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Risk factors associated with the bone loss around implants and development of peri-implantitis

Factores de riesgo asociados con la perdida ósea marginal alrededor del implante y con el desarrollo de la periimplantitis

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DECLARATION OF AUTHENTICITY

The investigative work that is exhibited in the following Doctoral Thesis, titled ***"Risk factors for peri-implant marginal bone loss and incident peri-implantitis,"*** was carried out by the doctoral candidate, Andrea Ravidà DDS MS, under our direction and guidance.

Once this work has been revised and redacted, it is suitable for being presented and allowing the doctoral candidate to aspire to the title of Philosophy Doctor (PhD) before the Tribunal he designates.

We also guarantee that co-authors of the four publications have agreed in writing to let these publications be included in the Candidate's thesis work.

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To my grandfather, Claudio, my great example of honesty and ethics,

and to my grandmother, Adelaide, the greatest love of my life.

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CONTENTS

ABSTRACT

Objectives:

The objective of this project is to make up the basis for this work examine the roles of various factors in marginal bone loss (MBL) around implants and in the development of Peri-implantitis (PI) in a variety of clinical scenarios and populations. A multitude of parameters related to the implant and to the patient were assessed.

Materials and Methods

One meta-analysis and three retrospective studies gathering long term data acquired from the physical and electronic charts of patients at the university of the dental school of the university Michigan and University of Granada school of dentistry were performed. In study #1, 165 partially edentulous adults (77 men, 88 women) aged 30–91 with ≥2 years of follow-up upon implant restoration were included. Implants with ≥1 interproximal thread exposed (no bone-to-implant contact) (n = 98, 35%) constituted the test group and those without exposed threads (n =182, 65%) the control group. Descriptive, binary, and multivariate regression analyses were evaluated for goodness of fit. Wald tests were used to evaluate for significance set at 0.05. In study #2 retrospective analysis of patients with a history of periodontitis (PR) who received nonsurgical and, if indicated, surgical corrective therapy prior to implant placement was performed. Periodontitis stage and grade were determined for each included patient based on data from the time of initiation of active periodontal therapy. Cox Proportional Hazard Frailty models were built to analyze the correlation between stage and grade of periodontitis at baseline with implant failure, as well as occurrence and severity of PI. In study #3, A retrospective cohort study was designed to evaluate the 5-year MBL results of OsseoSpeedTM Astra Tech TX implants with internal tapered conical connection. Age, gender, bone substratum, smoking habits, history of periodontitis, and prosthetic features were recorded. Mixed linear model was used to determine the influence of the different. Finally, in study #4 a systematic electronic

and manual search of randomized or non- randomized controlled or noncontrolled 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 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system guide. Variables on marginal bone loss.

Results:

Firstly, in Study #1 we showed that exposed (with no BIC) implant threads was the main risk factor for PI with the PI risk almost 8 (7.82) times greater than in patients with implants with no exposed threads. This risk increased almost 4-fold (3.77 times) with each additional thread exposed. Splinting increased the risk of PI by 3.49 times. Importantly, no other potentially confounding modifiable risk indicator was identified as statistically significant in incident PI in multivariate and univariate analyses, including a history of periodontitis (PR) (yes/no), despite the multitude of macro- or micro-surface design variables included.

Secondly, the history PR present at baseline in these maintenance-compliant patients was classified according to the 2017 World Workshop case definitions,we still found no correlation between PR stages or grades and neither prevalence nor incidence of PI at either implant- nor patient-levels. However, although the implant failure rate increased from stage I/II (0%) to stage IV (6.5%), this trend was not statistically significant, but there was a statistically significant increase in implant failure from grade A (0%) to grade C (5.9%).

Thirdly, we studied patients with at least one completely edentulous arch who had lost their teeth due to severe PR and had received implant-supported fixed full-arch metal-ceramic restorations. We found that the implants performed well and experienced limited MBL, even in patients with prior severe PR. This was even the case in one patient who had full-arch rehabilitation in both edentulous jaws.

Finally, in Study #4 we explored the soft tissue adjacent to the implants via a systematic review and meta-analysis. The approach was necessitated by the lack of sufficient information available for harvest from dental charts in a retrospective study design. Specifically, we focused on KMW and concluded that compared to implants with ≥2 mm KMW, implants associated with <2 mm KMW did not exhibit increased MBL; and there is insufficient evidence for KMW <2 mm being a risk factor for incident PI. In a recent systematic review and meta-analysis, <2 mm KMW was found to be associated with increased rates of MBL and PI. Despite the conclusion of an association only, which is not a causal relationship, the authors still state "Hence, in the cases lacking KT, clinicians might consider soft-tissue grafting to increase KT to promote peri-implant soft- and hard-tissue stability."

Conclusion

implant thread exposure after the initial expected bone remodeling was the only statistically significant potential risk indicator for incident PI that was identified. No statistically significant association between periodontitis severity (staging) and rate of progression (grading) at baseline, with prevalence of peri-implantitis was found. However, when peri-implantitis was present, increased severity of marginal bone loss and probability of implant failure were found for grade C patients. Most of the internal conical connection implants supporting fixed full-arch metal-ceramic restorations in patients who lost all their teeth in that dental arch mostly as a consequence of severe periodontitis do not suffer from relevant MBL after 5 years in function. Particularly, those implants with transmucosal abutments longer than 2 mm show, in average, less than 0.5 mm from the implant shoulder to the marginal bone. Finally, implants associated with <2 mm KMW did not exhibit increased MBL, REC and PD compared to implants with ≥2 mm. 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.

Objetivo:

El objetivo de este trabajo es examinar el papel de varios factores implicados en la pérdida de hueso marginal (MBL) alrededor de los implantes y en el desarrollo de la periimplantitis (PI) en diferentes escenarios clínicos. Se evaluaron multitud de parámetros relacionados con el implante y con el paciente.

Materiales y métodos

Se realizó un metanálisis y tres estudios retrospectivos que recogieron datos a largo plazo, adquiridos de las historias clínicas y electrónicas de pacientes de la facultad de odontología de la universidad de Michigan y la facultad de odontología de la Universidad de Granada. En el estudio n.º 1, se incluyeron 165 adultos parcialmente desdentados (77 hombres, 88 mujeres) de 30 a 91 años con ≥2 años de seguimiento después de recibir la restauración con implantes. Los implantes con ≥1 rosca interproximal expuesta (sin contacto hueso-implante) (n = 98, 35 %) constituyeron el grupo de prueba y los que no tenían rosca expuesta (n = 182, 65 %) el grupo de control. Se realizaron análisis de regresión descriptivos, binarios y multivariados para determinar el buen ajuste. Se utilizaron pruebas de Wald para evaluar la significación establecida en 0,05. En el estudio #2 se realizó un análisis retrospectivo de pacientes con antecedentes de periodontitis (PR) que recibieron terapia no quirúrgica y, si estaba indicada, terapia quirúrgica antes de la colocación del implante. El estadio y el grado de la periodontitis se determinaron para cada paciente incluido en función de los datos desde el momento del inicio de la terapia periodontal activa. En el analisis, se construyeron modelos riesgo proporcional de Cox para analizar la correlación entre el estadio y el grado de la periodontitis al inicio del estudio con el fracaso del implante, así como la aparición y la gravedad de la periimplantitis. En el estudio n.º 3, se diseñó un estudio de cohortes retrospectivo para evaluar los resultados de la perdida de hueso marginal a 5 años de los implantes OsseoSpeedTM Astra Tech TX con conexión cónica interna. Se registró la

edad, el sexo, el sustrato óseo, el tabaquismo, los antecedentes de periodontitis y las características protésicas. Se utilizó un modelo lineal mixto para determinar la influencia entre los mismos. Finalmente, en el estudio #4 se realizó una búsqueda electrónica y manual sistemática de ensayos clínicos controlados o no controlados aleatorizados o no aleatorizados. Se analizó la revisión cualitativa, el metanálisis cuantitativo y el análisis de secuencia de prueba (TSA) de implantes insertados en sitios con <2 mm o ≥2 mm de KMW para comparar todas las variables de resultado predeterminadas. El nivel de evidencia sobre el papel de la anchura de la encia queratinizada en la salud periimplantaria se evaluó a través de la guía del sistema Grading of Recommendations, Assessment, Development and Evaluation (GRADE); son las variables sobre la pérdida de hueso marginal.

Resultados

El primer estudio demostró que las espiras expuestas del implante (sin contacto alguno hueso-implante) era el principal factor de riesgo de producir periimplantitis, casi 8 (7,82) veces mayor que en pacientes con implantes sin exposición de espiras. Este riesgo aumentó casi 4 (3,77) con cada espira adicional expuesta. Y si además nos encontrábamos con la situación en la que los implantes estaban ferulizados el riesgo de periimplantitis aumentaba un 3,49 más.

Cabe destacar la importancia de no encontrar otro indicador de riesgo modificable estadísticamente significativo en la periimplantitis, tanto en los análisis multivariados y univariados realizados, incluyendo la historia previa de peridontitis del paciente (si/no),y analizando la gran variedad de diseñoS de las microsuperficies de los implantes incluidas en este trabajo.

En el segundo estudio centramos la atención en la peridontitis presente al inicio del tratamiento de implates y clasificamos los pacientes de acuerdo a la World Workshop case definitions de 2017.Los resultados no encontraron una correlación directa entre los estadios de la periodontitis y la prevalencia e incidencia de la periimplantitis, sin embrago aunque la tasa de fracaso de los implantes aumentara en el estadio I/II(0%) al estadio IV(6,5%), esta tendencia no fue estadísticamente significativa, en cambio si

hubo un aumento estadísticamente significativo en el fracaso de los implantes del grado A (0%) al grado C (5,9%).

En el tercer estudio analizamos pacientes con al menos una arcada completamente edéntula, cuya causa de la perdida dental fue por una peridontitis grave y su rehabilitación posterior mediante coronas metal-cerámica atornilladas a implante. En general los implantes respondieron bien y experimentaron una poca o muy limitada perdida de hueso-implante, teniendo en cuenta la periodontitis severa previa de estos pacientes.

Finalmente, en el estudio #4, exploramos el papel del tejido blando adyacente a los implantes a través de una revisión sistemática y un metanálisis. tuvimos que centrar la búsqueda en un único dato por la falta suficiente de información disponible en nuestra recogida de datos y en el diseño del estudio restrospectivo en el que se basa esta tesis. El dato a valorar fue la anchura de la encía queratinizada y concluimos que en comparación con los implantes con ≥2 mm de anchura de la encia queratinizada, los implantes asociados con <2 mm de anchura no mostraron un aumento de la perdida de hueso marginal;

no hay evidencia suficiente de que la anchura de la encia queratinizada <2 mm sea un factor de riesgo para la periimplantitis.

Conclusion

La exposición de la rosca del implante después de la remodelación ósea esperada inicial fue el único indicador de riesgo potencial estadísticamente significativo para la peri-implantitis incidente que se identificó.

No se encontró una asociación estadísticamente significativa entre la gravedad de la periodontitis (estadio) y la tasa de progresión (grado) como base, con la prevalencia de periimplantitis. Sin embargo, cuando la periimplantitis estaba presente, la pérdida ósea marginal y probabilidad de perdida del implante en los pacientes de grado C era más grave.

La mayoría de los implantes de conexión cónica interna,que soportaron restauraciones fijas de metal-cerámica de arcada completa en aquellos pacientes que perdieron todos

sus dientes como consecuencia de la periodontitis severa, no sufrieron perdida de hueso marginal relevante después de 5 años en boca. En particular, aquellos implantes con pilares transmucosos de más de 2 mm mostraron, en promedio, menos de 0,5 mm de perdida desde el hombro del implante hasta el hueso marginal. Finalmente, los implantes asociados con <2 mm de anchura de encia queratinizada no mostraron un aumento de perdida de hueso marginal, recesion y profundidad de la bolsa en comparación con los implantes con ≥2 mm. La anchura de encia queratinizada de <2 mm se asoció con un aumento de placa alrededor de los implantes y más molestias durante el cepillado. Se determinó un nivel de evidencia bajo para los hallazgos relacionados con las medidas de la produnfidad de bolsa, placa y perdida de hueso marginal, y se determinó un nivel de evidencia muy bajo para los hallazgos relacionados con las medidas de recesion, nivel de ajuste clínico y dolor durante el cepillado. El nivel de evidencia con respecto a la tasa de supervivencia de los implantes y la incidencia de periimplantitis no se pudo determinar debido a la escasez de datos.

1. INTRODUCTION

With the popularization of dental implant placement, the rate of complications has also increased. Although dental implants have revolutionized dentistry, they have consequently also created many associated complications such as peri-implantitis (PI).[1] Implant complications may be categorized into early and late. Early complications are related to the surgical procedures, with the most frequent complications being infection of the implant site and loss of primary stability. Late complications can be classified as technical (prosthetic), biological, or esthetic. Prosthetic complications can be identified as implant fracture and prosthetic component misfit, loosening, chipping, or fracture. Biological complications include peri-implant soft tissue deficiencies (PSTDs), peri-implant mucositis or PI. Esthetic complications also include PSTDs, papilla height deficiencies, and suboptimal shape and/or color of the prosthetic reconstruction.[2-5] A study of 922 implants in patients from 87 United States practices followed for 4.2 ($\pm$0.6) years reported an implant failure rate of 18.7% and concluded that "*implant survival and success rates in general dental practices may be lower than those reported in studies conducted in academic or specialty settings*."[6] This sentiment was also reported from a Swedish national data registry, where greater risk of PI was seen among prosthetic restorations placed by general practitioners.[7]

PI is defined as an inflammatory lesion in the tissues surrounding the implant with progressing of bone loss beyond the expected physiologic bone remodeling.[8, 9]

Galindo-Moreno and colleagues showed that most of the implants (96%) that exhibited marginal bone loss (MBL) >2 mm at 18 months had MBL of $\geq$0.44 mm 6 months post-loading. Perhaps if this initial "physiological" bone loss during the healing/remodeling phase exceeds a certain threshold, it may potentially create a niche for pathogenic microorganisms, enabling a more anaerobic environment and promoting progressive bone loss.[10] Conceivably, an early increased peri-implant bone loss may be indicative of PI development *during* the remodeling phase.[11]

According to the American Academy of Periodontology/European Federation of Periodontology 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions (2017 World Workshop), a history of periodontitis (PR), poor plaque control, and lack of regular maintenance therapy might be considered risk factors for PI, whereas other factors,

such as smoking, diabetes, width of keratinized tissue (KT), titanium particles, and prosthesis design, needed to be further evaluated.[8] So far, it is accepted that PI is caused by bacterial challenge in a susceptible host, although detailed mechanisms and risk factors for this disease development remain unclear.[12] Several studies have focused on the roles of the patient (plaque control and compliance with professional maintenance visits) and of the provider (non-surgical or surgical therapies and maintenance) in the development of PI.[1, 13-20] However, the role of the implant topography needs in PI requires further investigation.[21] Implant design has been discussed extensively in the literature regarding osseointegration, but few studies have explored its role in disease onset. [22, 23]

History of PR

PI is a complex chronic inflammatory disease culminating in progressive loss of supporting bone around dental implants. The etiologies of both PI and PR are believed to be microbially mediated. One of the principal articles of the recent 2017 World Workshop indicated that there is a strong level of evidence that patients with a previous history of PR, inadequate biofilm control, and a lack of regular maintenance care are at an increased risk for developing PI.[8] However, PI etiology, risk factors, and management are less well understood compared to PR.

