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Title: The role of keratinized mucosa width as a risk factor for peri-implant disease: A systematic review, meta-analysis and trial sequential analysis

Running Head: Peri-implant keratinized mucosa width and peri-implant diseases

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS

A.R and H.L.W. conceived the concept/design, A.R. and C.A; participated in the data collection; A.R. and V.C.A.C. involved in the Data analysis/interpretation; G.T. conducted the statistics; M.T. and A.R. drafting the article; M.H.A.S. and H.L.W critical revision of article; All authors approved of article.

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Summary box

What is known:

An “adequate” amount of keratinized mucosa width (KMW) around implants is often regarded to be ≥2mm.

- Adequate KMW can prevent soft tissue recession and bone resorption
- Adequate KMW can facilitate adequate oral hygiene measures
- Adequate KMW can minimize the incidence of peri-implantitis

What this study adds:

This study showed the impact of amount of KMW (either <2mm or ≥2mm) as a risk factor for developing peri-implant disease remains low.

- Adequate KMW did not influence probing depth, soft tissue recession and marginal bone loss when compared to inadequate KMW.
- Adequate KMW had a lower plaque index when compared to inadequate KMW.

ABSTRACT

Background: Studies have examined the benefit of having keratinized peri-implant mucosa width with mixed results.

Purpose: This study examines whether the lack of a prespecified (2 mm) amount of keratinized mucosa width (KMW) is a risk factor for peri-implant diseases.

Methods: A systematic electronic and manual search of randomized or non-randomized controlled or non-controlled clinical trials was conducted. Qualitative review, quantitative meta-analysis, and trial sequence analysis (TSA) of implants inserted at sites with <2 mm or ≥2 mm of KMW were analyzed to compare all the predetermined outcome variables. The level of evidence concerning the role of KMW in peri-implant health was evaluated via the GRADE system guide.

Results: Nine studies were included in the qualitative analysis and 4 in the meta-analysis and TSA. No significant inter-group difference ($p>0.05$) and a low power of evidence were found for probing depth, soft tissue recession and marginal bone loss. A significant difference favoring ≥2 mm KMW had a lower mean plaque index (MD = 0.37, 95% CI: [0.16, 0.58], $p=0.002$) (3 studies, 430 implants, low-quality evidence). GRADE system showed very low and low quality of evidence for all other outcome measures.

Conclusion: Based on the available studies, the impact of amount of KMW (either <2mm or ≥2mm) as a risk factor for developing peri-implant disease remains low. Future control studies with proper sample size and longer follow-up are needed to further validate current findings.

1 | Introduction

Peri-implant phenotype comprises of keratinized mucosa width (KMW), mucosal thickness (MT), supracrestal tissue height (STH) and peri-implant bone thickness [1]. KMW is used to denote the height of keratinized soft tissue that runs apico-coronally from the mucosal margin to the mucogingival junction [1]. It is often thought that KMW at healthy implant sites is roughly 1 mm less than the keratinized tissue width at contralateral natural teeth [2]. Studies have examined the benefit of having peri-implant KMW with conflicting results. An "adequate" amount of KMW around implants is often regarded to be ≥2mm since this is the amount that requires to prevent soft tissue recession, bone resorption and to facilitate adequate oral hygiene measures [6-10]. It was hence advocated to develop adequate KMW at planned implant sites [3]. A systematic review concluded that soft tissue grafting procedures to increase KMW resulted in more favorable peri-implant health (e.g., improvement in bleeding indices and higher marginal bone levels)[4]. On the other hand, some studies have demonstrated implants with by lining mucosa can also possess with high long-term success[5,6] and have no association between peri-implant mucosal inflammation and the lack of a certain amount of KMW[7,8].

Upon answering the question of whether there is a need for peri-implant KMW to maintain health and tissue stability, the 3rd EAO Consensus Conference (2012) concluded that no longitudinal studies have showed the association between "inadequate" KMW and higher plaque index in well-maintained populations [9]. The same was also found for gingival inflammation as measured via gingival index and soft tissue recession. In the 6th EAO Conference Consensus Report suggested that mucosal recession, gingival index and plaque control are improved when KMW is increased via soft tissue augmentation procedures [10]. This leads to the working group's clinical recommendation that augmenting KM may be advised to improve the aforementioned parameters. Nonetheless, the results were based on the pooled data of one randomized controlled trial (RCT), one prospective cohort study and one retrospective cohort study.

This illustrates that the role of a specific KMW threshold in obtaining and maintaining peri-implant health remains to be determined. Contemporary thought suggests that the benefits of KMW are limited to simplifying oral hygiene procedures for patients with an implant, which in turn may result in less susceptibility to inflammation [11]. While such a notion may be supported by multiple observational studies [12,13], the presented quality of evidence thus far may not justify considering the lack of any amount of KMW as a risk factor for peri-implant disease. Only longitudinal studies of interventions are capable of identifying risk factors for disease, while observational, cross-sectional and retrospective studies may only describe risk indicators, since a cause-effect relationship cannot be detected [14]. Hence, results from previously performed systematic reviews and meta-analyses including cross-sectional studies should be interpreted with caution [15,16]. In particular, the lack of KMW could be the consequence of peri-implant disease progression and not necessarily the cause of it.

Based on the actual literature it remains unclear if a minimum amount of KMW is required for peri-implant health and stability, for such reasons, the aim of the present systematic review and meta-analysis was to answer the question of whether the lack of prespecified (2 mm) KMW is a risk factor for peri-implant disease.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

The present review was developed according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses"(PRISMA) [17] guidelines and the Cochrane Handbook [18]. Moreover, the review was registered on the online database PROSPERO (International prospective register of systematic reviews) with the registration number CRD42021233756.

2.2 | PECO question

The focused clinical question of this systematic review was formatted according to the PECO (Patient, Exposure, Comparison, Outcome) framework [19]: Does the presence of peri-implant keratinized mucosa width (KMW) contribute to peri-implant health and stability in adult human subjects?

- **Population:** Systemically healthy adult human subjects undergoing implant therapy.
- **Exposure:** The presence of <2 mm of KMW at the time of implant placement
- **Comparison:** The presence of ≥2 mm of KMW at the time of implant placement
- **Outcome:**
    1. Clinical: Implant survival rate, changes in probing depth (PD), soft tissue recession (REC), clinical attachment level (CAL), mean gingival index (mGI), mean plaque index (mPI), incidence of peri-implantitis (combined clinical and radiographic).
    2. Radiographic: Marginal bone loss (MBL).
    3. Patient-reported outcomes (PROMs): Assessment of brushing discomfort (immediately following toothbrushing)

2.3 | Eligibility Criteria

Selected clinical studies must have fulfilled the following inclusion: (i) randomized or non-randomized controlled or non-controlled clinical trials, (ii) at least 1 year of follow-up from restoration delivery, (iii) human subjects of ≥18 years of age, (IV) investigations evaluating the presence or absence of KMW as <2mm versus ≥2 mm (to enable data pooling).

