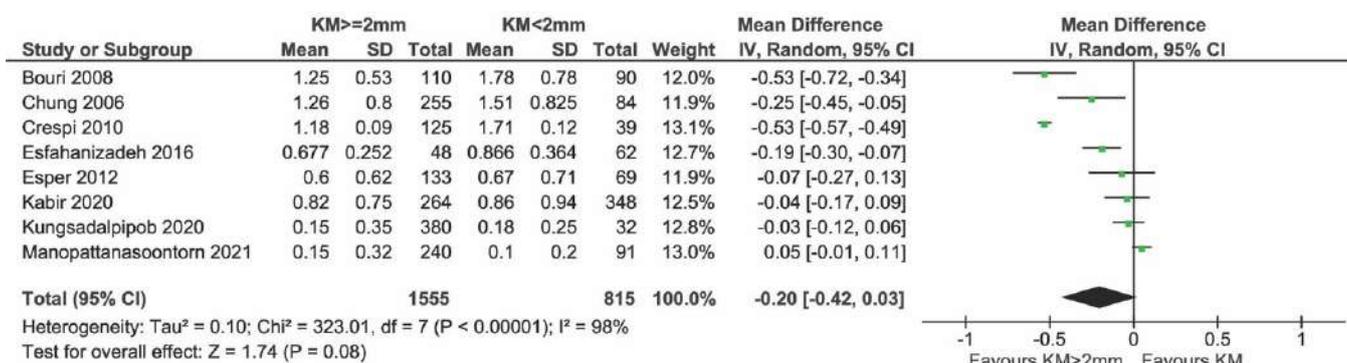


Figure 11. Sensitivity analysis of PI and mPI excluding the study of Monje & Blasi [11,12,26–29,33,35].

3.4.8. Bone Level (Figures 12–14)

Eight studies presented data on the bone level and all were included in the meta-analysis (Figure 12). In total, 1894 and 778 implants with KM ≥ 2 mm and KM < 2 mm, respectively, were compared. There was weak evidence of a reduced bone level change in the group with KM ≥ 2 mm (mean difference = -0.18 mm; 95% CI = -0.36, 0.00 mm; p = 0.05). Significant heterogeneity in effects was detected among the studies (I² = 80%; p < 0.0001). Sensitivity analysis after removing the study by Ladwein et al. [24] showed no evidence of a difference in bone level change between the two groups (Figure 13, p = 0.08). Heterogeneity was reduced, but still significant (I² = 82%, p = 0.08) while the sensitivity analysis performed after removing Monje et al. [23] showed a heterogeneity reduction from 80% to 70% (Figure 14).

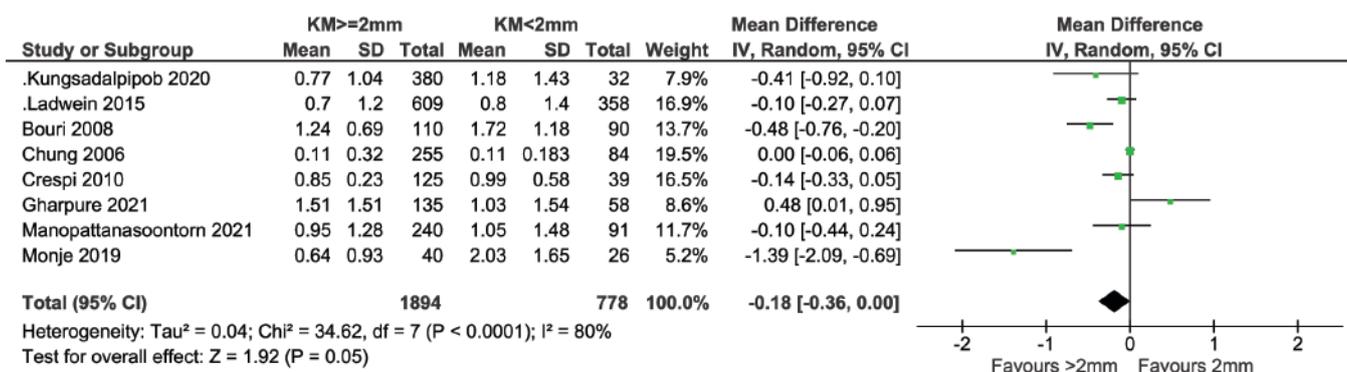


Figure 12. Cross-sectional studies reporting on MBL included in the meta-analysis [11,23,24,28,29,33–35].