PR, much like PI, is a chronic inflammatory disease caused by a biologically destructive interaction between the host immunoinflammatory response and subgingival microbial biofilm.[24, 25] Studies have reported that periodontal pockets can act as a bacterial reservoir for colonization by the pathogenic microflora of the peri-implant sulcus and the microbiome of the oral cavity before implant placement influences the microbial composition around the implants.[26] In PI, especially in the stabilized and advanced lesion of the pathogenetic process, the response of the host seems to be characterized by a greater apical extension of the inflammatory infiltrate and by a greater bone resorption probably due to the absence of periodontal ligament.

Furthermore, the greater genetic susceptibility of a part of the population to develop PR results in a redundant and uncontrolled inflammatory response towards pathogens. In these patients, it is plausible to expect a possibly similar reaction also around the implants which would result in

more pronounced peri-implant tissue damage. Possible theories for a linkage between PR and PI include that PR patients might harbor more pathogenic bacterial species, a higher bacterial load, or an impaired host immune response.[27] Several studies included in a recent narrative review showed a greater risk (between 2.2 and 19 times) of PI in patients with a history of treated PR.[28]. A meta-analysis demonstrated that PR patients had 2.3-fold greater risk of developing PI compared to periodontally healthy patients.[29] In addition, implants placed in patients with prior tooth loss due to PR were significantly more likely to develop PI and exhibited on average 0.5 mm greater MBL after 5 years.[30]

Aoki and colleagues demonstrated that periodontal pathogens that reside in deeper pockets, such as *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Treponema denticola*, and *Fusobacterium nucleatum* can be transmitted from affected teeth to adjacent implants.[31] Pjetursson's team also demonstrated that PR patients with residual periodontal probing depths (PPD) ≥5 mm had significantly greater risk for development of PI and implant loss.[32] Residual PPD ≥6 mm involving more than 10% of sites after treatment in severe PR patients was shown to be a significant risk indicator for development of PI.[33] Daubert and team reported that severe PR was the strongest risk indicator for PI of all examined variables.[34] In addition, a systematic review by Ong and colleagues found that PR patients had an overall greater proportion of biologic complications, including implant failures, than non-PR patients.[35] However, it should be noted that conflicting findings exist regarding the association between a history of PR and subsequent development of PI.[36, 37] Differences in results can possibly be attributed to the use of different case definitions in previous studies.[28] Adaptation of the 2017 World Workshop case definitions of PR and PI to investigate potential associations can lead to more accurate interstudy analyses and comparisons, both between different populations and among the same population over time.

Implant related variables

Implant topography can be categorized as macro- and micro-design. The macro-design pertains to the shape of the implant body, as well as the design and number of threads. The macro-design is established as a key factor for osseointegration, being a crucial element for primary stability of

the implant and possibly for bone-to-implant contact (BIC).[38-40] However, implant macro-design has also been hypothesized to be a possible factor contributing to peri-implant disease.[7, 21, 41, 42] In support of this hypothesis, greater PI prevalence was found in implants with triple-thread, with a micro-threaded collar, and with a cylindric shape.[42] The micro-design is related to the (chemical or mechanical) treatment applied to modify the implant surface, such as acid etching, sandblasting, titanium plasma spraying, and hydroxyapatite coating.[43-45] For that matter, a recent systematic review concluded that due to the limited quality of evidence on the topic, more studies are necessary to evaluate the relationship between implant micro-design and PI.[46]

It seems logical that, if threads are exposed in the oral cavity due to physiological bone remodeling or PI, its features, such as depth, pitch, or number, and surface characteristics, like surface roughness, may facilitate plaque retention and microorganism adherence. Consequently, the patient's plaque control is impaired. Recent studies showed that implants with greater thread pitch and thread depth appeared to have more residual biofilm after application of different plaque removal protocols.[21]

Since poorer plaque control is considered a major risk factor for peri-implant disease, we hypothesize that patients with implant thread exposure have greater risk of developing PI than those without thread exposure. A clinical study observed that small bony buccal dehiscence defects developed greater than expected vertical bone loss 6 months post implant placement.[47] However, no study has explored the impact of the interproximal thread exposure on the development of PI.

Periodontal literature has historically reported that a minimum of approximately 2 mm distance from the restorative margin to the alveolar crest is indispensable for adequate formation of the supracrestal tissue attachment around teeth and maintenance of a healthy periodontium.[48, 49] Similar to periodontal therapy, it would seem logical to extend equivalent expectations towards implant restorations. However, several key differences between the peri-implant and the periodontal apparatus make drawing parallels between both fairly nebulous.[50-54] The last decade was marked by a great interest in understanding whether abutment height may play a role in influencing MBL and subsequent development of peri-implant disease. Appropriate selection of

abutment height is essential, allowing placement of the crown margin in a position that favors adequate formation of supracrestal tissue adhesion (STAd) or supracrestal tissue height,[52] and minimizes marginal bone loss.[11] Several recent clinical studies have demonstrated a greater magnitude of peri-implant MBL when short abutments are used compared to longer ones.[55-60]

Abutment height is often selected considering that the prosthetic margin should be placed at or slightly below the level of the peri-implant mucosa to support a cleanable and esthetic prosthetic design.[61] It has been suggested that in cases of thick vertical mucosa (>3 mm), abutment selection should consider establishing an adequate STAd (2-4 mm) to minimize the risk of MBL. On the other hand, when mucosal height is thin, the selection of a short abutment maximizes esthetics while compromising sufficient biologic dimensions for STAd formation. This potentially leads to greater MBL. However, Linkevicius and colleagues showed abutment height selection was based on vertical mucosal thickness or supracrestal tissue height, and it was demonstrated that significantly greater MBL occurred when vertical mucosal thickness / supracrestal tissue height was ≤2 mm.[62-64] Based upon this concept, soft tissue grafting procedures for vertical soft tissue augmentation are recommended in sites with a thin phenotype when shallow placement is necessary.[65, 66] Such procedures may permit selection of a longer abutment.[65, 67]

Vervaeke's team demonstrated that planning implant vertical positioning (i.e., subcrestal or equicrestal) based on soft tissue thickness was highly successful in avoiding implant surface exposure.[68] A similar concept was reported in a study by Siqueira et al., where implants placed subcrestally with longer abutments (>2.5 mm) did not exhibit thread exposure after 5 years follow-up.[59] Subcrestally placed implants facilitate adequate distance for establishment of an ideal STAd and may be associated with a reduced risk for thread exposure. This concept is valid for implants with abutment-fixture connections characterized by minimal micromovement. If an implant does not allow such features, MBL is expected to happen apically to the implant platform regardless of vertical implant position. The abutment height concept can be seen as the building block for analyzing outcomes of clinical studies reporting MBL. It should be noted that a key limitation of several studies on this topic is the absence of accurate soft tissue measurements.[61, 69]

Challenging the relationship between vertical mucosal thickness / supracrestal tissue height and MBL, Spinato and team showed in a randomized clinical trial (RTC) that implants restored with short abutments (1 mm) consistently demonstrated twice the bone loss of identical implants restored with long abutments (3 mm), irrespective of vertical mucosal thickness (groups with $\leq$2 mm or >2 mm) [60] Clinically, the utilization of a long abutment (> 2 mm) may not be feasible if the implant is placed equicrestally in areas with thin vertical mucosal thickness due to the esthetic compromise. This would necessitate a more obtuse emergence profile and possibly expose the abutment surface above the mucosal margin.

Although the aforementioned evidence revealed the role of abutment height and supracrestal tissue height in MBL, long-term data on the effectiveness of this approach in reducing the risk of PI is scarce. One consideration is that the deeper the position of the crown-abutment margin, the greater the prevalence of undetected cement.[70] The authors reported that the greatest quantity of cement remnants was found when margins were positioned 2-3 mm subgingivally. Consequently, the balance between vertical implant positioning and abutment height must be considered to minimize the risk for retained cement after crown delivery.

Keratinized gingiva

Following tooth loss, a series of soft and hard tissue dimensional changes ensue.[71] Depending on the magnitude of these changes, implant site development and/or tissue augmentation are often indicated during or following implant placement. These changes will correspond to components of the per-implant tissue collectively known as the peri-implant phenotype and individually known as keratinized mucosa width (KMW), mucosal thickness (MT), supracrestal tissue height (STH), and peri-implant bone thickness.[52] Typically, peri-implant KMW is used to denote the height of keratinized soft tissue that runs apicocoronally from the mucosal margin to the mucogingival junction.[52] While KMW is not expected to significantly change following unassisted socket healing or alveolar ridge preservation,[72] depending on baseline site characteristics and therapeutic factors, the peri-implant mucosa will either be keratinized or non-keratinized. As a general rule, the KMW at healthy implant sites is roughly 1 mm less than the KT width at contralateral natural teeth.[73] In general, anterior implants not diagnosed with PI may be expected

to exhibit facial soft tissue dehiscence when placed too buccally and/or when the peri-implant phenotype is thin.[74]

Studies have examined the benefit of having keratinized peri-implant mucosa with mixed results. It is commonly suggested that an "adequate" amount of KMW around implants is required to prevent soft tissue recession (REC) and to facilitate adequate oral hygiene measures.[75-77] Block and Kent stated that in the presence of plaque-induced inflammation, KMW prevents bone resorption. [78] The cut-off value for KMW beneath which plaque build-up and marginal inflammation are expected to be more frequent is 2 mm.[76, 79] It was hence advocated that KMW may offer case-specific advantages, warranting surgical interventions to develop adequate KMW at planned implant sites. [80] A recent systematic review even concluded that soft tissue grafting procedures resulted in more favorable peri-implant health in terms of gain in KMW with a greater improvement in bleeding indices and higher marginal bone levels. [81] On the other hand, earlier literature demonstrated that very high long-term success rates can be expected at implant sites bordered chiefly (46–74%) by lining mucosa only.[82, 83] Several recent studies failed to find any association between the lack of a certain amount of KMW and peri-implant mucosal inflammation.[84, 85]

Upon answering the question of whether there is a need for peri-implant KMW to maintain health and tissue stability, the 3rd European Association of Osseointegration (EAO) Consensus Conference in 2012 concluded that longitudinal studies showed no association between "inadequate" KMW and greater plaque index score (PIS) in well-maintained populations.[86] The same was found for gingival inflammation as measured via gingival index and REC. More recently, the 6th EAO Conference Consensus Report suggested that REC, gingival index, and plaque control are improved when KMW is increased via soft tissue augmentation procedures. [87] This set the basis for the working group's clinical recommendation that augmenting KMW may be advised to improve the aforementioned parameters. This, however, is based only on the pooled data of one RCT, one prospective cohort study, and one retrospective cohort study.

This simply illustrates that the true role of a specific KMW threshold in obtaining and maintaining peri-implant health remains to be determined. Contemporary thought suggests that the benefits of keratinezed mucosa (KM) are limited to facilitating oral hygiene procedures for patients with

implants, which in turn may result in less susceptibility to inflammation.[88] While such a notion may be supported by multiple observational studies,[89, 90] the presented quality of evidence thus far may not justify considering the lack of any specific threshold amount of KMW as a risk factor for peri-implant disease. Only longitudinal interventional studies are capable of identifying risk factors for disease, while observational, cross-sectional studies may only describe risk indicators, since a cause-effect relationship cannot be detected.[91] Hence, results from previously performed systematic reviews and meta-analyses including cross-sectional studies should be interpreted with caution.[92, 93] In particular, the lack of KMW could be the consequence of peri-implant disease progression and not necessarily the cause thereof.

2. HYPOTHESIS AND OBJECTIVES

The main hypothesis was that several factors influence MBL and the development of PI.
Based on the lack of clarity in the existing literature regarding exactly which factors are important in MBL and incident PI, the following objectives were pursued in this work:

Overarching Goal:

The overarching aim of this work was to explore the roles of various factors in MBL and the development of PI.

Specific Goals:

The specific aims of this work were to:

A) investigate whether interproximal radiographic implant thread exposure after physiological bone remodeling may be a risk factor for PI (**Study #1)**[94]

   A1) evaluate several other potential risk indicators, including a history of PR, to ensure they were not confounding factors in the investigation in Specific Goal #1 (**Study #1)**[94]

B) determine whether a history of PR associated with higher-level stage (severity) and grade (rate of progression) according to the 2017 World Workshop case definitions[95] increases the risk of PI and implant failure **(Study #2)**[17]

   B1) investigate whether PR stage and grade[95] have an influence on the severity of subsequent PI **(Study #2)**[17]

C) investigate the implant- and prosthetic parameters that influence the long-term MBL of implants in fully edentulous patients with a history of severe PR **(Study #3)**[96]

D) assess whether lack of prespecified KMW ($\geq$2 mm) is a risk factor for peri-implant diseases **(Study #4)**[97]

3. STUDY #1

Title:

Interproximal implant thread exposure after initial bone remodeling as a risk indicator for PI[94]

Materials and methods

The study protocol was approved by the University of Michigan Medical School Institutional Review Board (Study #HUM00194509) and was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. This retrospective investigation included implants placed by graduate students or faculties and restored at the university's School of Dentistry between January 2000 and September 2017. Eligible participants needed to fulfill the following inclusion criteria: 1) partially edentulous area restored with >1 implant with a documented follow-up period of ≥2-years after implant loading; 2) available periapical radiographs at the time of implant placement (T0), prosthetic restoration (T1), 1 year after prosthetic restoration (T2, radiograph exposed at that time as per institutional protocol), and at follow-up of ≥2 years after prosthetic restoration (T3); 3) available information about the implant brand as well as the surface micro- and macro-structure; 4) presence of opposing teeth/restored implants (occlusion): 5) Patients not presenting active PR at the time of implant placement. Exclusion criteria were a) fully edentulous patients with full mouth rehabilitation (no natural teeth); b) ambiguous or incomplete data; c) presence of PI in the test group at T2; d) medically compromised patients (history of uncontrolled diabetes mellitus, radiation or chemotherapy, psychologic or psychiatric issues); e) receipt of treatment or maintenance visits external to the University of Michigan School of Dentistry; and f) data inaccessible due to bad debt or destroyed records. Potentially eligible physical and digital records were screened and evaluated by four examiners (AS, MQ, MS, LW) who subsequently extracted the data. Any disagreement that arose during the screening for eligibility and data collection process was resolved through discussion with the supervising investigator (AR).