The exclusion criteria were as follows: (i) case reports, case series, retrospective cohort and cross-sectional clinical studies; (ii) experimental in vivo, ex vivo and in vitro studies.

2.4 | Information sources and search strategies

A comprehensive and systematic electronic search was conducted using the National Library of Medicine (MEDLINE via PubMed), Scopus, Web of Science and the Medicine Grey Literature Report to identify articles that potentially satisfied the eligibility criteria. Supplementary Table 1 details of search strings were used in the selection process in each online database. The protocol for the bibliographic search comprised MESH terms and free text words combined through Boolean operators (AND, OR). The following combination of words was used ("dental implant" OR "dental implantation" OR "oral implant" OR "implant" OR "dental implants") AND ("gingival height" OR "tissue thickness" OR "tissue biotype" OR "tissue phenotype" OR "tissue width" OR "keratinized mucosa"). No search restriction was set regarding language of the article, publication date, or publication status.

A manual search through relevant scientific journals, namely: *Clinical Oral Implants Research, International Journal of Oral and Maxillofacial Implants, Journal of Implant Dentistry and Related Research, International Journal of Oral Implantology, European Journal of Oral Implantology, Journal of Dental Research , Implant Dentistry, Journal of Oral Implantology, Journal of Clinical Periodontology, Journal of Periodontology, International Journal of Periodontics and Restorative Dentistry, Journal of Oral and* Maxillofacial Surgery; was also conducted to ensure a thorough screening process. The bibliographies of pertinent review articles and all studies finally included for data extraction were also screened. When necessary, additional data was requested by emailing the corresponding author(s) of an investigation.

2.5 | Study selection and data collection

The titles and abstracts of the selected studies were evaluated in duplicate and independently by two reviewers (A.R. and V.C.A.C.). Studies determined to be eligible were included in the second round, during which all the full-text articles were thoroughly assessed. At the end of the second round, only studies fulfilling the eligibility criteria were included in the systematic review and underwent data extraction. Cases of disagreement were resolved by discussion in a joint session between the authors; a third author (G.T.) was responsible for calculating the screening inter-reviewer agreement which is described in the statistical analysis section of this manuscript. A pre-piloted data extraction spreadsheet was generated to collect pertinent data from the included studies. For each study, when applicable, the following data were extracted: first author, year of publication, country of the cohort, study design, observational period duration from implant placement, implant brand, total number of implants placed per study group, survival rate, brushing discomfort assessment, periodontal and radiographic parameters (i.e., CAL, PD, mPI, mGI, REC, MBL), type of prosthesis and implants, implant placement and loading protocols. In two cases of

missing data, the authors of the article were contacted. A response was received by one[20] and no response was received by the other[21].

2.6 | Risk of bias assessment

Risk of bias was assessed by two authors (V.C.A.C. and C.A.) independently; disagreements were resolved by open discussion and consensus. The non-randomized controlled trials (non-RCT) were assessed using the ROBINS-I tool [22]. The prospective cohort study were assessed using Newcastle-Ottawa scale [23]. The domains for each of the tools used are summarized in the appendix.

2.7 | Data synthesis and summary of findings

The data synthesis and summary of findings methodology – the latter evaluated via the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for each comparison between the study groups at the outcome level [24] – are summarized in the appendix. Briefly, regarding the pooled analysis, the mean differences (calculated as the difference between follow-up and baseline) of PD, mPI, MBL, and REC were extracted and entered in Review Manager version 5.4 (Cochrane Collaboration, 2014). Pooled mean differences (MD) and 95% confidence intervals (CI) were the outcomes analyzed for continuous outcomes. A fixed or random effects model was used based on the presence/absence of heterogeneity (I^2 > 50%). Differences between groups were analyzed using the inverse of variance test, setting a *P* value lower than .05 as the threshold of statistical significance.

3 | RESULTS

3.1 | Study selection

Following duplicate removal, a total of 1,264 records remained for screening by title and abstract. Results of the number of records obtained for each database is reported in Supplementary Table 1. A total of 26 articles were then considered for full-text screening. Finally, 9 studies fulfilled the eligibility criteria and were selected for data extraction [7,20,21,25-30]. The reasons due to 17 articles were excluded are summarized in Figure 1 and Supplementary Table 2. Kappa scores for inter-examiner agreement for title and abstract review as well as full-text review were 0.85 and 0.87, respectively. The flowchart of the entire selection process is reported on Figure 1.

3.2 | Characteristics of the included studies

3.2.1 | Study design

Five of the studies were prospective cohort studies [7,21,25,28,29], 3 were non-RCTs [26,27,30] and 1 was an RCT [20]. Seven studies were carried out solely in academic settings [20,21,26-30], while the remaining 2 were conducted

in both academic and private practice settings [7,25]. All but one of the studies [7] were single-centered clinical trials. All the studies included as participants patients undergoing dental implant therapy in which the experimental intervention included implant positioning in keratinized mucosa characterized by a width cut-off point of 2 mm.

3.2.2 | Clinical scenarios

Recipient arch distribution and characteristics varied between the included studies (Table 1). Four studies reported having only mandibular implants [7,20,26,29] and 4 studies reported having both maxillary and mandibular implants [21,25,27,30]. One study did not report the location of implant placement [28].

Three studies included partially edentulous arches only [27,28,30], 4 included completely edentulous arches exclusively [7,20,26,29] and 1 study involved the treatment of both partially and completely edentulous arches [25].

3.2.3 | Treatment approaches/interventions

Detailed information regarding the type of implants and prostheses included, as well as the type of implant placement and prosthesis loading protocols employed are described in Table 1.

3.2.4 | Observational periods

The follow-up period ranged between 1 and 5 years (Table 1). One study reported a 1-year follow-up period [26], 1 study reported a 2-year follow-up period [25], 2 studies reported a 4-year follow-up [27,30], 1 study reported a 4.5-year follow-up period [28] and 4 studies reported a 5-year follow-up period [7,20,21,29].