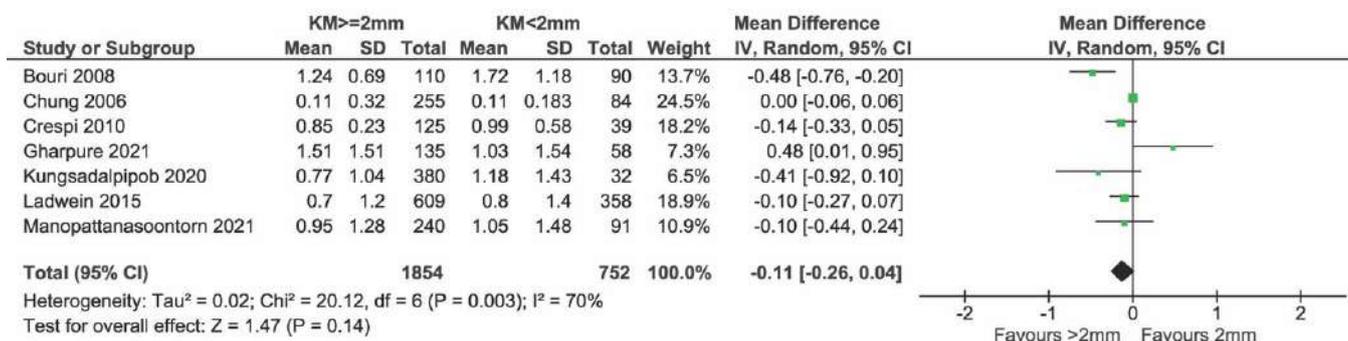


Figure 13. Sensitivity analysis of MBL excluding the study of Monje & Blasi [11,24,28,29,33–35].

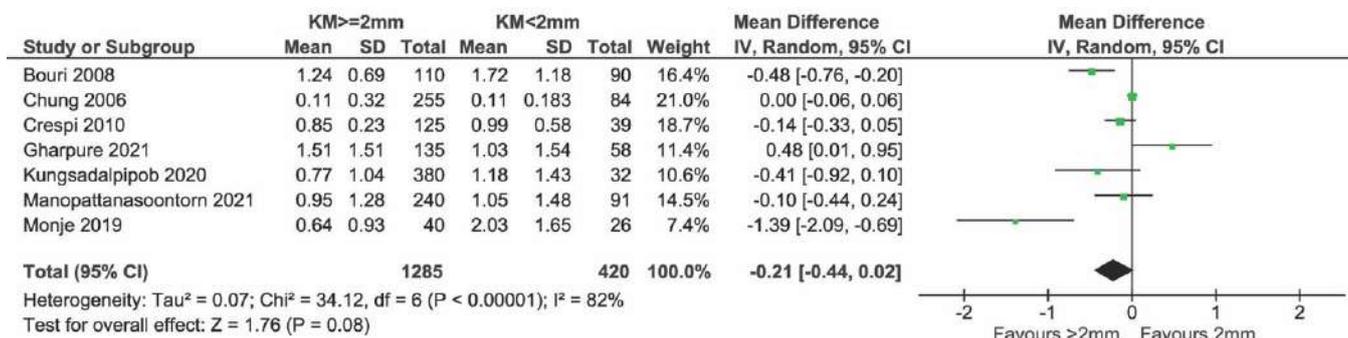


Figure 14. Sensitivity analysis excluding high-risk studies reporting on MBL (Ladwein et al. [24]) and [11,23,28,29,33–35].