Data collection and classification

Relevant patient information was extracted, including age at the time of implant placement (T0), sex, smoking habit (≥1 cigarette/day), diabetes mellitus (validated via the patient's medical records), history of PR, and number of maintenance appointments. A positive history of PR was determined following the case definition for PR proposed by the 2017 World Workshop[95] based on each patient's periodontal charts. Detailed implant specific data collected included the number of implants and their positions (location in the edentulous jaw area, implant design [bone or soft tissue level], brand, length, diameter, neck design, retention type of restoration (cement or screw), and splinting. Type of implant-abutment connection, and neck designs was also collected. Moreover, data were collected on the implant macro-surface, such as thread design (buttress, reverse buttress, square, progressive square, V shaped) and distance between threads (pitch). Details about the micro-surface recorded included type of surface (microtextured and sandblasted, large grit, acid-etched). The implants were divided into four different categories according to their roughness (Sa): smooth (Sa <0.5 µm); minimally rough (Sa 0.5 - 1.0 µm), moderately rough (Sa >1.0-2.0 µm) and rough (Sa >2.0 µm).[98, 99]

Implants were divided by radiographic evaluation of interproximal (mesial/distal) BIC 1 year after prosthetic restoration (T2): 1) absence of BIC with ≥1 proximal implant thread (test group), 2) no thread without BIC (control group) (Figure 1). A thread was regarded radiographically exposed when the adjacent bone did not completely cover its surface.[100]

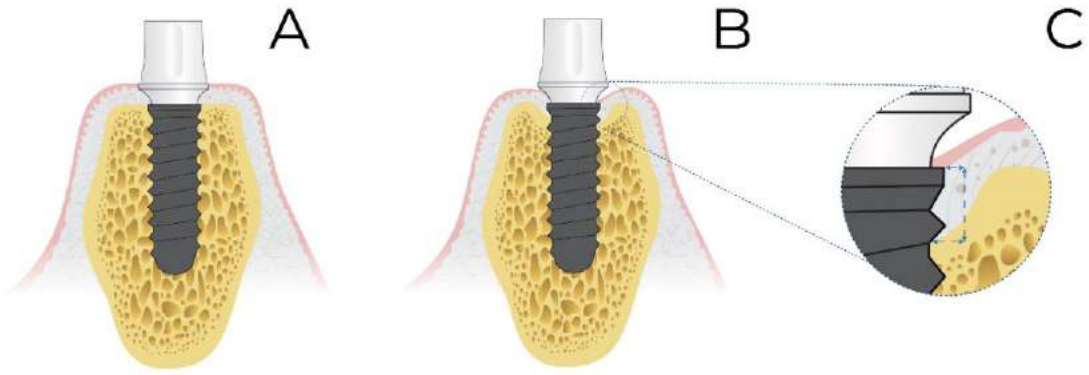

Figure 1. Development of marginal bone loss leading to exposed implant thread (no bone-to-implant contact). (A) Implant placed at bone level (T1). (B) Bone loss after remodeling 1 year after

implant prosthetic restoration (T2). (C) Close-up from Panel B showing the most coronal implant thread exposed. (Conceptual model not showing any prosthetic restoration.)

Definition of outcomes

Based on our predefined outcomes, data analyses for implant failure, prevalence of PI, marginal bone loss, and numbers of thread exposed was performed. Two distinct follow-up periods were defined prior to data acquisition: a) follow-up to assess implant survival, and b) follow-up to assess occurrence of PI, marginal bone loss, and number of interproximal (mesial or distal) threads exposed (with no BIC). The follow-up duration based on implant survival was defined as the time between implant placement (T0) and T4, defined as the last visit, during which each implant was classified as present or explanted. The follow-up based on the occurrence of PI, marginal bone loss, and number of threads exposed, was defined as the duration of time between T2 and exposure of the last radiograph on which peri-implant bone could be clearly visualized (T3). The time between T2 and T3 is referred to as the "radiograph period." In case of concomitancy between T3 and T4 (the last x-rays available and the last patient visit), the 2 follow-up durations were identical.

Implant failure was defined as a removed, lost, mobile, or fractured implant.[101] Peri-implantitis was defined as proposed by the 2017 World Workshop[9] and was used to classify cases in a binary fashion as either positive (1) or negative (0) for PI. Because baseline data were available, a PI diagnosis was based on 1) progressive bone loss beyond initial bone remodeling, 2) increased probing depth, and 3) presence of bleeding and/or suppuration on gentle probing. The marginal bone level was defined as the distance between the most coronal portion of the implant expected to present radiographic bone contact (for tissue level implants: the interface between the polished collar and rough surface, and for bone level implants: the platform level) to the most coronal point of the implant body in contact with bone. MBL and count of the exposed threads at T2 and T3 were radiographically assessed by two authors (AR, MS) at the mesial and distal aspects of the affected implants using the publically available, open source image analysis platform software written in Java named ImageJ (ImageJ.org). If significant differences arose (>0.5mm for MBL and >1 thread), a third reviewer (HLW) was included for reassessing the radiographs in a joint session to provide a final judgment. Repeated measurements of 15 implants

were initially conducted to quantify the mean inter-examiner agreement measurement errors for MBL: 0.32 (±0.2) mm.

Statistical analysis

The statistical analysis included descriptive analyses of categorical (absolute and relative frequencies) and continuous (mean, standard deviation [SD], range, and median) variables for the total sample and stratified by study group (exposed/non-exposed threads) using the dedicated software ImageJ. The outcome PI diagnosis (yes/no) was related to all independent variables using multi-level binary logistic regression with generalized estimation equations (GEE). Raw odds ratios and 95% confidence intervals (CIs) were obtained from the Wald´s Chi^2 statistic. Then, multivariate models were applied to adjust by potential confounding factors. The goodness of fit of different GEE estimates (for different matrix correlations) was assessed by QIC (Quasi likelihood under the Independence model Criterion) statistic. Significance level in all analysis was set to 5% (α=0.05). A post-hoc power analysis was conducted. A sample size of 280 independent implants would provide 90.9% power with a confidence of 95% to detect an odds ratio (OR) of 3 as significant, using logistic regression models. Since the implants were not independent due to the two-level (patient and implant) data structure, this power needed correction. With each patient providing 1.75 implants on average and assuming a within-subject correlation of 0.5 (moderate), the correcting coefficient (D) was 1.35. Therefore, 280 dependent implants provide the same power as 207 independent implants, estimated at 80.4% under the mentioned conditions.

Results

Clinical characteristics and demographic profiles

Records from a total of 4,325 active patients who had received implant therapy at the university of Michigan School of Dentistry were screened for potential inclusion. A total of 1,287 patients were excluded due to <2 years post-implant restoration follow-up period, 2,423 patients due to absence of >1 radiographs or periodontal charts, 352 patients due to lack of information about

brand and other implant characteristics, 53 patients due to presence of fixed full-arch restorations, and 45 due to ambiguous or incomplete charts. Hence, 165 patients were included in the study, including 77 males (46.7%) and 88 females (53.3%) with a mean age of 62.5 (± 11.7) years ranging from 30 to 91 years at baseline (T0). A total of 280 implants were included (n = 98 test group, n = 182 control group). Characteristics of the sample at patient and implant levels are displayed in Table 1.

Table 1. Characteristics of the implant sample placed in the165 patients (N=280 implants).

Characteristic	Total Mean ±SD or n (%)	Non-exposed (0 Thread Exposed) Mean ± SD or n (%)	Exposed (≥1 Thread Exposed) Mean ± SD or n (%)
Number of implants	280	182 (65.0)	98 (35.0)
Patient age at T0, y	63.0 ± 11.3	62.7 ± 11.1	63.3 ± 11.5
Sex			
Male	123 (43.9)	76 (41.8)	47 (48.0)
Female	157 (56.1)	106 (58.2)	51 (52.0)
Smoking (≥1 cigarette/day)			
No	241 (86.1)	161 (88.5)	80 (81.6)
Yes	39 (13.9)	21 (11.5)	18 (18.4)
Diabetes			
No	245 (87.5)	155 (85.2)	90 (91.8)
Yes	35 (12.5)	27 (14.8)	8 (8.2)
History of PR[95]			
No	185 (66.1)	122 (67.0)	63 (64.3)
Yes	95 (33.9)	60 (33.0)	35 (35.7)
Duration of follow-up period			
T0-T1, months	8.81 ± 4.72	8.41 ± 4.57	9.55 ± 4.94
T2-T3 (radiograph period), y	4.60 ± 2.52	4.51 ± 2.66	4.78 ± 2.25
T0-T4 y	7.67 ± 2.63	7.53 ± 2.45	7.91 ± 2.93

Edentulous Site			
Incisor/Canine (I/C)	20 (7.2)	12 (6.6)	8 (8.2)
Premolar (PM)	110 (39.3)	70 (38.5)	40 (40.8)
Molar (M)	150 (53.6)	100 (54.9)	50 (51.0)
Arch			
Maxilla	99 (35.4)	65 (35.7)	34 (34.7)
Mandible	181 (64.6)	117 (64.3)	64 (65.3)
Implant surface			
MTX	105 (37.5)	87 (47.8)	18 (18.4)
TiUnite™	103 (36.8)	32 (17.6)	71 (72.4)
SLA	43 (15.4)	42 (23.1)	1 (1.0)
SLA active	2 (0.7)	2 (1.1)	0
Friadent® plus	7 (2.5)	7 (3.8)	0
Nanotite®	9 (3.2)	6 (3.3)	3 (3.1)
RBT	10 (3.6)	6 (3.3)	4 (4.1)
CMI	1 (0.4)	0 (0.0)	1 (1.0)
Roughness (S_a)			
Smooth/Minimally rough (S_a $\leq$1.0 µm)	7 (2.5)	7 (3.8)	0
Moderate (S_a >1.0-2.0 µm)	170 (60.7)	143 (78.6)	27 (27.6)
Rough (S_a >2.0 µm)	103 (36.8)	32 (17.6)	71 (72.4)
Connection			
Internal hexagon	124 (44.4)	99 (54.4)	25 (25.8)
External hexagon	52 (18.6)	8 (4.4)	44 (45.4)
Morse taper	45 (16.1)	44 (24.2)	1 (1.0)
Internal hexagon with Morse taper	20 (7.2)	12 (6.6)	8 (8.2)
Internal tri-lobe	31 (11.1)	12 (6.6)	19 (19.6)
Morse taper cone connection	7 (2.5)	7 (3.8)	0

Neck Design			
0.5 Machined collar (Zimmer)	25 (9.0)	17 (9.3)	8 (8.2)
0.5 MTX colla	67 (24.0)	58 (31.9)	9 (9.3)
1.0 Machined collar (Zimmer)	13 (4.7)	12 (6.6)	1 (1.0)
Fine micron feature	9 (3.2)	6 (3.3)	3 (3.1)
Laser-Lok® collar	10 (3.6)	6 (3.3)	4 (4.1)
Misc. Machined collar (Nobel)	22 (7.9)	8 (4.4)	14 (14.4)
Micro-rough shoulder	7 (2.5)	7 (3.8)	0
Micro-threads	29 (10.4)	16 (8.8)	13 (13.4)
Smooth collar	44 (15.8)	43 (23.6)	1 (1.0)
Threaded	53 (19.0)	9 (4.9)	44 (45.4)
Thread Design			
Buttress	46 (16.4)	44 (24.2)	2 (2.0)
Progressive square	7 (2.5)	7 (3.8)	0
Reverse buttress	93 (33.2)	26 (14.3)	67 (68.4)
Square	20 (7.1)	12 (6.6)	8 (8.2)
V-shaped	114 (40.7)	93 (51.1)	21 (21.4)
Implant level			
Bone level	197 (70.6)	110 (60.4)	87 (89.7)
Tissue level	82 (29.4)	72 (39.6)	10 (10.3)
Length			
<11mm	79 (28.3)	52 (28.6)	27 (27.8)
11-12mm	131 (47.0)	88 (48.4)	43 (44.3)
>12mm	69 (24.7)	42 (23.1)	27 (27.8)
Diameter			
<4mm	52 (22.4)	34 (20.0)	18 (29.0)
4-4.5mm	81 (34.9)	63 (37.1)	18 (29.0)
>4.5mm	99 (42.7)	73 (42.9)	26 (41.9)
Retention			

Cemented	201 (72.0)	134 (73.6)	67 (69.1)
Screwed	75 (26.9)	45 (24.7)	30 (30.9)
Overdenture	3 (1.1)	3 (1.6)	0
Splinted			
No	204 (72.9)	144 (79.1)	60 (61.2)
Yes	76 (27.1)	38 (20.9)	38 (38.8)
Number of annual maintenance visits during radiograph period (T2 to T3)			
≤1	63 (23.1)	41 (22.8)	22 (23.7)
>1-≤2	104 (38.1)	73 (40.6)	31 (33.3)
>2-≤3	77 (28.2)	47 (26.1)	30 (32.3)
>3	29 (10.6)	19 (10.6)	10 (10.8)
Number of annual maintenance visits (T0 to T4)			
≤0.5	61 (22.4)	43 (24.0)	18 (19.4)
>0.5-≤1	59 (21.7)	45 (25.1)	14 (15.1)
>1-≤1.5	91 (33.5)	54 (30.2)	37 (39.8)
>1.5	61 (22.4)	37 (20.7)	24 (25.8)

Number of or N or number*;* MTX, microtextured surface; PI, peri-implantitis; PR, periodontitis; SD*,* standard deviation; SLA, sand blasted large grit acid etched; T0, time of implant placement; T1, time of prosthetic restoration; T2, 1 year after prosthetic restoration; T3, time of exposure of last radiograph on which peri-implant bone could be clearly visualized; T4, time of last patient visit; y, year(s).

PI and MBL

Overall, the PI rate was 9.6% (27/280) of the total sample of implants. About one-fifth (19.4%) of the implants in the test group and 4.4% in the control group developed PI. Results from simple binary logistic regression using GEE (Table 2) show that an increasing number of threads exposed, and the square thread design significantly increased the probability of developing PI. Moreover, increasing patient age significantly decreased this probability.

Table 2. Risks of incident PI by patient, implant, and prosthesis characteristics during the total study period (T0 to T4): Results from unadjusted binary logistic regression analyses with GEE. (N=280 implants).