3.3 | Quality of the evidence and risk of bias assessment

Results of risk of bias assessment according to the specific assessment tools of included studies are collected in Supplementary Table 3 and Supplementary Table 4. When considering the non-randomized included studies, three studies reported low risk of bias[20,27,31], while the studies by Lim et al. and Perussolo et al. were considered respectively at moderate and high risk of bias[21,30], respectively. Finally, half of the prospective cohort studies demonstrated low risk of bias [7,29], while two studies [25,28] demonstrated high risk of bias.

The GRADE ratings pertaining to the outcome-centered quality of the evidence and pooled summary estimates (where applicable) have been outlined in the summary of findings table (Table 3). The overall quality concerning comparisons between interventions for the assessed outcomes of interest ranged between very low (REC) and low (MBL and PD) quality of evidence.

Briefly, the analysis of the level of quality of evidence found by the GRADE tool indicated that there is low quality evidence to support that the presence of < 2 KMW is associated with either increased MBL or peri-

implant PD and very low-quality evidence to support that the presence of < 2 KMW is associated with increased REC (Table 3).

3.4 | Quantitative assessment of outcomes

Four publications [20,27,29,30] were statistically comparable and were included for quantitative synthesis. Quantitative data of the studies is shown in Table 2. Overall, 685 implants were analyzed (178 in the KMW <2 mm group, 507 in the KMW ≥2 mm group).

3.4.1 | Meta-analysis and TSA for the outcome marginal bone loss (MBL)

Two studies [20,30] including a total of 257 implants (103 with KMW < 2mm and 154 with KMW ≥ 2mm) were entered in meta-analysis for MBL. The pooled MD and 95% CI showed a lower MBL rate when a higher KMW (≥ 2mm) was present: MD = 0.17 mm (95% CI: [0.01, 0.32]); such findings were statistically significant (overall effect p-value = 0.03) in the absence of heterogeneity (I^2 = 0%) (Figure 2A). However, such results were not confirmed after adjusting for types 1 and 2 errors in TSA; the absence of statistical significance in TSA can also be graphically noticed on Figure 2B since the z-curve (blue line) crosses only the conventional threshold (horizontal dark red line) but not the trial sequential boundary (red inclined line). TSA also showed as such findings were underpowered since the number of included implants (274) were lower than the calculated RIS of 424 implants.

3.4.2 | Meta-analysis and TSA for the outcome probing depth (PD) reduction

Three studies [27,29,30] including a total of 430 implants (265 with KMW ≥ 2mm and 165 with KMW < 2mm) were entered in meta-analysis for PD reduction. The pooled MD and 95% CI at fixed-effect model, showed the absence of a statistically significant difference (overall effect p-value = 0.55) in PD reduction when a wider KMW (≥ 2mm) was present: MD = 0.03 mm (95% CI: [-0.08, 0.15]); such results were characterized by a low rate of heterogeneity (I^2 = 35%) (Figure 2C). Such findings were also confirmed after adjusting for types 1 and 2 errors in TSA, the absence of statistically significance results is also graphically shown on Figure 2D since the final value of z-curve (blue line) didn't cross both the conventional threshold (horizontal dark red line) and the trial sequential boundary (red inclined line). Results are also characterized by a very low power of evidence since the number of included implants (430) is lower than the calculated RIS of 2171 implants.

3.4.3 | Meta-analysis and TSA for the soft tissue recession (REC)

Two studies [20,27] including a total of 219 implants (52 with KMW ≥ 2mm and 167 with KMW < 2mm) were entered in meta-analysis for soft tissue recession. The pooled MD and 95% at random-effect model, showed the absence of a statistically significant difference (overall effect p-value = 0.39) in soft tissue

recession when a wider KMW (≥ 2mm) was present: MD = 0.35 mm (95% CI: [-0.45, 1.15]); such results were characterized by a high rate of heterogeneity (I^2 = 92%) (Figure 3A). They were also confirmed after adjusting for types 1 and 2 errors in TSA, the absence of statistically significance results is also graphically shown on Figure 3B since the final value of z-curve (blue line) was lower of both the conventional threshold (horizontal dark red line) and the trial sequential boundary (red inclined line). Such findings are characterized by a very low power of evidence since the number of included implants (430) is lower than the calculated RIS of 2525 implants.

3.4.4 | Meta-analysis and TSA for the outcome mean plaque index (mPI)

Three studies [27,29,30] including a total of 430 implants (265 with KMW ≥ 2mm and 165 with KMW < 2mm) were entered in meta-analysis for mPI. The pooled MD and 95% CI showed a statistically significant difference (overall effect p-value < 0.001) in mPI when a wider KMW (≥ 2mm) was present: MD = 0.37 (95% CI: [0.16, 0.58]); such results were characterized by a high rate of heterogeneity (I^2 = 84%) (Figure 3C). They were also confirmed after adjusting for types 1 and 2 errors in TSA, the statistically significance of results is also graphically shown on Figure 3D since the final value of z-curve (blue line) crosses both the conventional threshold (horizontal dark red line) and the trial sequential boundary (red inclined line). Such findings are characterized by a good power of evidence since the number of included implants (430) overcome the calculated RIS of 310 implants.

3.4.5 | Meta-analysis and TSA for the outcomes: Implant survival rate, CAL, GI and incidence of peri-implantitis

Comparable articles concerning these four variables were not found, and quantitative analysis were not performed.

3.4.6 | Brushing discomfort assessment

One study assessed the brushing discomfort in both clinical scenarios [30]. VAS scores at 4 years of follow-up showed that the level of discomfort experienced was higher for patients with KMW <2 mm (mean 12.28 ± 17.59; median 2.0 [range 0–56]), than in patients with KMW ≥2 mm (mean 4.25 ± 8.39; median 0.0 [range 0–36]). At both baseline and the 4-year follow-up, most patients with KM≥2 reported no discomfort while 51.4% of patients with KM<2 mm reported some level of discomfort.

4 | DISCUSSION

4.1 | Summary of main findings

The aim of this systematic review was to assess whether and to what extent - the need for KMW to achieve and maintain peri-implant health. Although this issue has been somehow answered under the umbrella of

peri-implant soft tissue augmentation procedures, however, the level of evidence has not been ideal. Interestingly, the data from this systematic review and meta-analysis demonstrated that implant sites with KMW ≥2 mm were statistically comparable to implant sites with KMW <2 mm in terms of MBL (after adjusting for both types 1 and 2 error in TSA), REC and PD. Also, a lack of KMW was showed to be related to increased mPI and more discomfort after brushing.