The RCT and one cohort study [30,32] reported a significant difference in bone levels between the groups in favor of the presence of KM ≥ 2 mm, while Buyukozdemir et al. [31] reported no differences.

3.4.9. REC (Figure 15)

Five cross-sectional studies reported on REC and were included in the meta-analysis (Figure 15). In total, 856 and 248 implants with KM ≥ 2 mm and KM < 2 mm, respectively, were compared. There was evidence of a difference in REC in favor of the group with KM ≥ 2 mm (mean difference = -0.33 mm; 95% CI = -0.40, -0.25; p < 0.0001). Highly significant heterogeneity in effects was detected among the studies (I² = 98%; p < 0.0001). No sensitivity analysis was performed.

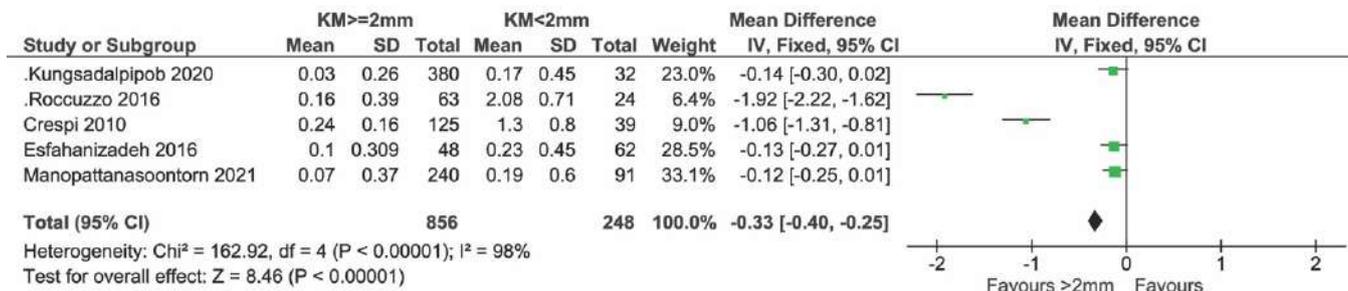


Figure 15. Cross-sectional studies reporting on REC included in the meta-analysis [25,26,28,33,35].

REC was reported only in one cohort prospective study [31] showing no statistically significant difference between the groups.

4. Discussion

The present systematic review aimed at assessing the role of KM on peri-implant tissue health, esthetics and patient-related variables. The presence of KM ≥ 2 mm was

associated with less marginal inflammation (GI, mGI, BI, and msBi), plaque accumulation (PI, mPI), recession, biological complications and less soreness or discomfort during oral hygiene procedures, while no differences were found for implant failures, PPD and bone levels. BoP resulted in being significantly lower in the $KM \geq 2$ mm groups in the three prospective studies [30–32]. These results should be considered with caution. Only one RCT study with 18 months [30] of follow-up could be included and we decided to analyze studies with data given at the implant level since very few studies used the patient level. Only two studies [25,27] at low risk of bias were included, while studies presented high heterogeneity and few had long follow-ups.

Even if some differences between groups were statistically significant, their clinical importance should be determined, since small differences between groups were found. These differences were even smaller when excluding one study [23] in which patients with erratic compliance were included. In particular, no differences were found for PPD and bone loss. The mean values reported for these variables showed that the population examined presented shallow PPD and little bone loss, so the results should be applied to patients with generally healthy peri-implant tissue. The only exception was presented by Monje et al. [23] where pockets deeper than 4 mm were present in the group with $KM < 2$ mm and its results suggest that the presence of KM could be important in patients in which compliance is suboptimal.