Characteristic	Total Mean ± SD or n (%)	PI n (%)	OR	95% CI	*p*-value
Number of implants	280	27 (9.6)			
Study group					
Non-exposed (0 thread exposed)	182 (65.0)	8 (4.4)	1		
Exposed (≥1 thread exposed)	98 (35.0)	19 (19.4)	5.23	2.10 – 13.0	**<0.001*** **
Patient age at T0, y	63.0 ± 11.3		0.95	0.92 – 0.99	**0.008** **
Sex					
Male	123 (43.9)	16 (13.0)	1		
Female	157 (56.1)	11 (7.0)	0.50	0.18 – 1.40	0.190
Smoking (≥1 cigarette/day)					
No	241 (86.1)	26 (10.8)	1		
Yes	39 (13.9)	1 (2.6)	0.22	0.03 – 1.77	0.154
Diabetes					
No	245 (87.5)	23 (9.4)	1		
Yes	35 (12.5)	4 (11.4)	1.25	0.26 – 5.93	0.783
History of PR[95]					
No	185 (66.1)	15 (8.1)	1		
Yes	95 (33.9)	12 (12.6)	1.64	0.61– 4.43	0.331
Duration of follow-up period					
T0-T1, months	8.81 ± 4.72		1.05	0.93 – 1.18	0.458
T2-T3 (radiograph period), y	4.60 ± 2.52		1.08	0.84 – 1.39	0.546
T0-T4, y	7.67 ± 2.63		1.03	0.79 – 1.33	0.841
Edentulous site					0.552
Incisor/Canine (I/C)	20 (7.2)	1 (5)	1		
Premolar (PM)	110 (39.3)	12 (10.9)	2.33	0.42 – 12.9	0.334
Molar (M)	150 (53.6)	14 (9.3)	1.96	0.26 – 15.0	0.519

Arch					
Maxilla	99 (35.4)	9 (9.1)	1		
Mandible	181 (64.6)	18 (9.9)	1.10	0.38 – 3.21	0.856
Implant Surface					0.194
MTX	105 (37.5)	6 (5.7)	1		
TiUniteTM	103 (36.8)	15 (14.6)	2.81	0.82 – 9.61	0.099
SLA	43 (15.4)	2 (4.7)	0.81	0.15 – 4.37	0.801
SLA active	2 (0.7)	0	n/a	n/a	n/a
Friadent® plus	7 (2.5)	0	n/a	n/a	n/a
Nanotite®	9 (3.2)	1 (11.1)	2.06	0.18 – 23.9	0.563
RBT	10 (3.6)	3 (30.0)	7.07	0.77 – 64.9	0.084
CMI	1 (0.4)	0	n/a	n/a	n/a
Roughness (S_a)					
Smooth/Minimally rough (S_a <1.0 µm)	7 (2.5)	0	n/a	n/a	n/a
Moderate (S_a 1.0-2.0 µm)	170 (60.7)	12 (7.1)	1		
Rough (S_a >2.0 µm)	103 (36.8)	15 (14.6)	2.24	0.82 – 6.13	0.115
Connection					0.275
Internal hexagon	124 (44.4)	10 (8.1)	1		
External hexagon	52 (18.6)	6 (11.5)	1.49	0.40 – 5.47	0.550
Mores taper	45 (16.1)	2 (4.4)	0.53	0.11 – 2.62	0.437
Internal hexagon with Morse taper	20 (7.2)	5 (25.0)	3.80	0.82 – 17.7	0.089
Internal tri-lobe	31 (11.1)	4 (12.9)	1.69	0.37 – 7.72	0.499
Morse taper cone connection	7 (2.5)	0	n/a	n/a	n/a
Neck Design					0.308
0.5 Machined collar (Zimmer)	25 (9.0)	3 (12.0)	1		
0.5 MTX collar	67 (24.0)	3 (4.5)	0.34	0.04 – 2.78	0.317
1.0 Machined collar (Zimmer)	13 (4.7)	0	n/a	n/a	n/a

Fine micron feature	9 (3.2)	1 (11.1)	0.92	0.06 – 13.5	0.317
Laser-Lok® collar	10 (3.6)	3 (30.0)	3.14	0.27 – 36.9	0.362
Machined collar (Zimmer)	22 (7.9)	2 (9.1)	0.73	0.10 – 5.62	0.765
Micro-rough shoulder	7 (2.5)	0	n/a	n/a	n/a
Micro-threads	29 (10.4)	7 (24.1)	2.33	0.37 -14.9	0.309
Smooth collar	44 (15.8)	2 (4.5)	0.35	0.05 – 2.65	0.309
Threaded	53 (19.0)	6 (11.3)	0.94	0.16 – 5.66	0.943
Thread Design					0.080
Buttress	46 (16.4)	2 (4.3)	1		
Progressive square	7 (2.5)	0	n/a	n/a	n/a
Reverse buttress	93 (33.2)	13 (14.0)	3.58	0.77 – 16.6	0.105
Square	20 (7.1)	5 (25.0)	7.33	1.16 – 46.4	**0.034***
V-shaped	114 (40.7)	7 (6.1)	1.44	0.28 – 7.39	0.663
Implant level					
Bone level	197 (70.6)	22 (11.2)	1		
Tissue level	82 (29.4)	5 (6.1)	0.52	0.16 – 1.69	0.274
Length					0.280
<11mm	79 (28.3)	5 (6.3)	1		
11-12mm	131 (47.0)	17 (13.0)	2.21	0.76 – 6.41	0.146
>12mm	69 (24.7)	5 (7.2)	1.16	0.29 – 4.67	0.838
Diameter					0.978
<4mm	52 (22.4)	4 (7.7)	1		
4-4.5mm	81 (34.9)	7 (8.6)	1.14	0.19 – 6.63	0.888
>4.5mm	99 (42.7)	9 (9.1)	1.20	0.21 – 6.81	0.837
Retention					0.409
Cemented	201 (72.0)	22 (10.9)	1		
Screwed	75 (26.9)	5 (6.7)	0.58	0.16 – 2.11	0.409
Overdenture	3 (1.1)	0	n/a	n/a	n/a
Splinted					

No	204 (72.9)	14 (6.9)	1		
Yes	76 (27.1)	13 (17.1)	2.80	0.98 – 8.02	0.055
Number of annual maintenance visits during radiograph period (T2 to T3)					0.079
≤1	63 (23.1)	5 (7.9)	1		
>1-≤2	104 (38.1)	4 (3.8)	0.46	0.11 – 1.96	0.296
>2-≤3	77 (28.2)	12 (15.6)	2.14	0.56 – 8.22	0.267
>3	29 (10.6)	5 (17.2)	2.42	0.44 – 13.2	0.309
Number of annual maintenance visits (T0 to T4)					0.280
≤0.5	61 (22.4)	5 (8.2)	1		
>0.5-≤1	59 (21.7)	4 (6.8)	0.82	0.17 – 3.92	0.798
>1-≤1.5	91 (33.5)	6 (6.6)	0.79	0.16 – 3.95	0.775
>1.5	61 (22.4)	11 (18.0)	2.46	0.64 – 9.44	0.188

Number of or N or n, number; CI, confidence interval; GEE, generalized estimation equations; MTX, MicroTextured surface; OR, odds ratio; PI, peri-implantitis; PR, periodontitis; SD, standard deviation; SLA, Sand-blasted Large-grit Acid-etched; T0, time of implant placement; T1, time of prosthetic restoration; T2, 1 year after prosthetic restoration; T3, time of exposure of last radiograph on which peri-implant bone could be clearly visualized; T4, time of last patient visit; y, year(s).
p-value by Wald´s test.
*p<0.05; **p<0.01; ***p<0.001.

A multi-variate model (Table 3) considering these findings and adjusting for potential confounders (duration of and mean annual number of maintenance visits during the radiographic period (T2 to T3)) showed that thread exposure remained a significant factor for increasing the likelihood of PI, with the risk of PI increasing almost 8-fold with each additional exposed thread (OR=7.82; 95% CI: 1.91 – 32.03; p=0.004).

Table 3. Risk of incident PI by patient, implant, and prosthesis characteristics during the radiograph period (T2 to T3): Results from multi-variate logistic regression with GEE adjusting for duration and mean annual number of maintenance visits (N=280 implants).

Characteristic	Total Mean (±SD) or n (%)	PI n (%)	OR	95% CI	p-value

Number of implants	280	27 (9.6)			
Study group					
Non-exposed (0 threads exposed)	182 (65.0)	8 (4.4)	1		
Exposed (≥1 thread exposed)	98 (35.0)	19 (19.4)	7.82	1.91 – 32.0	**0.004****
Patient age at T0, y	63.0 ± 11.3		0.95	0.90 – 0.99	**0.016***
Thread design					0.205
Buttress	46 (16.4)	2 (4.3)	1		
Progressive square	7 (2.5)	0	n/a	n/a	n/a
Reverse buttress	93 (33.2)	13 (14.0)	0.35	0.04 – 3.11	0.348
Square	20 (7.1)	5 (25.0)	2.02	0.26 – 15.9	0.506
V-shaped	114 (40.7)	7 (6.1)	0.23	0.20 – 2.28	0.211
Splinted					
No	204 (72.9)	14 (6.9)	1		
Yes	76 (27.1)	13 (17.1)	3.49	1.02 – 12.0	0.047*
Duration of radiograph period (T2 to T3), y	4.60 ± 2.52		1.19	0.95 – 1.50	0.136
Number of annual maintenance visits during radiograph period (T2 to T3)					0.052
≤1	63 (23.1)	5 (7.9)	1		
>1-≤2	104 (38.1)	4 (3.8)	0.84	0.20 – 3.52	0.811
>2-≤3	77 (28.2)	12 (15.6)	3.23	0.57 – 13.9	0.114
>3	29 (10.6)	5 (17.2)	5.16	0.73 – 36.4	0.101

Number of or N or n, number; CI, confidence interval; GEE, generalized estimation equations; OR, odds ratio; PI, peri-implantitis; SD, estándard deviation; T2, 1 year after prosthetic restoration; T3, time of exposure of last radiograph on which peri-implant bone could be clearly visualized; y, year(s).
p-values by Wald´s test.
*p<0.05; **p<0.01

Overall, splinting was associated with greater risk for PI (OR=3.49; 95% CI: 1.02 – 12.05; p=0.047). Also, each year of increased age was associated with 5% lower risk of a PI diagnosis (OR=0.95; 95% CI: 0.92 – 0.99; p=0.016).

No association was found between PI and any other implant macro- or micro-surface design.

Table 4. Risk for PI in test group with >1 threads exposed at T2 by thread exposure and duration and mean annual number of maintenance visits during radiograph period (T2 to T3), respectively (N=98 implant).

Characteristic	OR	95% CI	p-value
Number of exposed threads	3.77	1.82 – 7.82	**<0.001*** **
Radiograph period (T2 to T3), y	0.92	0.73 – 1.15	0.454
Number of annual maintenance visits during radiograph period (T2 to T3)			0.184
≤1	1		
>1-≤2	0.20	0.03 – 1.29	0.092
>2-≤3	1.18	0.29 – 4.86	0.818
>3	2.24	0.37 – 13.7	0.384

CI, confidence interval; OR, odds ratio; PI, peri-implantitis; T2, 1 year after prosthetic restoration; T3, time of last radiograph; y, years.
***p<0.001

The mean annual crestal bone loss between T2 to T3 was 0.26 (± 0.65) mm in the exposed (test group) versus 0.11 (± 0.31) mm per year in the non-exposed (control) group (P=0.05). Each additional exposed thread significantly increased the odds of PI almost 4-fold (OR=3.77; 95% CI: 1.82 – 7.82; p<0.001) (Figure 2 Panel A, Table 4).

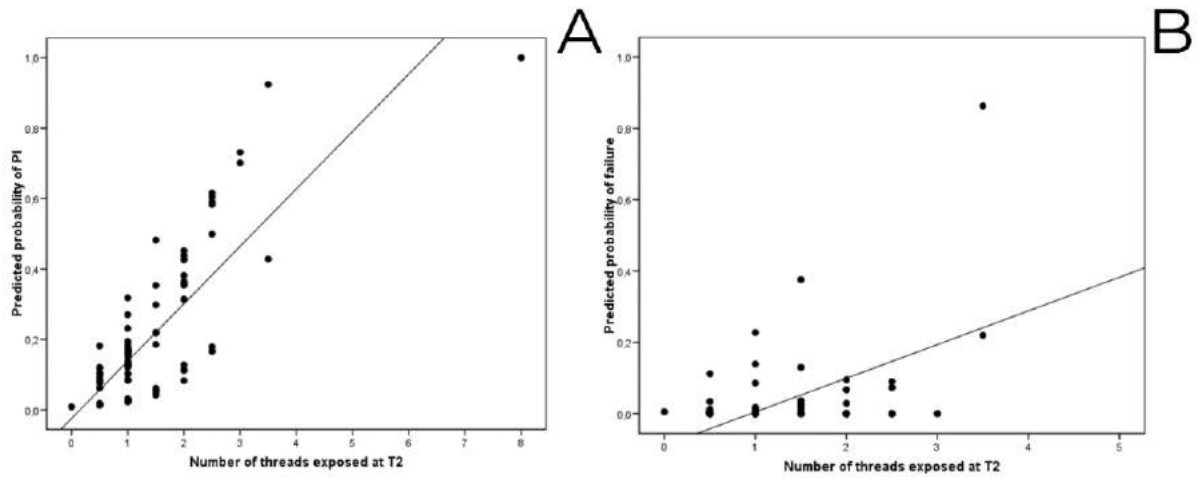

Figure 2. Predicted probability of PI (A) and of implant failure (B) by the number of exposed threads at T2 (N=280 implants).
PI, peri-implantitis; T2, 1 year after prosthetic restoration.

Implant failure

Each group lost 4 implants. The failure rate was at 2.9% (8/280) in the total sample (4.1% in the test group and 2.2% in the control group), a statistically non-significant difference (p=0.470) (Table 5).

Table 5. Risk for incident implant failure (removed, lost, mobile, or fractured) by patient, implant, and prosthesis characteristics during the total study period (T0 to T4): Results from unadjusted binary logistic regression analyses with GEE. N=280 implants).