4.2 | Level of evidence for KMW as a risk factor

The present study conducted the analysis using the GRADE assessment to observe the strength of recommendation for the results of the current review. Overall, the outcome-centered quality of the evidence was determined to be low for the findings associated with MBL and PD. As for mPI and REC, the associated quality of the evidence was determined to be very low. Based on our focused question (i.e., does the presence of peri-implant KMW contribute to peri-implant health and stability in adult human subjects?) and the studies assessed, the indirectness domain was determined to be at a serious risk of bias, since at least one of these sources was detected for each assessed parameter. Inconsistency was evaluated according to values of heterogeneity (I^2), and a high heterogeneity was obtained between the studies in terms of study design, treatment approach, timing of assessment etc., setting the inconsistency domain at a serious risk of bias for the mPI and a very serious risk of bias for tissue REC. The imprecision domain was assessed from the sample size and its confidence intervals, which did not reveal a serious risk of bias. For the risk of publication bias, it is indicated that an extensive literature search including the grey literature to be performed to avoid an under- or an over-estimation of the beneficial or harmful effect due to the selective publication of studies [32]. Since that was performed in the present review without restriction regarding date of publication and language, a low risk of publication bias was detected in the current study. As for the use of a funnel plot to assess this type of bias, due to the limited number of studies included in the meta-analysis (n=4), this could not be properly evaluated.

4.3 | Agreements and disagreements with previous findings

4.3.1 | Does <2mm of peri-implant KMW have an influence on interproximal bone level?

There is an absence of robust data in the literature to support the increased risk for MBL at implant sites with <2mm, so-called “inadequate”, KMW. A longitudinal study revealed no differences in MBL between “adequate” and “inadequate” KMW [27]. Two of the studies in this review failed to demonstrate a clinically significant difference [20,30]. The experimental study utilizing ligature-induced plaque accumulation in implants bordered by KM supports the same conclusion [33]. Conversely, a systematic review reported that soft tissue augmentation procedures for gain of MT and/or KMW resulted in significantly different interproximal MBL favoring soft tissue grafting over time [4]. However, the reported difference cannot be considered clinically significant (a 0.11 to 0.18 mm difference between test and control) and based on the

pooled data of 2 to 4 studies. The one soft tissue parameter that seems play a more significant role in minimizing MBL is the peri-implant STH[1]. This was first demonstrated in an experimental canine model[34]. Later on, studies have demonstrated that this tissue dimension plays an important role in reducing MBL [35,36].

4.3.2 | Does < 2mm of KM at implant sites influence peri-implant probing depth?

The 2017 world workshop on periodontal and peri-implant diseases and conditions identified the PD increase as one of the key parameters for establishing a diagnosis of peri-implantitis [37]. Clinically, the progression of the peri-implant condition from peri-implant mucositis to peri-implantitis was most associated with increase PD and BOP values [38]. One study has shown increased PD at baseline was a positive predictor for the amount of early REC expected to ensue [25]. As for the relationship between KMW and PD, this review identified no increase in PD (0.03 mm) associated with sites of KMW <2 mm. This is in agreement with the evidence available[39]. Even studies that have correlated increased PI and GI with no KMW failed to identify a similar correlation with PD [26].

While finding from a recent network meta-analysis indirectly suggests that KMW augmentation results in significant PD reduction (0.78 mm) [40], such findings are to be interpreted with caution. This due to the authors reporting significant increase in KMW with all apically positioned flap (APF) based procedures. However, significant PD reduction is only reported with APF plus a graft material and only non-significant PD reduction (0.56 mm) is reported when both APF alone and APF plus a graft are grouped into the analysis. And while KMW is increased with the APF alone treatment approach, significant PD reduction is not observed with this treatment arm. This raises the speculation of whether the PD reduction is a function of KMW increase as reported by the authors or predominantly a function of increase in MT. This speculation is further supported by Thoma and coworkers, who report significantly lower PD values favoring APF plus autogenous tissue versus APF alone [4].

4.3.4 | Does < 2mm of KM at implant sites have an influence on tissue recession?

This review included 2 prospective longitudinal studies that investigated the potential effect of KMW on REC. The magnitude of REC was not significantly different between implant sites with or without "adequate" KMW. It has been reported that the lack of KMW was a poor predictor of peri-implant REC [25]. Roccuzzo et al. (2016) comparing implants with keratinized mucosa versus those with alveolar mucosa reported that REC was significantly more likely at implants with a lack of KMW[41]. Also, the 3rd EAO Consensus Conference (2012) found that all the studies that showed REC at implant sites with KMW <2 mm exhibited REC exclusively within the first 6 to 12 months of the 2 to 5 years follow-up, supporting the tissue remodeling concept. This may refute the perception that KMW influences REC of peri-implant tissues.

4.3.5 | Does < 2mm of KM at implant sites influence the performance of oral hygiene measures?

The longitudinal studies included in this review showed significant difference in mPI between implants with KMW <2 mm and ≥2 mm. The presence of KMW results in a more stable seal around the implant which enhances the plaque removal by self-performed oral hygiene practices [42]. This study also observed that implant sites with KMW <2 mm had significantly higher mPI scores than sites with KMW ≥ 2 mm [42]. A possible explanation for these findings could be: 1) the presence of a shallow vestibule prevents adequate access when KMW is absent and 2) the increased discomfort when toothbrushing a site with a lack of KM.

4.3.6 | Is 2 mm the correct KMW cutoff?

For this review, the 2-mm cutoff was determined when devising the eligibility criteria after thorough study of the current literature to maximize the likelihood of conducting a quantitative analysis of the data. However, although 2 mm has been the most utilized cutoff number for research, this remains an arbitrarily determined value that may not be as flexible with the multi-faceted composition of peri-implant health and disease as necessary. With little supporting this value as the true cutoff versus other potential cutoff points, it may be theorized that the minimum amount of KMW necessary to maintain pristine peri-implant health is dependent on the other site-specific characteristics of an individual case such as MT, STH, peri-implant bone thickness, PD and superstructure design.

4.4 | Strengths, weaknesses, and limitations

One of the main strengths of the present study is the eligibility restriction to longitudinal prospective study designs, which are the only studies capable of establishing a risk factor. It may be argued that this is a limitation due to prospective studies being characterized by shorter term results, and pathologic bone loss with subsequent increased PD and REC will need significant time to occur. However, the 4 studies included in the quantitative synthesis had a follow-up ranging from 4 to 5 years. Furthermore, the lack of power due to the limited number of prospective studies may be considered a limitation. Nonetheless, with one of the primary goals of the present investigation being the assessment of whether the lack/insufficiency of KMW can be considered a risk factor for peri-implant disease, knowledge of the lack of sound and homogenous evidence coming from longitudinal study design is a key finding that sheds light on the need for a particular study design. As aforementioned, cross-sectional studies fail to represent causal relationships between variables, and longitudinal study designs are necessary. This is not to say that the present investigation illustrates that KM is not important for peri-implant health, as there is a great deal of empirical evidence firsthand and in the literature from which the importance of KM can be drawn. However, a higher quality of evidence is necessary if we are to (1) confidently determine the extent to which KM could be considered a risk factor for peri-implant disease and (2) determine a less arbitrary and more precise, well-evidenced KMW cut-off value.