A reason behind the small differences found between groups could be the choice of the cut-off for sorting a patient into one group or another. Most of the studies used the presence of at least 2 mm of KM as the criteria for describing one group [7,25]. This measure could be difficult to record and similar cases could be assigned to different groups, altering the results. Additionally, using this definition, cases with a presence of KM were pooled with cases with an absence of KM. A minimal presence of KM could have different clinical significance with respect to its complete absence. Only three studies considered the presence or absence of KM as the case definition [24,25,28]. The meta-analysis conducted without these studies did not alter the results. Moreover, the presence of attached mucosa was never analyzed and this could be an important issue when evaluating the results. If KM plays a role in maintaining a peri-implant soft tissue seal that contributes to maintaining the state of health, it ideally means that KM should have characteristics of stability and that it must adhere to the underlying hard tissues. KM consists histologically of a dense, collagen-rich connective tissue covered by a keratinized epithelium. Adherent KM has a lamina propria firmly connected to the underlying periosteum, while free KM lacks this connection. This can be due to the implant position or bone resorption leaving supracrestal peri-implant soft tissue of an adequate thickness to avoid recession but without attachment to the underlying periosteum. This lack of attachment could negatively affect the soft tissue seal around implants. Therefore, measuring a vertical dimension of keratinized tissue without defining its characteristics (free or adherent) may not be sufficient. From a clinical point of view, in fact, it may be sufficient to have 1 mm of adherent KM while perhaps the presence of >2 mm of non-adherent KM may not be adequate.

The presence of KM should be evaluated also in relation to other clinical conditions. None of the included studies reported on the vestibule depth. A shallow vestibule, often present in the lower jaw and particularly in patients who underwent tooth extraction for periodontal reasons, should be taken into consideration as it hampers oral hygiene procedures resulting in plaque accumulation and inflammation. Future studies should take into account the presence or absence of attached keratinized mucosa and report on the depth of the vestibule to better define the role of KM in peri-implant health. Interestingly, no studies clearly indicated implant failure and complications as outcome variables. Even if failure is a rare occurrence, it should be analyzed and reported. Two studies [30,32] reported on complications but they were recorded as drop outs, which could alter the real results. In cases without adequate KM, four complications linked to infection (two in Crespi et al. [33], two in Oh et al. [30]), two failures for infection and one failure due to fracture [32] were present, while in the group with $KM > 2$ mm only one implant was

lost due to fracture and one complication was due to infection [30]. In one study in the cross-sectional groups, biological complications were reported in 51.4% of cases without KM and in 12.7% of cases with KM [25].

Other systematic reviews [7,8,18,36] on this topic reached conclusions similar to the ones reported in the current manuscript, although differences in the inclusion criteria, methods of analysis, outcomes analyzed and risk of bias assessments were present. In this review, only RCT, prospective cohort and cross-sectional studies were considered, excluding studies with a retrospective design (for example, [15,17]). These strict eligibility criteria were set to improve the quality of the included studies. The original plan, as described in the statistical analysis, was also to only include studies that performed analysis at the patient level, but since only two papers fulfilled this criteria [25,27], we decided to include implant-level analysis studies and meta-analysis was conducted at the implant level. This is a clear limitation of both the included studies and of the current review. All the studies in which the analysis was conducted at the implant level were judged to be at least at moderate risk of bias.

In the review by Gobbato et al. and Longoni et al. [7,18], recessions and bone level were not analyzed as they recognized difficulties in standardizing measurement methods. We agree with their considerations, but since we believe that both parameters are important to evaluate, we have decided to analyze these data. Bone level can be considered a surrogate outcome of implant failure, which requires a longer follow-up. Since none of the included papers reported on implant failure, it appeared reasonable to analyze bone stability over time. Interestingly, no differences were found in terms of bone level in patients with or without KM.

In accordance with Longoni et al. [18], to increase the statistical power of the analysis, we pooled outcomes that measured the same clinical parameters as a group (GI, mGI, BI, mBI and PI, mPI). Since we recognized that the indices were different, we normalized them to be able to perform the statistical analysis. We observed that definitions were often used incorrectly and or associated with a wrong reference [26,27,29,33]. We advise a uniform use of indices. A dichotomous index indicating the presence or absence of marginal inflammation, BoP and plaque would be easier to apply and more useful for the comparison of different studies. Data presented as percentages would be easier to interpret clinically.