Characteristic	Total Mean (±SD) or n (%)	Implant Failure n (%)	OR	95% CI	p-value
Number of implants	280	8 (2.9)			
Study group					
Non-exposed (0 threads exposed)	182 (65.0)	4 (2.2)	1		
Exposed (≥1 threads exposed)	98 (35.0)	4 (4.1)	1.89	0.34 – 10.7	0.470
Patient age at T0, y	63.0 ± 11.3		0.97	0.94 – 1.00	**0.049***

Sex					
Male	123 (43.9)	5 (4.1)	1		
Female	157 (56.1)	3 (1.9)	0.46	0.08 – 2.77	0.396
Smoking (≥1 cigarette/day)					
No	241 (86.1)	8 (3.3)	1		
Yes	39 (13.9)	0	n/a	n/a	n/a
Diabetes					
No	245 (87.5)	6 (2.4)	1		
Yes	35 (12.5)	2 (5.7)	2.41	0.26 – 22.2	0.436
History of PR^{95}					
No	185 (66.1)	6 (3.2)	1		
Yes	95 (33.9)	2 (2.1)	0.64	0.11– 3.60	0.614
Duration of follow-up period					
T0-T1, months	8.81 ± 4.72	n/a	0.74	0.42 – 1.30	0.295
T2-T3 (radiograph period), y	4.60 ± 2.52	n/a	1.29	0.97 – 1.71	0.078
Edentulous Site					0.552
Incisor/Canine (I/C)	20 (7.2)	0 (0)	n/a	n/a	n/a
Premolar (PM)	110 (39.3)	3 (2.7)	1		
Molar (M)	150 (53.6)	5 (3.3)	1.23	0.31 – 4.95	0.771
Arch					
Maxilla	99 (35.4)	2 (2.0)	1		
Mandible	181 (64.6)	6 (3.3)	1.66	0.28 – 9.76	0.573
Implant Surface					0.886
MTX	105 (37.5)	3 (2.9)	1		
TiUnite™	103 (36.8)	4 (3.9)	1.37	0.20 – 9.27	0.744
SLA	43 (15.4)	1 (2.3)	0.81	0.07 – 9.01	0.864
SLA active	2 (0.7)	0	n/a	n/a	n/a
Friadent® plus	7 (2.5)	0	n/a	n/a	n/a
Nanotite®	9 (3.2)	0	n/a	n/a	n/a

RBT	10 (3.6)	0	n/a	n/a	n/a
CMI	1 (0.4)	0	n/a	n/a	n/a
Roughness (S_a)					
Smooth/Minimally rough (S_a <1.0 µm)	7 (2.5)	0	n/a	n/a	n/a
Moderate (S_a 1.0-2.0 µm)	170 (60.7)	4 (2.4)	1		
Rough (S_a >2.0 µm)	103 (36.8)	4 (3.9)	1.68	0.30 – 9.28	0.554
Connection					0.492
Internal hexagon	124 (44.4)	3 (2.4)	1		
External hexagon	52 (18.6)	0	n/a	n/a	n/a
Mores taper	45 (16.1)	1 (2.2)	0.92	0.08 – 10.2	0.944
Internal hexagon with Morse taper	20 (7.2)	1 (5.0)	2.12	0.17 – 26.3	0.558
Internal tri-lobe	31 (11.1)	3 (9.7)	4.32	0.52 – 35.8	0.175
Morse taper cone connection	7 (2.5)	0	n/a	n/a	n/a
Neck Design					0.514
0.5 Machined collar (Zimmer)	25 (9.0)	2 (8.0)	1		
0.5 MTC collar	67 (24.0)	1 (1.5)	0.47	0.03 – 7.97	0.604
1.0 Machined collar (Zimmer)	13 (4.7)	0	n/a	n/a	n/a
Fine micron feature	9 (3.2)	0	n/a	n/a	n/a
Laser-Lok® collar	10 (3.6)	0	n/a	n/a	n/a
Machined collar (Nobel)	22 (7.9)	1 (4.5)	1.49	0.09 – 24.8	0.781
Micro-rough shoulder	7 (2.5)	0	n/a	n/a	n/a
Micro-threads	29 (10.4)	3 (10.3)	3.61	0.29 -44.6	0.316
Smooth collar	44 (15.8)	1 (2.3)	0.73	0.05 – 11.8	0.823
Threaded	53 (19.0)	0	n/a	n/a	n/a

Thread Design					0.937
Buttress	46 (16.4)	1 (2.2)	1		
Progressive square	7 (2.5)	0	n/a	n/a	n/a
Reverse buttress	93 (33.2)	3 (3.2)	1.50	0.13 – 16.8	0.742
Square	20 (7.1)	1 (5.0)	2.37	0.14 – 38.9	0.550
V-shaped	114 (40.7)	3 (2.6)	1.22	0.11 – 13.6	0.874
Implant level					
Bone level	197 (70.6)	5 (2.5)	1		
Tissue level	82 (29.4)	3 (3.7)	1.46	0.24 – 8.90	0.683
Length					0.994
<11mm	79 (28.3)	3 (3.8)	1		
11-12mm	131 (47.0)	5 (3.8)	1.01	0.26 – 3.92	0.994
>12mm	69 (24.7)	0	n/a	n/a	n/a
Diameter					0.625
<4mm	52 (22.4)	1 (1.9)	1		
4-4.5mm	81 (34.9)	3 (3.7)	1.96	0.20 – 19.5	0.566
>4.5mm	99 (42.7)	2 (2.0)	1.05	0.09 – 12.0	0.968
Retention					0.253
Cemented	201 (72.0)	4 (2.0)	1		
Screwed	75 (26.9)	4 (5.3)	2.78	0.48 – 15.9	0.253
Overdenture	3 (1.1)	0	n/a	n/a	n/a
Splinted					
No	204 (72.9)	4 (2.0)	1		
Yes	76 (27.1)	4 (5.3)	2.78	0.48 – 15.9	0.253
Number of annual maintenance visits during radiograph period (T2 to T3)					0.210
$\leq$1	63 (23.1)	1 (1.6)	1		
>1-$\leq$2	104 (38.1)	1 (1.0)	0.60	0.04 – 9.51	0.602
>2-$\leq$3	77 (28.2)	3 (3.9)	2.51	0.21 – 29.6	0.464
>3	29 (10.6)	3 (10.3)	7.15	0.58 – 87.7	0.124

Number of annual maintenance visits (T0 to T4)					0.453
≤0.5	61 (22.4)	1 (1.6)	1		
>0.5-≤1	59 (21.7)	0	n/a	n/a	n/a
>1-≤1.5	91 (33.5)	3 (3.3)	2.05	0.18 – 23.7	0.567
>1.5	61 (22.4)	4 (6.6)	4.21	0.41 – 42.9	0.225

N or n, number; CI, confidence interval; GEE, generalized estimation equations; (MTX, Microtextured surface; OR, odds ratio; PR, periodontitis; T0, time of implant placement; T1, time of prosthetic restoration; T2, 1 year after prosthetic restoration; T3, time of exposure of last radiograph on which peri-implant bone could be clearly visualized; T4, time of last patient visit; y, year(s).
p-value by Wald´s test; *p<0.05

The probability of failure increased with the number of exposed threads, with each additional thread increasing the probability of failure about 3 times (OR=3.13; 95% CI: 1.01 – 9.66; p<0.001) (Figure 2 Panel B; Table 6). Other than older age (OR: 0.97; 95% CI: 0.94 – 1.00; p=0.049), there were no other variables identified that potentially could diminish the risk for implant failure.

Table 6. Risk of implant failure (removed, lost, mobile, or fractured) by number of exposed threads and duration and mean annual number of maintenance visits during the radiograph period (T2 to T3) (N=280 implants).

Characteristic	OR	95%CI	p-value
Number of exposed threads	3.13	1.01 – 9.66	0.048*
Duration of radiograph period (T2 to T3), y	0.77	0.30 – 2.02	0.595
Number of annual maintenance visits during radiograph period (T2 to T3)	2.21	0.37 – 13.1	0.381

CI, confidence interval; OR, odds ratio; T2, 1 year after prosthetic restoration; T3, time of exposure of last radiograph on which peri-implant bone could be clearly visualized; y, year(s).
*p<0.05

4. STUDY #2

Title:

The correlation between history of PR according to the 2017 classification system and the prevalence and severity of PI[17]

Materials and methods

The study was conducted in compliance with the Helsinki Declaration of 1975, as revised in 2013. The protocol of this study was approved by the University of Michigan, School of Dentistry, Institutional Review Board for Human Studies (HUM00157260).

Data were acquired from the physical and electronic charts of patients who received nonsurgical and, if indicated, surgical corrective therapy between January 1996 and January 2018 at the University of Michigan, School of Dentistry, Ann Arbor, Michigan, USA. Patients treated for periodontal disease (scaling and root planing [SRP] and/or surgical therapy) with a complete medical history, baseline periodontal charting, and full-mouth radiographs were included in the present study. All included patients were maintained after active periodontal therapy with at least one session of supportive periodontal therapy (SPT) per year at the University of Michigan, School of Dentistry. Furthermore, the following exclusion criteria were implemented: non-periodontal patients, patients receiving implant-related or periodontal care outside the School of Dentistry, periodontal patients that did not receive a dental implant or received an implant with a follow-up period of less than one year, and patients with incomplete or unclear data.

Staging and grading algorithms published by Tonetti and Sanz in 2019[102] were utilized to classify patient periodontal status. Determination of baseline periodontal staging and grading was conducted by a single investigator (MS) using clinical and radiographic data collected at the time of initial active periodontal therapy (T0).[103] Data on pertinent patient characteristics, the number of SPT visits per year, and relevant medical history (history of diabetes status and self-reported smoking at baseline) were collected. Radiographic bone loss (RBL, % of root length) at baseline was measured from periapical radiographs to assess PR stage and grade.[104] Tooth-specific data on clinical parameters including PPD, clinical attachment level (CAL) calculated as the difference between PPD and the distance from the free gingival margin to the cemento-enamel junction,

bleeding on probing (BOP), and furcation involvement were also recorded. Information about masticatory dysfunction, drifting, flaring, bite collapse, and plaque accumulation were retrieved from patient records where available. As part of the data collection process, additional information was gathered at the time of implant placement including: age, tobacco usage and diabetic history, the number of implants placed and their locations, implant characteristics (brand, length, diameter, soft tissue/bone level), mechanism of crown retention (screw or cement-retained), number of follow-up visits and maintenance appointments, type of implant-abutment connection, as well timing of bone grafting (prior/during implant placement).

Survival rate and PI definition

Based on the goal of conducting data analyses for both implant survival rates as well as PI prevalence/severity, two distinct follow-up periods were defined prior to data acquisition. These were (a) follow-up based on implant survival, and (b) follow-up based on the occurrence of PI. Follow-up based on implant survival was defined as the time occurring between implant placement and the last follow-up of the implant. At this date, each individual implant was classified as present or explanted.[105] Follow-up based on the occurrence of PI was defined as the duration of time between implant-supported prosthetic placement and the last radiograph in which peri-implant bone could clearly be visualized. The definition for PI proposed by the 2017 World Workshop guidelines[106] was used to classify cases in a binary fashion as either positive or negative for PI (0 for peri-implant health, 1 for PI). The marginal bone level changes were radiographically examined by two authors (AR, MV) at the mesial and distal aspects of the affected implants using ImageJ. If significant differences arose, a third reviewer (HLW) was included for reassessing the radiographs in a joint session and to give a final judgment. Interproximal marginal bone levels were radiographically recorded as a percentage of implant length, utilizing the most coronal bone-implant contact point to represent the marginal bone level, in order to classify implants based on the severity of bone loss (<25%; 25%–50%; or >50% of the implant length). For implants with a polished collar, the length was measured from the smooth-rough interface to the apex. For bone level implants, the platform level was used as the

coronal demarcation point when evaluating implant length for calculation of radiographic peri-implant bone levels.

Statistical analysis

Descriptive statistics were employed for analysis of categorical (absolute and relative frequencies) and continuous (mean, SD, range, and median) variables considering both implant failure events and PI diagnosis. At the implant-level, time-to-event 'implant failure' and time-to-event 'PI diagnosis' were analyzed using Kaplan-Meier survival methodology. Cumulative survival functions were plotted and compared between different patient profiles and clinical factors using a Log-rank test. In order to consider dependence between observations (implant-level data clustered by patients), univariate Cox regression frailty models were performed analyzing the influence of individual factors and covariates on failures and PI diagnosis. Hazard ratio (HR) estimations and corresponding 95% CIs were obtained. Wald test was used to consider within-patient correlations. Then, multiple Cox regression frailty models were used to adjust for potential confounders. Schoenfeld's tests for proportional hazard and residual analysis were carried out to validate theoretical hypotheses.

For non-failed PI-afflicted implants, severity of bone loss (<25% or ≥25%) was related to stage and grade, adjusting by radiographic follow-up duration using logistic regression with GEE. Odds ratios and 95% CIs were obtained using the Wald's Chi^2 statistic. The significance level for statistical analyses was set at 5% ($\alpha = 0.05$). Regarding the power analysis, a post-hoc estimation was obtained.

A sample size of 221 independent implants provided 96.5% power at 95% confidence to detect a relative risk (RR) of 3.0 as significant using a Cox multiple regression model to assess the influence of a two-level factor (e.g., maxillary or mandibular implant location), assuming that 80% of observations were censored (the proportion of no PI diagnosis was roughly 80%). In the power calculation, correction was performed to account for the two-level structure of the data. Each patient provided 2.23 implants on average and within-subject correlation CCI = 0.5 (moderate) was assumed, leading to a correcting coefficient D = 1.62. Therefore, 221 dependent implants

provided the same power as 137 independent implants, calculated at 84% under the described conditions (RR=3.0; 95% confidence).

Results

Characteristics of the patient cohort

In total, 99 patients composed of 49 males (49.5%) and 50 females (50.5%), with a mean age of 60.6 (± 10.2) years at the time of implant placement (range 38 - 86 years) were included in the present study. Overall, 221 implants were followed for a mean duration of 10.6 (± 4.5) years from implant placement, and 10.0 (±4.5) years from prosthetic insertion. Demographic characteristics of the included cohort are displayed in Table 7.

Table 7. Demographic characteristics of the sample and PR status at baseline, as well as results of Kruskal-Wallis test (KW) for comparison between different levels of stage and grade.

Characteristic	Total Mean ± SD or n (%)	Mean n of annual maintenance visits	p-value (KW)	Follow up since Implant placement (years)	Follow up since crown placment (years)
N	99	2.2 ± 1.0		10.6 ± 4.5	10.0 ± 4.5
Age, y	60.6 ± 10.2				
Gender					
Male	49 (49.5)				
Female	50 (50.5)				
Smoking					
No	63 (63.6)				
Former smoker	20 (20.2)				
Yes (<10 cigarettes/day)	8 (8.1)				
Yes (≥10 cigarettes/day)	8 (8.1)				
Diabetes					
No	90 (90.9)				

Yes	9 (9.1)				
Stage					
1	7 (7.1)	2.7 ± 2.0	0.515	6.8 ± 3.4	6.1 ± 3.5
2	27 (27.3)	1.9 ± 0.8		9.8 ± 4.8	9.2 ± 4.8
3	56 (56.6)	2.2 ± 0.9		11.3 ± 4.0	10.7 ± 4.0
4	9 (9.1)	2.2 ± 1.3		12.1 ± 5.5	11.1 ± 5.7
Grade					
A	5 (5.1)	2.2 ± 1.0	0.526	10.0 ± 2.9	9.4 ± 3.0
B	68 (66.7)	2.2 ± 1.0		10.1 ± 4.6	9.5 ± 4.6
C	26 (26.3)	2.2 ± 1.0		12.2 ± 4.1	11.5 ± 4.2
Extent					
Localized	78 (78.8)				
Generalized	21 (21.2)				

KW, Kruskal-Wallis test; SD, standard deviation.