Another weakness of the present article is that publication bias could not be properly evaluated because of the limited number of studies included in the meta-analysis (n = 4). It is noteworthy to mention that this systematic review and meta-analysis is not investigating the influence of KMW following soft tissue augmentation procedures. This is critical because as previously mentioned, other site-specific characteristics, such as most notably the phenotype modification, may simultaneously play an indiscernible synergistic or masking role in the outcomes. Other limitation of the study is the inability (due to the nature of the available data) to discriminate through analysis the difference between machined and roughened implant surfaces. This is clinically relevant due to the difference in plaque accumulation between the two types of implant surfaces. Finally, there was a discrepancy in implant therapy protocol and this contributes to the heterogeneity of the data, further warranting new homogenous evidence.

5 | CONCLUSION

Based on the quantitative analysis, implants associated with <2 mm KMW did not exhibit increased MBL, REC and PD compared to implants with ≥2 mm KMW. Peri-implant KMW <2 mm was associated with increased mPI and more discomfort after toothbrushing. Low level of evidence was determined for the findings related to the outcome measures PD, mPI and MBL, and very low level of evidence was determined for the findings related to the outcome measures REC, CAL and PROMs. The level of evidence regarding implant survival rate and incidence of peri-implantitis could not be determined due to data scarcity. The present review does not deem the presence of KM inessential for peri-implant health, but that the quality of evidence supporting KM as a risk factor for peri-implant disease and the 2-mm cut-off point used in the literature is low at best.

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Tables and Figures Legends

Tables

Table 1: Characteristics and qualitative data of the included studies.

Table 2 Quantitative data of the included studies.

Table 3: Summary of findings table with the GRADE approach quality of the evidence assessment.

Supplementary Table 1: Details of search strings used in the selection process in each online database.

Supplementary Table 2: List of excluded studies with the pertinent reasons for exclusion.

Supplementary Table 3: Risk of bias of included prospective cohort studies.

Supplementary Table 4: Risk of bias of included non-RCTs.

Figures

Figure 1: PRISMA flowchart of the selection process.

Figure 2: Meta-analysis (A) and trial sequential analysis (B) of marginal bone loss; meta-analysis (C) and trial Sequential Analysis (D) of probing depth change.

Figure 3: Meta-analysis (A) and trial sequential analysis (B) of soft tissue recession; meta-analysis (C) and trial sequential analysis (D) of mean plaque index.

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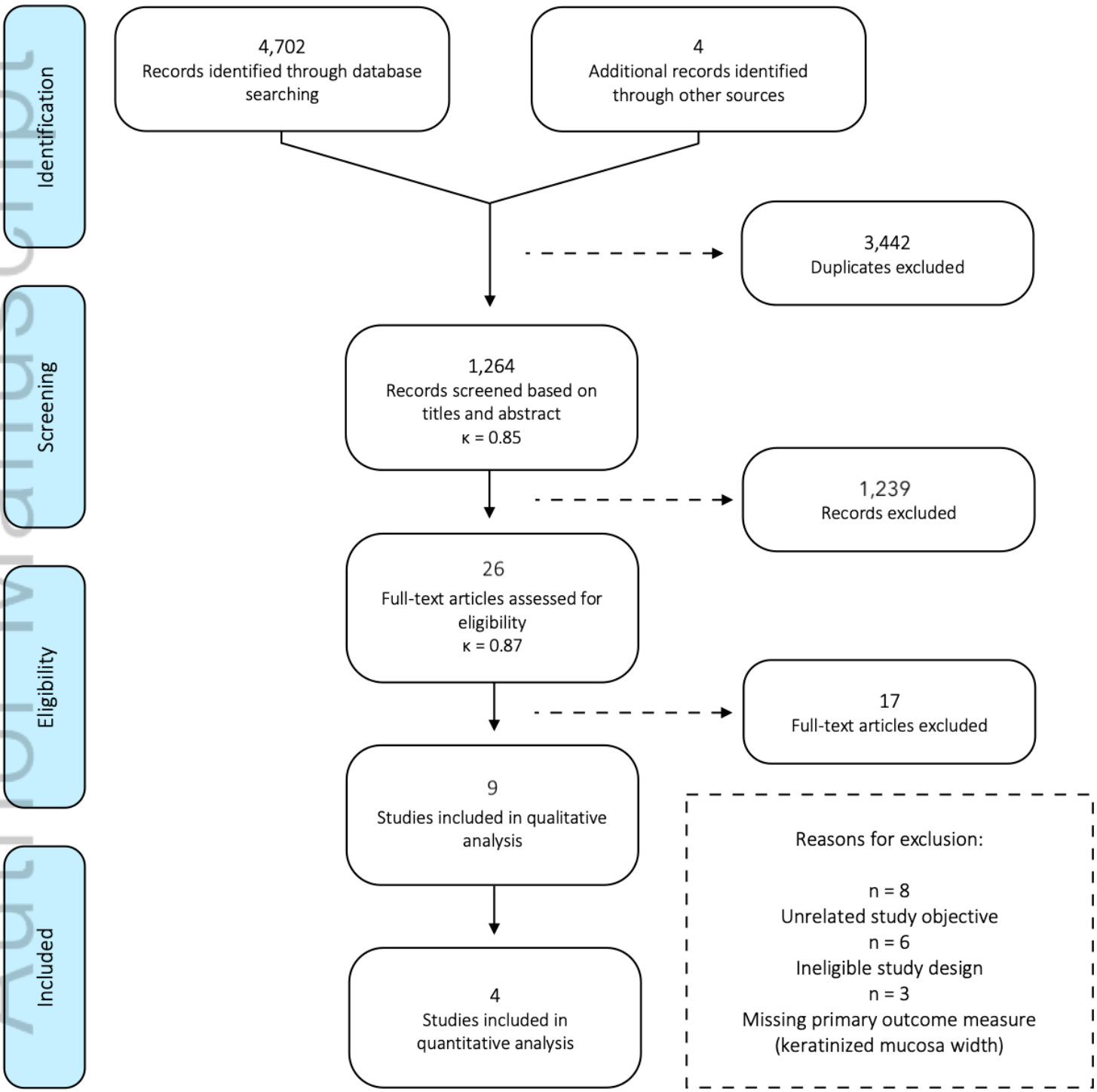