Moraschini et al. [37] performed an overview to assess the methods, quality, and outcomes of the systematic reviews on the importance of KM. The major limitations that were highlighted consisted of the lack of standardization methods and the absence of evaluation of possible confounding factors. The study in the present manuscript was performed according to PRISMA guidelines and a standardized tool for the risk of bias assessment was applied. Gobbato et al. [7] mentioned the risk of bias in the methods section but it was not reported in the final results and Brito et al. [36] did not perform a risk of bias evaluation. Lin et al. [8] used a non-standardized risk of bias, while Longoni et al. [18] applied the Newcastle–Ottawa modified scale. In the present review, the Joanna Briggs tool was chosen as it includes two questions focused on the presence of confounding factors and strategies for their management. In particular, referring to KM significance, we considered the following as major confounding factors: smoking habits, a history or actual presence of periodontal disease, the type of implant surface (rough or machined), the type of implant-supported reconstruction, the implant position and the maintenance protocol. Only a few papers reported all this information [25,35]; apart from when data were given at the implant level, patient-related variables were impossible to apply to the analysis. Rocuzzo et al. [25] provided data on smoking habits but very few smokers were included to allow a powerful statistical analysis. Manopatonasontorn et al. [35] performed a univariate and multivariate regression analysis adjusted for confounding factors (oral hygiene, smoking status, history of chronic periodontitis, implant prosthesis type, and diabetes). This type of analysis could be useful for data interpretation. The type of maintenance was rarely reported [25] even if it represents a key aspect of peri-implant health.

In our manuscript, a sensitivity analysis was performed, excluding the paper by Monje & Blasi [23] in which only erratic maintenance patients were included. In this group of patients, the presence of KM demonstrated a crucial role. On the other side, Manoppatana-soorn et al. [35] concluded that no association was observed between keratinized mucosa width and plaque accumulation, mucosal inflammation, and interproximal bone level in a population that adhered to implant maintenance therapy and demonstrated optimal oral hygiene. Only Rocuzzo et al. [25] provided detailed information on the maintenance care protocol. We believe that the maintenance protocol after implant positioning is a crucial point for implant survival. When strict maintenance schedules and oral hygiene were consistently adhered to by patients, no association between keratinized mucosa width and peri-implant diagnostic parameters were observed in many studies [12,38–40].

Brito et al. [36] included only studies with more than 12 months of follow-up, while Longoni et al. [18] examined studies with at least 4 months of follow-up. We decided to include studies with at least 6 months of follow-up, in accordance with Gobbato et al. [7] and Lin et al. [8], since this allowed the inclusion of a larger number of studies, given that few studies have long follow-ups. Fifteen studies were included in the final analysis while only eight studies had a follow-up lasting longer than 3 years [11,23,24,28,29,32–34] and only one study had a 10-year follow-up [25] so data on implant survival were difficult to explore. A long follow-up was deemed necessary to adequately answer the review question and in particular to evaluate one of the most important primary outcomes of this review that is implant failure. According to the data in the literature, indeed, the likelihood of complications increases after 5 years from loading. If we could analyze data from studies with follow-ups of more than 5 years, we could perhaps achieve results that are very different and more significant than those reported in this review.

PROMs have become a crucial endpoint of clinical studies and should be included in every implant-related clinical study to capture patient satisfaction and quality of life [41]. None of the included studies evaluated the quality of life of patients with or without KM and none reported on esthetic perception. The only parameter assessed regarding the patient-related outcome was brushing discomfort and this was reported in four studies [23,25,32,34]. It was not possible to perform a meta-analysis because data were analyzed in different ways. In the literature, there is a trend towards greater discomfort in the absence of mucosa but more studies are needed to evaluate this variable and there is a need for more uniformity in data collection.