Correlation between stage and grade and implant failure

Analysis at the patient-level revealed that five patients (5.1%) experienced implant failure at least at one site (one patient experienced two failures). At the implant-level, a mean survival rate of 97.3% was found at the end of the follow-up period, as six implants (2.7%) failed. The cumulative survival rate (Kaplan Mayer analysis) was 99% at 5-years, 98% at 10-years, 94% at 15-years, and 92% at 20-years follow-up (shown in Supplemental Figure S1 Panel A in APPENDIX #2.1). In the present study, the only cause of implant failure found was PI (shown in Supplemental Figure S1 Panel B in APPENDIX #2.1). Univariate analysis according to clinical variables related to the patient, implant position and characteristics, as well as surgical-related parameters, is shown in Table 8.

Table 8. Kaplan Meier survival analysis of time-to-event data based on clinical variables related to the patient, implant position, characteristics, and surgery.

Characteristic	Total Mean ±SD or n (%)	Failure Rate	p-value
N	221	6 (2.7)	
Age, y	60.3 ± 9.3		
Gender			0.516
Male	110 (49.8)	2 (1.8)	
Female	111 (50.2)	4 (3.6)	
Smoking			0.141
No	121 (54.8)	2 (1.7)	
Former smoker	48 (21.7)	0 (0.0)	
Yes (<10 cigarettes/day)	18 (8.1)	1 (5.6)	
Yes (≥10 cigarettes/day)	34 (15.4)	3 (8.8)	
Diabetes			0.104
No	204 (92.3)	5 (2.5)	
Yes	17 (7.7)	1 (5.9)	
Stage			p=0.411 (Stage 1/2 vs. 3 vs. 4)
1	8 (3.6)	0 (0.0)	p=0.226 (Stage 1/2 vs. 3/4)
2	48 (21.7)	0 (0.0)	p=0.267 (Stage 1/2 vs. 3)
3	134 (60.6)	4 (3.0)	p=0.131 (Stage 1/2 vs. 4)
4	31 (14.0)	2 (6.5)	
Grade			**0.048***(Grade A/B vs. C)
A	5 (2.3)	0 (0.0)	
B	131 (59.3)	1 (0.8)	
C	85 (38.5)	5 (5.9)	
Extension			0.465
Localized	171 (77.4)	4 (2.3)	
Generalized	50 (22.6)	2 (4.0)	

Arch			0.172
Maxilla	122 (55.2)	5 (4.1)	
Mandible	99 (44.8)	1 (1.0)	
Position			0.223
Anterior	37 (16.7)	0 (0.0)	
Posterior	184 (83.3)	6 (3.3)	
Prosthesis type			0.956 (Single vs. Splinted)
Single	153 (69.2)	3 (2.0)	
Splinted	59 (26.7)	2 (3.4)	
Overdenture	9 (4.1)	1 (11.1)	--
Level			0.806
Soft	48 (21.7)	1 (2.1)	
Bone	173 (78.3)	5 (2.9)	
Connection			0.769 (Internal vs. External)
Internal	200 (90.5)	5 (2.5)	
External	18 (8.1)	1 (5.6)	
Locator	3 (1.4)	0 (0.0)	--
Retention			**<0.001*****(Cemented vs. Screw)
Cemented	204 (92.3)	4 (2.0)	
Screwed	14 (6.3)	1 (7.1)	
Ball attachment	3 (1.4)	1 (33.3)	--
Implant length			0.110
≤11mm	66 (29.9)	1 (1.5)	
11.5mm	45 (20.4)	3 (6.7)	
12mm	34 (15.4)	1 (2.9)	
≥13mm	76 (34.4)	1 (1.3)	
Implant diameter			0.183
<4mm	52 (23.5)	0 (0.0)	
4 - 4.5mm	90 (40.7)	3 (3.3)	

>4.5mm	79 (35.7)	3 (3.8)	
Bone graft			0.755
No	149 (68.3)	4 (2.7)	
Yes	69 (31.7)	2 (2.9)	
Failure			
No	215 (97.3)		
Yes	6 (2.7)		
PI			<**0.001*****
No	176 (79.6)	0 (0.0)	
Yes	45 (20.4)	6 (13.3)	

PI, peri-implantitis; SD, standard deviation; y, year(s)
*p<0.05; ***p<0.001.

Regarding PR staging, four implant failures were recorded in patients with stage III PR at baseline, while the remaining two failures occurred in patients with a history of stage IV disease (p>0.05). Mean implant failure rates were 0% for stages I-II, 3% for stage III, and 6.5% for stage IV. Cumulative implant survival rates are shown in Figure 3 Panel A and Table 9.

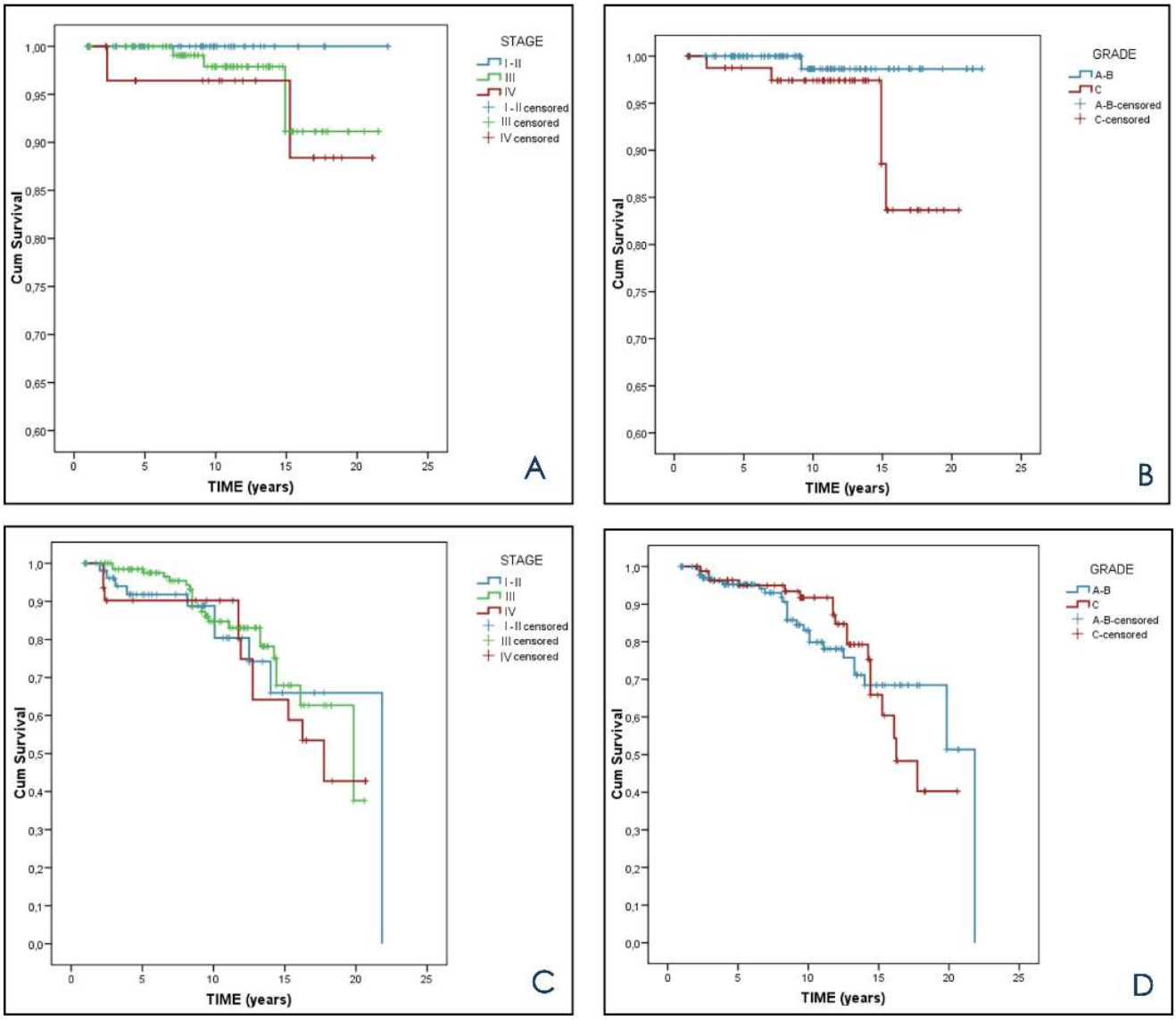

Figure 3. (A) Implant failure survival analysis by stage; (B) Implant failure survival analysis by grade; (C) PI prevalence survival analysis by stage. The drop of the blue curve (represents stages I-II) at 23 years follow-up is due to the reduced sample size at that time. (D) PI prevalence survival analysis by grade. The drop of the blue curve (represents grades A/B) at 23 years follow-up is due to the small sample size at that time.
PI, peri-implantitis.

Table 9. Survival 38time-to-event failure by PR stage: cumulative survival probability at different time-points.

Time	PR Stage					
	½		3		4	
	Survival	SE	Survival	SE	Survival	SE
1 y	1.000	0.000	1.000	0.000	1.000	0.000
2.5 y	1.000	0.000	1.000	0.000	0.964	0.035
5 y	1.000	0.000	1.000	0.000	0.964	0.035
10 y	1.000	0.000	0.979	0.015	0.964	0.035
15 y	1.000	0.000	0.911	0.048	0.884	0.083
20 y	1.000	0.000	0.911	0.048	0.884	0.083

PR, periodontitis; [95] SE, standard error; y, year(s)

In terms of grading, one failure was recorded in a patient with a history of PR grade B, while the remaining five failures occurred in patients with a history of grade C disease. The mean failure rate was 0% for grade A, 0.8% for grade B, and 5.9% for grade C ($p<0.05$) (Figure 3B and Table 10).

Table 10**.** Survival hazards of time-to-event failure by PR grade: cumulative survival probability at different time-points.

Time	PR Grade			
	A/B		C	
	Survival	SE	Survival	SE
1 y	1.000	0.000	1.000	0.000
2.5 y	1.000	0.000	0.988	0.012
5 y	1.000	0.000	0.988	0.012
10 y	0.986	0.014	0.974	0.018
15 y	0.986	0.014	0.886	0.062
20 y	0.986	0.014	0.836	0.076

PR, periodontitis; [95] SE, Standard error; y, year(s)

Cox proportional hazard regression analysis showed that implants placed in grade C patients were associated with a trend towards a higher failure rate than those placed in grade A/B patients (HR=6.57; p=0.075). The same model (Table 11) demonstrated that implants placed in current high smokers were associated with a significantly higher failure rate compared to never-smokers (HR=4.71; p=0.04). Six implants were lost in patients with a history of stage III/IV PR, while no implants were lost in those with a history of stage I and II PR. Stage was not a significant predictor of implant failure (p=0.635) when stage IV was compared to stage III (Table 17). It should be noted that stages I-II were excluded from the model because of a lack of convergence since these categories were both associated with 0% implant failure rates.

Table 11.Cox proportional 40azard regression model illustrating time-to-event failure by clinical variables related to the patient, implant position, characteristics, and surgery.

Characteristic	HR	95% CI	p-value
Age, y	1.02	0.95 – 1.10	0.538
Gender			
Male	1		
Female	1.75	0.36 – 8.60	0.491
Smoking			0.102
No	1		
Former smoker	--	--	--
Yes (<10 cigarettes/day)	1.82	0.21 – 15.6	0.578
Yes (≥10 cigarettes/day)	4.71	1.08 – 20.6	**0.040***
Diabetes			
No	1		
Yes	5.79	0.63 – 53.5	0.122
Stage			
1-2	--	--	--
3	1		
4	1.54	0.26 – 9.17	0.635
Grade			
A-B	1		
C	6.57	0.82 – 52.4	0.075
Extent			
Localized	1		
Generalized	1.86	0.40 – 8.58	0.429
Arch			
Maxilla	1		
Mandible	0.25	0.03 – 2.18	0.209

Position			
Anterior	--		
Posterior	--	--	--
Prosthesis type			
Single	1		
Splinted	1.04	0.10 – 10.5	0.971
Overdenture	--	--	--
Level			
Soft	1		
Bone	1.31	0.16 – 10.9	0.801
Connection			
Internal	1		
External	0.72	0.07 – 7.29	0.777
Locator	--	--	--
Retention			
Cemented	1		
Screwed	51.9	4.89 – 550.4	**0.001****
Ball attachment	--	--	--
Implant length (mm)	1.05	0.79 – 1.39	0.743
Implant diameter (mm)	2.23	0.79 – 6.26	0.128
Bone graft			
No	1		
Yes	1.30	0.25 – 6.94	0.756
Failure	--	--	--
No			
Yes			
PI	--	--	--
No			
Yes			

HR, hazard ratio; PI, peri-implantitis; y, years.
*p<0.05; **p<0.01.

Analysis of the association between stage and grade with the onset and severity of PI

A total of 45 implants (20.4%) were diagnosed with PI during the follow-up period. At the implant-level, the cumulative probability of PI occurrence (based on Kaplan Mayer analysis) was 5% at 5-years, 15% at 10-years, 35% at 15-years, and 54% at 20-years follow-up (Figure 4 Panel A). At the patient-level, the cumulative probability of PI occurrence is shown in Figure 4 Panel B. Univariate analysis according to clinical variables (implant position, implant characteristics, as well as patient-specific and surgical-related parameters) is shown in Table 12.

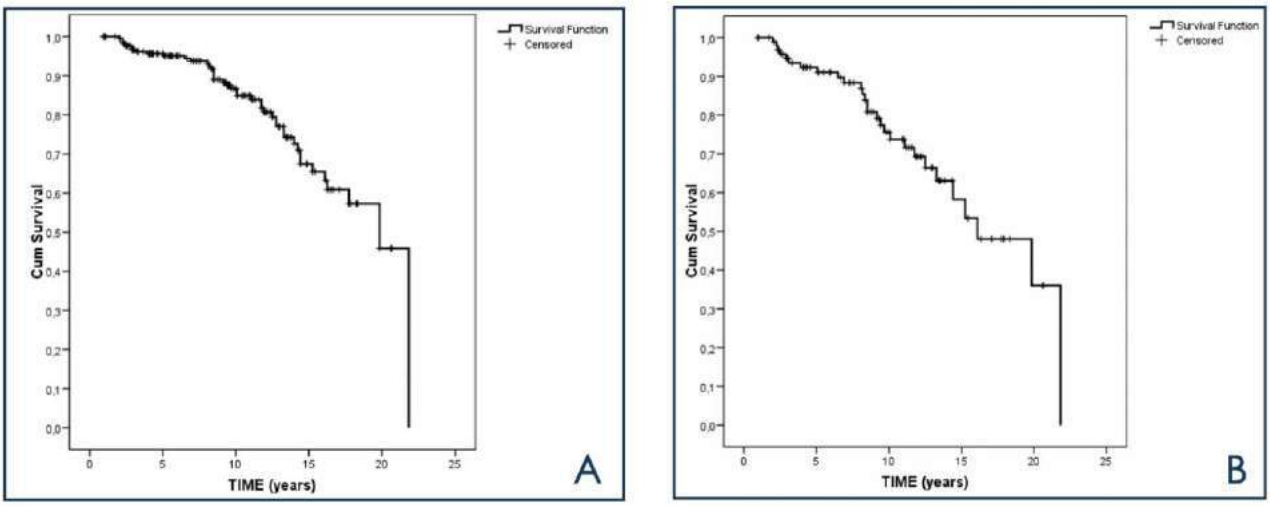

Figure 4. (A) Cumulative survival function estimated by Kaplan Meier's method illustrating implant level time-to-PI diagnosis events throughout the follow-up; (B) Cumulative survival function estimated by Kaplan Meier's method illustrating patient-level time-to-PI diagnosis events.
"Cum Survival" (Y-axis in both panels) denotes PI diagnosis even.