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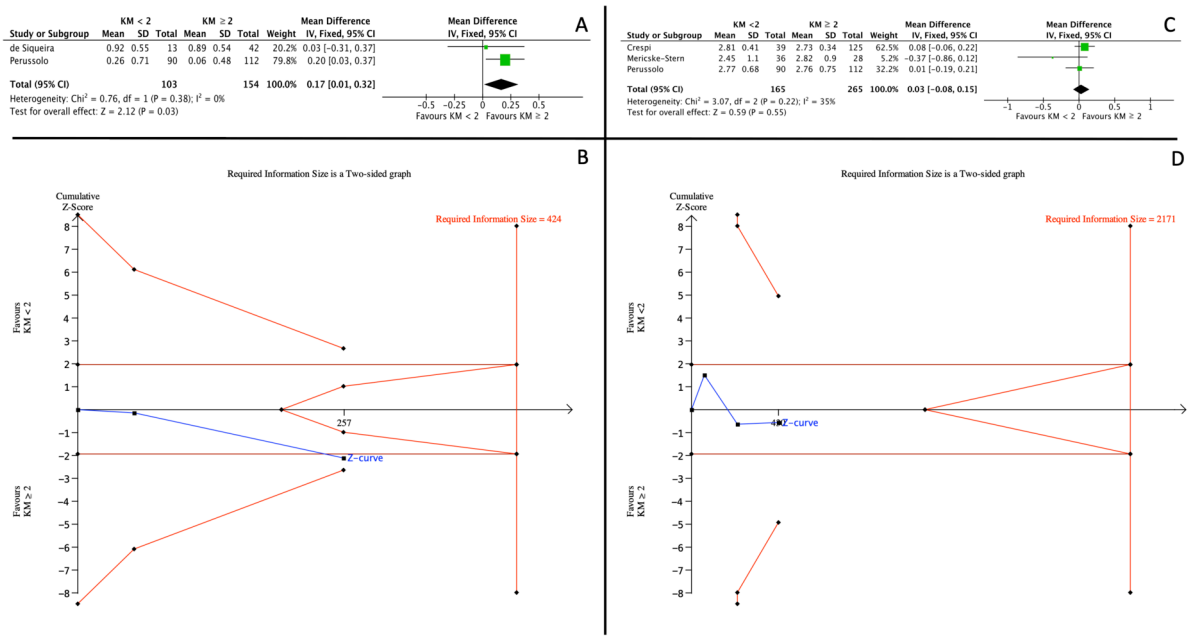

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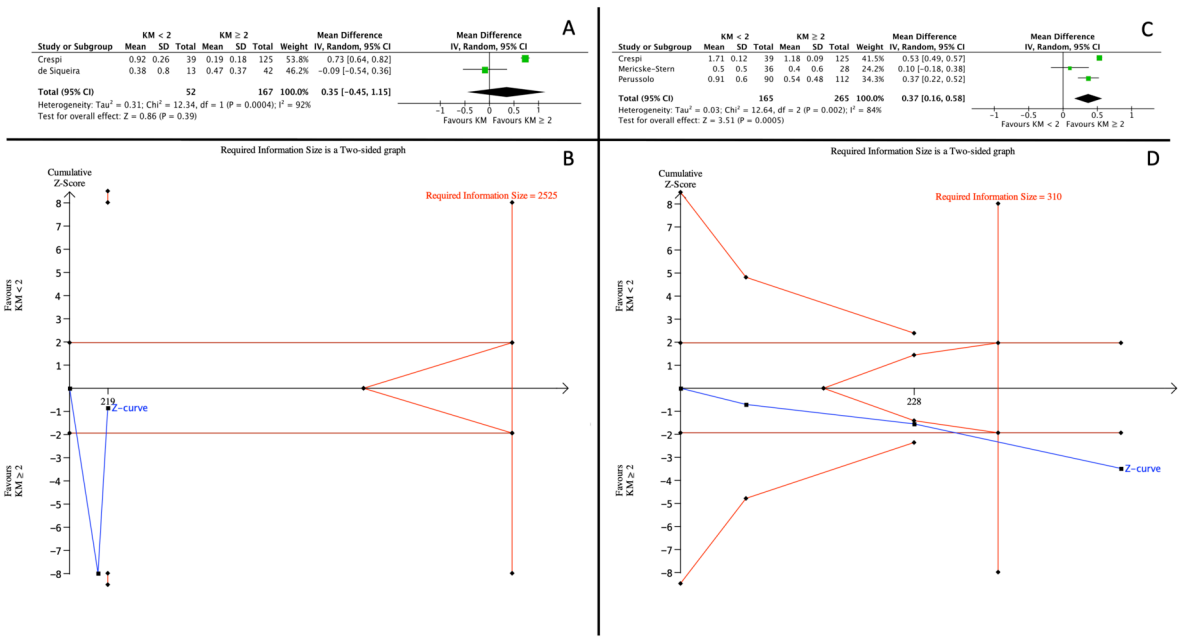

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Supplementary Table 2: List of excluded studies with the pertinent reasons for exclusion.

(Bhat, Thakur et al. 2015)	The comparison is made on soft tissue thickness
(Bittner, Schulze-Späte et al. 2019)	The comparison is made on soft tissue thickness
(Blanco, Pico et al. 2018)	Not related to the topic
(Bonino, Steffensen et al. 2018)	Not related to the topic
(Botticelli, Renzi et al. 2008)	Not optimal for the assessment
(ElSyad, Denewar et al. 2018)	Not related to the topic
(Garaicoa-Pazmino, Mendonça et al. 2020)	The comparison is made based on soft tissue thickness
(Gallucci, Doughtie et al. 2009)	Not optimal for the assessment
(Hof, Tepper et al. 2014)	Not optimal for the assessment (retrospective)
(Kim, Kim et al. 2009)	Not optimal for the assessment (retrospective)
(Linkevicius, Linkevicius et al. 2018)	Not related to the topic
(Mameno, Wada et al. 2019)	Not optimal for the assessment
(Radaelli, Federizzi et al. 2020)	Not related to the topic
(Romanos, Grizas et al. 2015)	Not related to the topic
(Roos-Jansaker, Renvert et al. 2006)	Not optimal for the assessment (retrospective)
(Schmidt, Auschill et al. 2019)	Not related to the topic
(Schwarz, Becker et al. 2018)	Not optimal for the assessment (retrospective)
(Shimomoto, Nakano et al. 2020)	Not optimal for the assessment
(Souza, Tormena et al. 2016)	Not optimal for the assessment (retrospective)
(Sukuroglu and Baltacioglu 2019)	Not related to the topic
(Weber, Kim et al. 2006)	Not optimal for the assessment