4.1. Main Limitations

Several limitations of the present review are worth mentioning.

Even if RCTs give stronger evidence of the effect of the presence or absence of KM, cross-sectional and prospective control studies were included. Additionally, different time point assessments in relation to implant placement were pooled and analyzed together.

Studies with data given at the implant level were included and the analysis was performed at the implant level. Even if potential confounding factors were presented in some studies, we were not able to analyze their influence on the effect of the presence or absence of KM.

In the case of data presented in a non-usable manner, the authors were not contacted and therefore some studies were excluded even though they could have potentially been of interest.

4.2. Recommendation for Future Research

The definition of KM should be more accurate. The description of a definite amount of attached KM versus that of non-attached KM seems more useful clinically. The depth of the vestibulum should be reported. A uniform use of indices for describing outcome measures is advisable, with an emphasis on data that could be easily interpreted clinically, such as the percentage of the presence of plaque, bleeding on probing, and marginal inflammation. Data should be given at the patient level and the mean and SD should be provided. Implant

failures and complications should be clearly described. PROMSs should be routinely included in clinical trials.

Confounding factors should be recorded and evaluated when performing statistical analyses. Long follow-ups should be preferred because the effect of the presence or absence of KM needs time for an adequate clinical evaluation.

5. Conclusions

No statistically significant differences between the presence of $KM \geq 2$ mm or <2 mm were found for implant failure, PPD or bone loss. BoP resulted in being significantly lower in the $KM \geq 2$ mm group only in the three prospective studies.

Less statistical marginal inflammation, plaque accumulation, and recession were associated with the presence of $KM \geq 2$ mm, but the differences were clinically small. More biological complications were described in the no KM/ $KM < 2$ mm group but the reduced number of cases does not allow us to draw any conclusions. Although a meta-analysis could not be performed, a consistent trend toward the worst pain/discomfort in $KM < 2$ mm was observed. These results should be considered with caution, since most of the studies were at a moderate and high risk of bias, follow-ups were short and data were given at the implant level. Furthermore, most of the included patients had low plaque levels and PPD values so these results may not be valid for patients with erratic compliance that presented as having higher benefits from KM presence.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/app13158631/s1>, Table S1: Cohort prospective studies and randomized controlled clinical trials included in the analysis.; Table S2: Cross-sectional studies included in the analysis.

Author Contributions: Conceptualization, M.S. and M.G.G.; methodology, A.P.; software, M.D.F.; validation, L.G., P.G. and G.L.; formal analysis, M.D.F.; investigation, M.S.; resources, A.P.; data curation, M.D.F.; writing—original draft preparation, M.S. and M.G.G.; writing—review and editing, M.S., A.P., L.G, P.G. and M.G.G.; visualization, G.Z.; supervision, A.S., G.L. and G.Z.; project administration, M.S.; funding acquisition, M.S. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest related to the contents of this study.

Appendix A

Search strategy

PubMed research: (“dental implants”[mh] OR “dental implantation”[mh] OR (“implant”[tiab] OR “implants”[tiab]) AND (dental[tiab] OR oral[tiab] OR tooth [tiab])) AND (“mouth mucosa”[mh] OR (“peri-implant”[tiab] OR “masticatory”[tiab] OR “attached”[tiab] OR “keratinized”[tiab] OR “keratinised”[tiab] OR “KT”[tiab]) AND (“mucosa”[tiab] OR “gingiva” [tiab]))).

EMBASE research: (dental:ab,ti AND implant:ab,ti OR ‘tooth implant’/exp/mj) AND (keratinized:ab,ti AND mucosa:ab,ti OR (keratinized:ab,ti AND tissue:ab,ti) OR (keratinized:ab,ti AND tissues:ab,ti) OR ‘attached gingiva’:ab,ti OR ‘attached mucosa’:ab,ti OR ‘soft tissue’/exp/mj) AND [embase]/lim.

Cochrane Central research: (“dental implants” AND “mucosa”).

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