Table 12. Kaplan Meier survival hazards of time-to-event PI diagnosis according to clinical variables related to the patient, implant position, characteristics, and surgery.

Characteristic	Total Mean ±SD or n (%)	PI Rate n (%)	p-value
N	221	45 (20.4)	
Age, y	60.3 ± 9.3		
Gender			0.825
Male	110 (49.8)	21 (19.1)	
Female	111 (50.2)	24 (21.6)	
Smoking			0.723
No	121 (54.8)	23 (19.0)	
Former smoker	48 (21.7)	11 (22.9)	
Yes (<10 cigarettes/day)	18 (8.1)	6 (33.3)	
Yes (≥10 cigarettes/day)	34 (15.4)	5 (14.7)	
Diabetes			0.094
No	204 (92.3)	40 (19.6)	
Yes	17 (7.7)	5 (29.4)	
Stage			0.411 (Stage 1/2 vs. 3 vs. 4)
1	8 (3.6)	1 (12.5)	
2	48 (21.7)	10 (20.8)	
3	134 (60.6)	23 (17.2)	
4	31 (14.0)	11 (35.5)	
Grade			0.990 (Grade A/B vs. C)
A	5 (2.3)	2 (40.0)	
B	131 (59.3)	25 (19.1)	
C	85 (38.5)	18 (21.2)	
Extent			0.650
Localized	171 (77.4)	33 (19.3)	
Generalized	50 (22.6)	12 (24.0)	

Time from 1st SRP to implant placement, y	12.9 ± 8.1		
Total follow up, y	10.7 ± 5.1		
Radiographic follow up, y	9.6 ± 5.1		
n maintenance visits/y	2.3 ± 1.0		
Arch			0.546
Maxilla	122 (55.2)	22 (18.0)	
Mandible	99 (44.8)	23 (23.2)	
Position			0.110
Anterior	37 (16.7)	8 (21.6)	
Posterior	184 (83.3)	37 (20.1)	
Prosthesis type			0.409 (Single vs. Splinted)
Single	153 (69.2)	20 (13.1)	
Splinted	59 (26.7)	18 (30.5)	
Overdenture	9 (4.1)	7 (77.8)	--
Level			0.120
Soft	48 (21.7)	5 (10.4)	
Bone	173 (78.3)	40 (23.1)	
Connection			**0.008**** (Internal vs. External)
Internal	200 (90.5)	41 (20.5)	
External	18 (8.1)	3 (16.7)	
Locator	3 (1.4)	1 (33.3)	--
Retention			**0.002***** (Cemented vs. Screw)
Cemented	204 (92.3)	39 (19.1)	
Screwed	14 (6.3)	3 (21.4)	
Ball attachment	3 (1.4)	3 (100)	--
Implant length			**0.009****
≤11mm	66 (29.9)	10 (15.2)	
11.5mm	45 (20.4)	12 (26.7)	

12mm	34 (15.4)	2 (5.9)	
≥13mm	76 (34.4)	21 (27.6)	
Implant diameter			**0.009****
<4mm	52 (23.5)	7 (13.5)	
4-4.5mm	90 (40.7)	22 (24.4)	
>4.5mm	79 (35.7)	16 (20.3)	
Bone graft			0.551
No	149 (68.3)	29 (19.5)	
Yes	69 (31.7)	14 (20.3)	
Failure			
No	215 (97.3)	39 (18.1)	
Yes	6 (2.7)	6 (100.0)	
PI			
No	176 (79.6)		
Yes	45 (20.4)		

N or n, number; PI, peri-implantitis; SRP, scaling and root planing; y, year(s).
**p<0.01; *** P<0.001.

Overall, no correlation was found between increased staging and grading and increased prevalence of PI at both implant- (Table 13, Figure 3 Panels C and D) and patient-levels (Figure 8 Panels A and B).

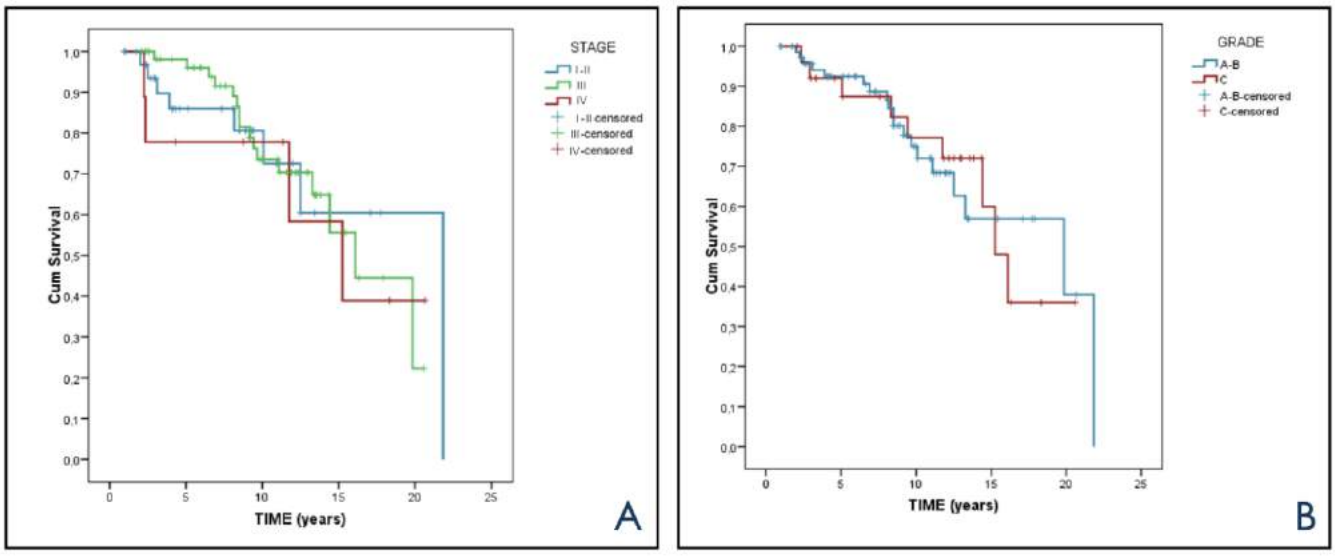

Figure 5. (A) Cumulative survival function estimated by Kaplan Meier's method illustrating implant level time-to-PI diagnosis events by stage; (B) Cumulative survival function estimated by Kaplan Meier's method illustrating implant-level time-to-PI diagnosis event by grade. "Cum Survival" on the Y-axis denotes PI diagnosis events; PI, peri-implantitis.

Cox proportional hazard regression analysis (Table 13) demonstrated a HR of 1.90 (p=0.027) based on implant diameter, such that each additional 1 mm increase in diameter was associated with a 1.9-fold increased risk of PI diagnosis.

Table 13. Results of Cox proportional hazard regression model illustrating time-to-event PI by clinical variables related to the patient, implant position, characteristics, and surgery.

Characteristic	HR	95% CI	p-value
Age, y	1.03	0.99 – 1.08	0.145
Gender			
Male	1		
Female	1.07	0.49 – 2.32	0.874
Smoking			0.820
No	1		
Former smoker	1.17	0.44 – 3.07	0.763
Yes (<10 cigarettes/day)	0.71	0.25 – 2.06	0.531

Yes (≥10 cigarettes/day)	0.68	0.22 – 2.14	0.513
Diabetes			
No	1		
Yes	2.21	0.72 – 6.82	0.166
Stage			0.805
1-2	1		
3	0.90	0.35 – 2.28	0.819
4	1.23	0.30 – 5.05	0.776
Grade			
A-B	1		
C	1.00	0.46 – 2.17	0.996
Extent			
Localized	1		
Generalized	1.16	0.48 – 2.82	0.740
Total follow up, y	--	--	--
Radiographic follow up, y	--	--	--
Arch			
Maxilla	1		
Mandible	1.20	0.59 – 2.45	0.607
Position			
Anterior	1		
Posterior	2.19	0.41 – 11.8	0.359
Prosthesis type			
Single	1		
Splinted	1.33	0.56 – 3.11	0.518
Overdenture	--	--	--
Level			
Soft	1		
Bone	2.07	0.54 – 7.92	0.289

Connection			
Internal	1		
External	0.11	0.02 – 0.68	**0.018***
Locator	--	--	--
Retention			
Cemented	1		
Screwed	5.43	1.15 – 25.8	**0.033***
Ball attachment	--	--	--
Implant length, mm	1.16	0.92 – 1.48	0.223
Implant diameter, mm	1.90	1.08 – 3.36	**0.027***
Bone graft			
No	1		
Yes	1.22	0.56 – 2.67	0.624

HR, hazard ratio; PI, peri-implantitis; y, year(s).Wald test *p<0.05.

Furthermore, external connections were associated with a lower risk of PI compared to internal connections (HR=0.11; p=0.018). Distribution of implants diagnosed with PI (n=45) according to the severity of bone loss is shown in Figure 6 Panel A. Severity of MBL was associated with increased grading (A-B *versus* C), but not with increased staging (Figure 6 Panel B).

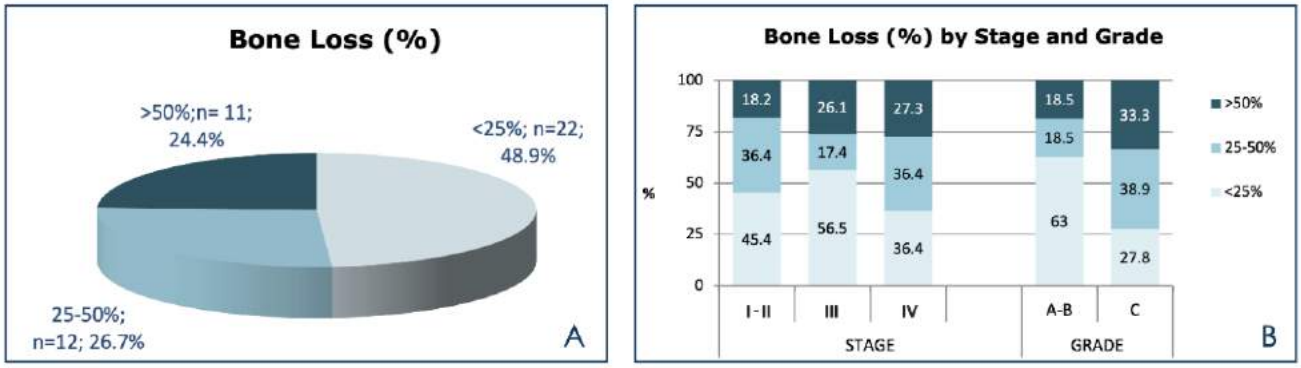

Figure 6. (A) Distribution of implants diagnosed with PI (n=45) according to MBL severity (<25%/25-50%/>50% of implant length); (B) Categorization of implants diagnosed with PI according to baseline staging/grading and severity of MBL.
MBL, marginal bone loss; PI, peri-implantitis.

Results from the binary logistic regression model using GEE with fixed follow-up, showed that grading significantly influenced the risk of high MBL (>25%) (p=0.022). Risk of severe MBL increased roughly 7.6 times for patients with a previous history of PR grade C compared to the reference grades A/B. Furthermore, there was no significant difference in risk of severe MBL according to stage (p=0.399) (Table 14).

Table 14. Risk of ≥25% bone loss according to PR diagnosis (stage and grade) adjusted by time since crown placement to radiographic analysis

	OR	95% CI	p-value
Stage			0.399
1-2	1		
3	0.26	0.04 – 1.93	0.186
4	0.25	0.03 – 2.16	0.209
Grade			
A-B	1		
C	7.61	1.35 – 43.1	**0.022***
Radiographic follow up, y	1.11	0.97 – 1.28	0.127

The results of the binary logistic regression model were evaluated using GEE, generalized estimation equations; adjusted odds ratio (OR), and 95% CI.
*P < 0.05.

STUDY #3

Title:

Limited MBL in implant-supported fixed full-arch rehabilitations after 5 years of follow-up in fully edentulous patients with history of PR[96]

Materials and methods

Study population

This retrospective cohort study was presented to and approved by the Ethics Committee for Human Research of the University of Granada, that waived the obtaining of informed consent (487/CEIH/2018).

Patients (n=19, number of implants=160) for the current study were selected from a pool of edentulous subjects due to severe periodontal disease restored with fixed implant-supported full-arch screw-retained rehabilitations, who have been in function for at least 5 years. Only those who attended at least 1 follow-up visit per year in which radiographic evaluation was performed were included. Type of implants and prosthesis, as described below, also defined inclusion. All those patients had been treated in a faculty clinic of the Department of Oral Surgery and Implant Dentistry of the University of Granada. If the patient's records indicated that the subject had undergone any kind of bone augmentation procedure, except sinus floor elevation when vertical bone in the posterior maxilla was less than 8 mm,[107] or was taking any kind of medications known to affect bone metabolism, data from that subject would not be included in the analysis. If the patient's records indicated an uncontrolled progression of periodontal disease in the opposing arch within the follow-up period of the study according to the definition by Lopez and collaborators,[108] data from that subject would not be included in the analysis either.

Surgical procedures

An experienced surgeon (P.G.-M.) performed all the surgeries under local anesthesia (Ultracain®, Aventis Inc., Frankfurt, Germany) with a regular implant placement protocol. No bone augmentation was needed in any case except maxillary sinus floor elevation. All implants

included in the current study were of the same type (OsseoSpeed™ Astra Tech TX implants with internal tapered conical connection, Dentsply Implants, Mölndal, Sweden).

The position of each implant was prosthetically driven with the following criteria by Misch and Silc:[109] 1) Implants on occlusal guides. So, for anterior disocclusion, implants were placed in the central incisors; for lateral group function or canine guide, implants were placed in the canine and the first premolars; finally, for molar occlusion, implants were placed in the position of each first molar; 2) No more than 2 pontics; 3) In addition, horizontal cantilevers were avoided by the appropriate bucco-lingual emergence of the implant. All implants were placed at the level of the bone crest.