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	Bengazi et al. 1996	Boynueğri et al. 2013	Crespi et al. 2010	de Siqueira et al. 2020	Mericke-Stern et al. 1994	Fernandes-Costa et al. 2019	Perussolo et al. 2018	Schrott et al. 2009
Study design	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal	Randomized controlled trial	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal
Country	Sweden	Turkey	Italy	Brazil	Switzerland	Brazil	Brazil	Germany
Setting	University + Private practice	University	University	University	University	University	University	University + Private practice
Follow-up (years)	2	1	4	5	5	4,5	4	5
Dropouts (patient)	1	0	0	0	6	12	26	15
Site of implant placement	Maxilla + mandible	Mandible	Maxilla + mandible	Mandible	Mandible	NR	Maxilla + Mandible	Mandible
Number Patients/implants	40/158	15/36	29/164	11/55	33/66	38/131	54/202	58/307
Mean age(Range)	55 (NR)	54 (NR)	49.5 (NR)	NR (45-65)	69 (50-82)	62.9 (37-78)	55.7 (NR)	58 (34-78)
Comparison	Recession	Plaque index, Gingival index, Probing depth, Bleeding on probing, IL-1β, TNF-α, PICF volume	Gingival index, Modified plaque index, Modified bleeding index, Probing depth, Gingival recession	Probing depth, Crestal bone loss, Soft tissue recession	Plaque index, Bleeding index, Probing depth, Level of attachment	Probing depth, Bleeding on Probing	Mean plaque index, Bleeding on probing, Probing depth, Clinical attachment	Plaque index, Mean bleeding index, distance between the implant shoulder to the peri-implant mucosa
Implant brand	Branemark	Straumann	NR	TitaMax CM	Straumann	NR	NR	Straumann
Survival Rate	97%	NR	100%	100%	97%	NR	98%	NR

	Number of implants	KMW<2	NR	17	39	13	36	NR	90	40
		KMW>2	NR	19	125	42	28	NR	112	346
	Years of loading		2	1	4	5	4,5	5	4	5
	Type of prosthetics		Partial and full-arch	Overdentures in edentulous mandible	Partial in the anterior jaw regions	Mandibular full-arch in complete edentulous	Mandibular overdentures	NR	Partial maxillary and mandibular	Full-arch mandibles
	One or two stage treatment protocol		NR	NR	NR	NR	One stage	NR	NR	NR
	Placement protocol		NR	Delayed placement	Immediate placement	NR	NR	NR	NR	NR
	Loading protocol		Delayed	Delayed	Immediate	Immediate	Delayed	NR	NR	Delayed

NR: not reported
KMW: keratinized mucosa width

Author (year/country)	Results
Bengazi, (1996, Italy & Sweden)	Baseline variables — Multiple regression with ΔREC: baseline-2 years as the dependent variable Estimate — Sign Lingual 0.792 P<0.001 Probing depth 0.279 P<0.001 Mandible 0.786 P<0.01 Female 0.533 P<0.01 Width of keratinized mucosa -0.084 ns Tissue mobility -0.047 ns
Boynuegri (2013, Turkey)	Bl — P value — 1yr — Pvalue PI KM<2 0.283 ± 0.376 0.00 (0.00–1.00) (NS) 0.583 ± 0.532 0.50** (0.00–1.75) <0.05 KM ≥2 0.120 ± 0.194 0.00 (0.00–0.75) 0.250 ± 0.486 0.50** (0.00–1.50) GI KM<2 0.375 ± 0.404 0.25 (0.00–1.25) <0.05 0.583 ± 0.595 0.50 (0.00–1.25) <0.05 KM ≥2 0.075 ± 0.148 0.00 (0.00–0.50) 0.067 ± 0.258 0.00 (0.00–1.00) BoP KM<2 0.500 ± 0.310 0.50 (0.00–1.00) NS 0.392 ± 0.356 0.50 (0.00–1.00) NS KM ≥2 0.258 ± 0.252 0.25 (0.00–0.75) 0.241 ± 0.304 0.13+ (0.00–1.00)
Crespi (2010), Italy	Width of keratinized mucosa at baseline (buccal sites) <2 mm — ≥2mm — Sign. Plaque index 1.7 1.2 P<0.01 Bleeding index 0.8 0.5 P<0.01 Gingival index 1.0 0.7 P<0.01 Probing depth 2.8 mm 2.7 mm ns Bone level 1.0 mm 0.9 mm ns Δrecession 1.3 mm 0.2 mm P<0.01
de Siqueira, (2020), Brazil	Width of keratinized mucosa at baseline <2 mm — ≥2 mm Marginal bone loss 0.915±0.551 0.895±0.538 Soft tissue recession (at buccal and lingual sites) 0.38 ± 0.80 0.47 ±0.37 Soft tissue recession (at mesial and distal sites) -0.01±0.67 0.20±0.45 Soft tissue recession for two levels of vertical mucosa thickness (MT) at the 4- 8-month and 60 months evaluation evaluations Vertical mucosa thickness >2mm — Vertical mucosa thickness <2 mm Implant surface Time Mean+SD Median(Min;Max) Mean+SD Median(Min;Max) Pvalue Buccal and lingual T4 0.29±0.28 0.30(-0.25;0.75) 0.50±0.41 0.50 (-0.17;1.25) .445

		T8	0.41±0.41	0.25(-0.13;1.25)	0.50±0.44	0.50 (-0.17;1.20)
		T60	1.13±0.41	1.00(0.50;2.00)	1.07 ± 0.50	1.00 (0.50; 3.00)
	Mesial and distal	T4	0.25 ± 0.37	0.13 (−0.20; 0.81)	0.46 ± 0.55	0.25 (−0.17; 1.50) 0.485
		T8	0.19±0.41	0.25 (−0.50; 0.75)	0.39 ± 0.51	0.42 (−0.10; 1.50)
		T60	1.22 ± 0.35	1.00 (0.75; 2.00)	1.25 ± 0.51	1.00 (0.50; 3.00)

Fernandes-Costa, (2019), Brazil

	PD				BoP			
	Worsening	Improvement	RR (CI 95%)	P	Worsening	Improvement	RR(CI 95%)	P
<2 mm	18(50.0)	18(50.0)	0.94(0.61-1.44)	.934	16(44.4)	20(55.6)	0.80(0.51-1.25)	.435
>2 mm	23(53.5)	20(46.5)			24(55.8)	19(44.2)		

Mericske-Stern, (1994), Switzerland

Year 5	Width of keratinized mucosa					
	Buccal sites		Sign.	Lingual sites		Sign.
	<2 mm	≥2mm		<2 mm	>2 mm	
Plaque index	0.5	0.4	ns	0.5	0.7	ns
Bleeding index	0.2	0.1	ns	0.2	0.4	ns
PD	2.5 mm	2.8 mm	ns	2.9 mm	3.1 mm	ns
Attachment level	3.2 mm	3.3 mm	ns	3.7 mm	3.2 mm	P<0.05

Perussolo (2018),Brazil

Width of keratinized mucosa

	Bl			4 years		
	≥2 mm	<2mm	P value	≥2 mm	<2 mm	P value
mPI	0.45±0.55	0.83±0.92	0.008	0.54±0.48	0.91±0.60	0.002
BoP	0.44±0.27	0.55±0.19	0.039	0.56±0.26	0.67±0.21	0.026
PD (mm)	2.43±0.77	2.30±0.52	0.188	2.76±0.75	2.77±0.68	0.395
CAL (mm)	2.56±0.77	2.64±0.61	0.325	2.94±0.80	3.09±0.81	0.319
Frequency distribution (%) of plaque index score						
0	66.1	48.3	<0.0001	51.5	37.1	0.002
1	26.1	35.6	0.551	38.8	43.8	0.543
2	7.6	15.4	0.116	8.5	15.7	0.217
3	0.3	0.7	0.593	1.2	3.4	0.319

Radiographic marginal Bone loss

	≥2 mm	<2 mm	Bone loss	≥2 mm	<2 mm	Bone loss
Mean	1.82±0.75	1.84±0.83	0.06±0.48	1.87±0.77	2.11±1.13	0.26±0.71
Distal	1.85±0.81	1.89±0.89	0.06±0.55	1.91±0.80	2.15±1.23	0.26±0.76
Mesial	1.79±0.79	1.80±0.85	0.05±0.54	1.84±0.84	2.08±1.10	0.27±0.76

Schrott (2009), USA	Year 5	Width of keratinized mucosa at baseline					
		Buccal sites			Lingual sites		
		<2 mm	≥2 mm	Sign.	<2 mm	≥2 mm	Sign.
	Plaque index	0.2	0.3	ns	0.7	0.4	P<0.001
	Bleeding index	0.1	0.1	ns	0.2	0.1	P<0.05
	Δ recession	0.2	0.1	ns	-	-	-

Table 2 Quantitative data of the included studies

PD: Pocked depth
BoP:Bleeding on probing
CAL: clinical attachment level
PI: Plaque index
NS: non specified

Keratinized mucosa width around dental implants

Population: **Systemically healthy adult human subjects undergoing implant therapy.**
Exposure: **The presence of <2 mm of keratinized mucosa width at the time of implant placement**
Comparison: **The presence of ≥2 mm of keratinized mucosa width at the time of implant placement**

Outcomes	Summary Estimates (WMD [95% CI] *P* value)	Favors	Heterogeneity (*I2*; %)	No of Participants/ Implants (studies)	Quality of the Evidence (GRADE)[a, b]	Comments
Changes in probing depth	0.03 mm (95% CI: [-0.08, 0.15])	KMW (≥ 2mm)	35%	430 (3)	⊕⊕◯◯ LOW	Overall, the included studies were found to have no serious risk of bias, inconsistency*, or imprecision**. Indirectness was found to be serious.
Soft tissue recession	0.35 mm (95% CI: [-0.45, 1.15])	KMW (≥ 2mm)	92%	219 (2)	⊕◯◯◯ VERY LOW	Overall, the included studies were found to have no serious risk of bias. Inconsistency, imprecision, and Indirectness were found to be serious.
Mean Plaque index	0.37 (95% CI: [0.16, 0.58])	KMW (≥ 2mm)	84%	430 (3)	⊕⊕◯◯ LOW	Overall, the included studies were found to have no serious risk of bias or imprecision. Inconsistency and Indirectness were found to be serious.
Radiographic MBL	0.17 mm (95% CI: [0.01, 0.32])	KMW (≥ 2mm)	0%	257 (2)	⊕⊕◯◯ LOW	Overall, the included studies were found to have no serious risk of bias, inconsistency, or imprecision. Indirectness was found to be serious.
PROMS [c]	See comment	NA	NA	202 (1)	⊕◯◯◯ VERY LOW	One study assessed the brushing discomfort in both clinical scenarios (Perussolo et al., 2018). VAS scores at 4 years of follow-up showed that the level of discomfort experienced was higher for patients with KMW<2 mm (mean 12.28 ± 17.59; median 2.0 [range 0–56]), than in patients with KMW ≥2 mm (mean 4.25 ± 8.39; median 0.0 [range 0–36]). At both baseline and the 4-year follow-up, most patients with KM>2 reported no discomfort while 51.4% of patients with KM<2 mm reported some level of discomfort.
Implant survival rate [c]	See comment	NA	NA	NA	NA	-
Clinical attachment level [c]	See comment	NA	NA	64 (1)	⊕◯◯◯ VERY LOW	One study (Mericske-Stern et al. 1994) assessed clinical attachment level (mm) in both scenarios. At 2 and 4 years, CAL was found to be less in the group with KMW ≥2 mm but without either clinical or statistical significance. CAL at 2 years was 2.56±0.77 (KMW ≥2 mm); 2.64±0.61 (KMW<2 mm) (p= 0.325). CAL at 4 years was 2.94±0.80 (KMW ≥2 mm); 3.09±0.81 (KMW ≥2) mm), (p=0.319).

Abbreviations: CI, Confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MBL, Marginal bone level; NA, Not applicable; PROMs, Patient-reported outcome measures; VAS, Visual analogue scale; WMD, Weighted mean difference.

GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.

[a]The GRADE level was changed as follows:

Certainty in the evidence downgraded by 1 level due to serious inconsistency.

Certainty in the evidence downgraded by 2 levels due to very serious inconsistency.

Certainty in the evidence downgraded by 1 level due to serious imprecision.

[*] The inconsistency was defined by the high value of I^2.

[**] The imprecision was defined by confidence interval.

[b]Based on the authors reporting no publication bias

[c]The number of studies were insufficient to preform analysis.