After the implant surgery, amoxicillin/clavulanic acid tablets (875/125 mg, TID for 7 days) or, if allergic to penicillin, clindamycin tablets (300 mg, TID for 7 days) were prescribed to all patients. In addition, anti-inflammatory drugs (Ibuprofen 600 mg every 4-6 hr as needed to a maximum of 3,600 mg/day) and pain-killers (metamizole 550 mg every 4-6 hr only if needed) were also indicated.

Restorative procedure

Eight weeks – or 6 months if maxillary sinus floor elevation was conducted – later the restorative process was initiated by experienced implantologists (MP-M and PG-M) with the necessary second stage. In all cases, uni-abutments (Dentsply Implants, Mölndal, Sweden) were interposed between the implants and the prosthesis for the design of metal-ceramic screw-retained restorations. Segmented restorations were fabricated in all cases. Only in one patient, both arches were restored simultaneously and, thus, considered for this study.

Radiographic evaluation of MBL

MBL after 5 years was evaluated by importing the panoramic radiographs into ImageJ in anonymous Digital Imaging and Communications in Medicine (DICOM) format. An experienced examiner (MP-M) analyzed all the radiographs. Linear measures were obtained from the shoulder of the implant to the most coronal aspect of the supporting crestal bone, assigning a negative value when it was apically located with respect to the implant shoulder. Measurements

on both the mesial and distal aspects of the implants were recorded, so that the average value could be calculated. Each measure was calibrated against the diameter of the implant.

Before the analysis of any of the study images, the examiner (MP-M) conducted an intra-examiner calibration exercise following the same methodology described above. Briefly, 16 implant positions were evaluated twice with a time window of 7 days between measurements. The Intraclass Correlation Coefficient for single measures was calculated with a two-way mixed model. The calculated intraclass correlation was 0.892.

Additional data recorded

Other data recorded included age, gender, dental arch, need of sinus graft and location, and length and diameter of each implant. Prosthetic variables included in this study were: 1) abutment height: 1, 2, 4 or 6 mm; 2) prosthesis height defined as the distance from the connection between the prosthesis and the abutment to the most occlusal aspect of the ceramic; 3) Prosthesis-to-implant ratio, calculated as the ratio between the length of the implant and the sum of the prosthesis and the abutment heights; 4) implants per bridge, that included how many implants were supporting each particular bridge; 5) crowns per bridge, considering how many crowns were included in each bridge; 6) bridge ratio, defined as the ratio between the number of implants and crowns per bridge; 7) opposing arch, to describe the type of dentition in the other arch, considering the whole arch as a unit: natural dentition, implant-supported full-arch screw-retained restoration, mixed, or removable denture (either implant-retained or conventional).

Statistical analysis

A total of 160 implants placed in 19 patients were explored in this retrospective study. Even when data beyond the 5-year follow-up were available, they were not considered in order to homogeneize the analysis. To this end, we used a mixed linear model to estimate the effects of graft, abutment height, and opposing arch on average MBL (distal and mesial), controlling for gender, age, implant location, implant length and diameter, and the remaining additional variables (crowns per bridge, prosthesis to implant ratio, implants per bridge, bridge ratio, and prosthesis height), while controlling for subject clustering. The covariance matrix was selected

(compound symmetry) using the Schwarz Bayesian Criterion. We used the IBM SPSS v23 program for Windows (IBM Corporation, Armonk, NY).

Results

From the initial pool of patients whose records were retrieved from the database according to the criteria defined earlier, no patient was excluded. Table 15 displays the distribution of non-metric variables in the sample. It can be seen that except for gender, all the other variables were significantly distributed using proportion test.

Table 15. Frequency distribution of the variables analyzed in the study

Variable					*P*
Gender	Women = 10	Men= 9			0.819
Implant location	Mandible = 61	Maxilla= 99			**0.003**
Maxillary sinus floor augmentation	No = 128	Yes = 32			**0.001**
Implant diameter	3.5mm = 42	≥4mm = 118			**0.001**
Abutment height, mm	1 = 31	2 = 78	4 = 34	6 = 17	**0.001**
Opposing arch	ND = 36	M = 66	ISFB= 51	RD = 7	**0.001**

ISFB: implant-supported fixed bridge; ; M: mixed; ND: natural dentition; RD: removable denture.
Note: For abutment height and opposing arch, proportions tests were done for the lowest category

Table 16 describes the metric variables, including the MBL.

Table 16. Descriptive statistics of the study population.

Variable	Mean	SE	95% CI
Age	55.625	0.613	54.414 – 58.836
Implant length, mm	11.809	0.192	11.429 – 12.189
Prosthesis height	12.849	0.279	12.299 – 13.400
Prosthesis-to-implant ratio	1.380	**0.048**	1.286 – 1.475
Implants per bridge	4.694	0.189	4.302 – 5.067
Crowns per bridge	7.956	0.324	7.317 – 8.595
Bridge ratio	1.695	**0.022**	1.652 – 1.739
MBL average	-0.423	0.069	-0.559 - -0.288

CI: confidence interval; SE: standard error; MBL: marginal bone level.

Results of the mixed linear model demonstrate a main effect on MBL of abutment height, $F(3,142)=6.917$, $p<0.001$), and implant diameter, $F(1,141)=15.059$, $p<0.001$. The magnitude of the random effect was 32.6%. As it can be seen in Table 17, no other effects were significant. MBL was greater for narrow (-0.510, SE=0.169) than for wide implants (-0.364, SE=0.190).

Table 17. Estimates from the mixed linear model.

Parameter	Regression Coefficient	SE	95% CI
Abutment height 1	-0.740	0.271	-1.276 - -0.205
Abutment height 2	-0.098	0.218	-0.529 – 0.333
Abutment height 4	0.078	0.216	-0.349 -0.505
Opposing arch 1	0.155	0.606	-1.104 – 1.414
Opposing arch 2	-0.015	0.597	-1.260 – 1.230
Opposing arch 3	0.740	0.700	-0.719 – 2.200
Maxillary sinus floor augmentation	-0.147	0.138	-0.419 – 0.126
Implant diameter	0.487	0.125	0.238 – 0.736
Gender	0.108	0.208	-0.343 – 0.559
Age	0.029	0.020	-0.013 – 0.072
Implant location	-0.117	0.184	-0.483 – 0.249
Implant length	0.021	0.059	-0.097 – 0.139
Crown height	0.010	0.037	-0.062 – 0.083
Crown/implant ratio	0.318	0.349	-0.373 – 1.008
Implant per bridge	0.410	0.238	-0.061 – 0.881
Crown per bridge	-0.243	0.140	-0.521 – 0.034
Bridge ratio	0.543	0.505	-0.456 – 1.542

Note: Abutment height, opposing arch and maxillary sinus floor augmentation were considered as factor, and the reference was the last category.
CI, confidence interval; SE, standard error.

Regarding abutment height, Bonferroni corrected pairwise comparisons showed that MBL was greater for abutment height = 1mm (MBL= -0.987, SE=0.186) compared to the remaining heights: -0.335 (0.171), -0.169 (0.192), and -0.247 (0.267), namely 2mm, 4mm, and 6mm, respectively (Figure 7).

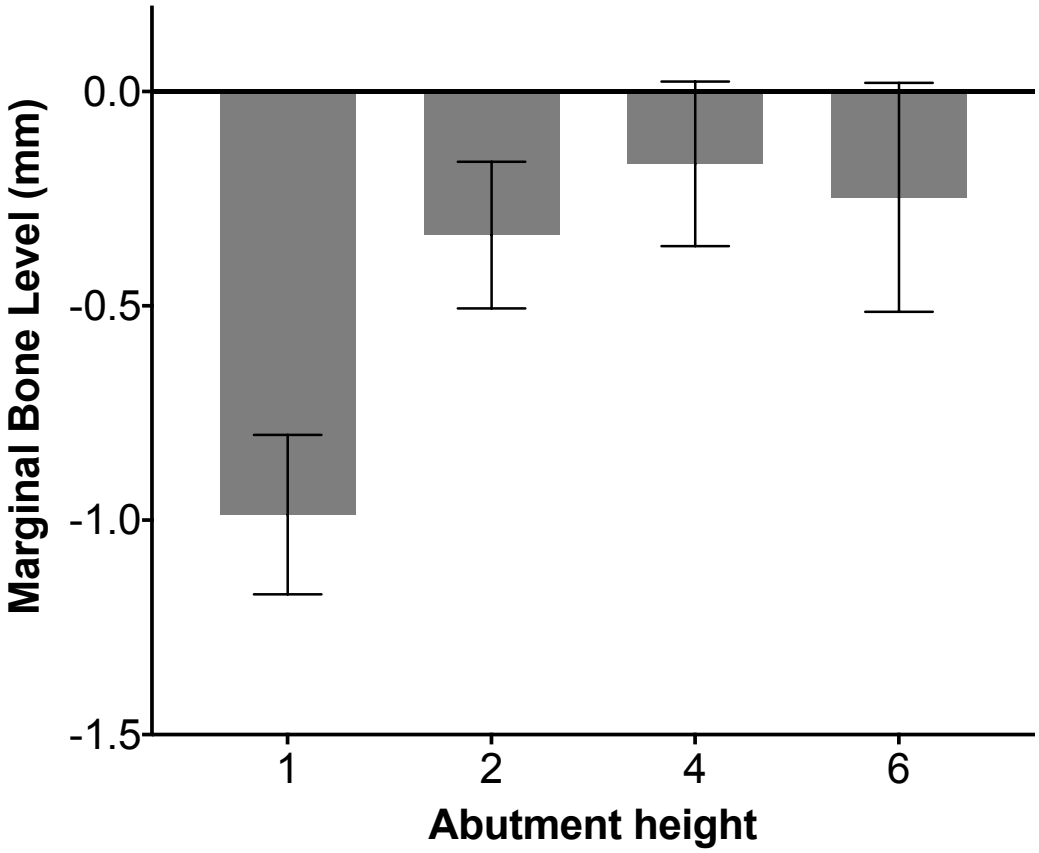

Figure 7. Average MBL level (in mm) for the different abutment heights. MBL for the abutment height 1 mm was significantly greater than for the other 3 abutment heights.
MBL, marginal bone level.

The adjusted and unadjusted mean MBLs by abutment height are displayed in Table 18.

Table 18. Adjusted and unadjusted mean MBL according to abutment height in mm.

Abutment Height:	1mm	2mm	4mm	6mm
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Adjusted MBL	-0.987 (0.186)	-0.335 (0.171)	-0.169 (0.192)	-0.247 (0.267)
Unadjusted MBL	-1.241 (0.188)	-0.295 (0.077)	-0.202 (0.076)	0.045 (0.024)

MBL, marginal bone level; SE, standard error of the mean.

In addition, we performed a tabulation of the MBL as a function of abutment height (Table 19 and Figure 8) in order to compare with the stratification proposed by Derks and coauthors.[7]

Table 19. Frequency distribution of MBL (in mm).as a function of implant abutment height.

	MBL						N Implants
Abutment Height	<-4	≥-4, <-3	≥-3, <-2	≥-2, <-1	≥-1, <0	≥0	
1 mm	0	5	7	3	13	3	31
2 mm	1	0	0	5	40	32	78
4 mm	0	0	1	1	22	10	34
6 mm	0	0	0	0	4	13	17
N patients	0	0	0	3	11	5	19
Worst case (mm)	-4.28	-3.06	-2.67	-1.91	-0.96	0	

MBL, marginal bone level; N, number.
Note: The patient's frequency data is based on patient's averages. The worst case is the worst MBL for the set of patients showing each category of MBL.

As can be observed, most implants have less than 1.00 mm of MBL in all abutment heights; MBL greater than 3.00mm are only present in 5 implants that were restored with abutments of 1.00 mm of height. Furthermore, according to the criterion of 2 mm of MBL to distinguish between success or survival implants from the 2008 Pisa Consensus Conference,[110] only 14 (8.75%) implants can be considered as survival implants while the others can be considered successful in terms of bone maintenance. No failure was reported after 5 years of follow-up.

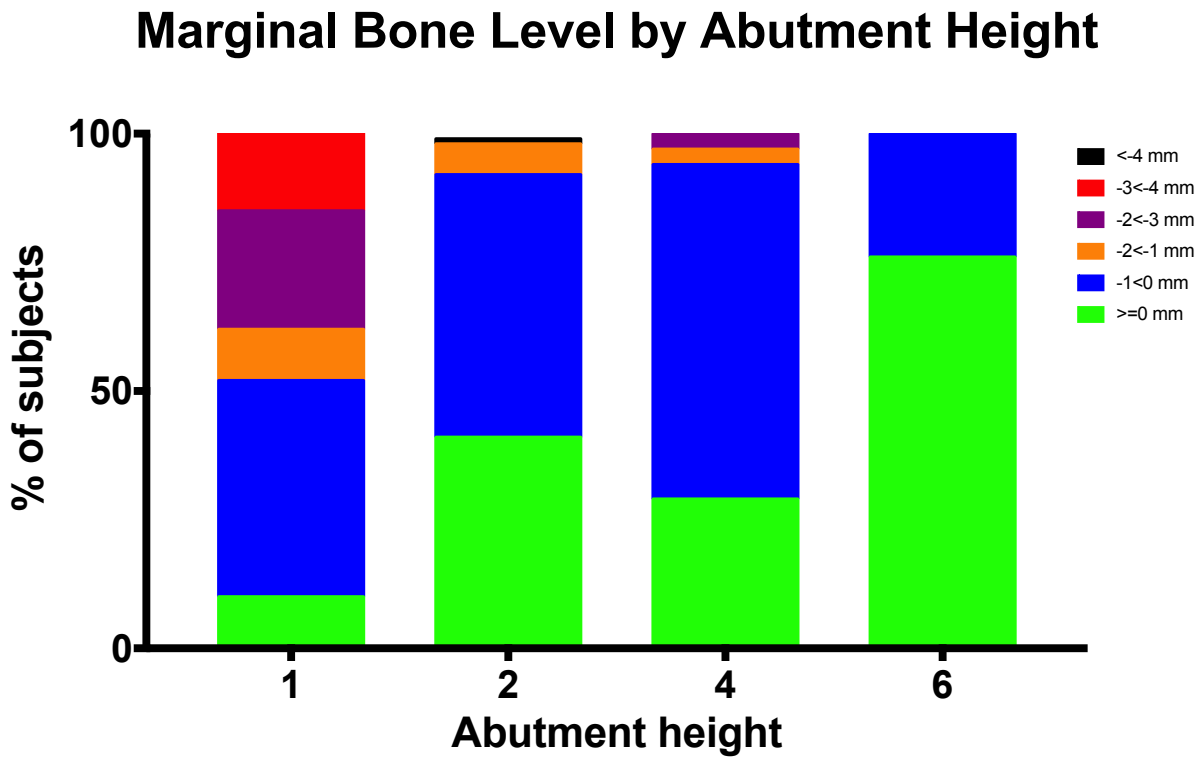

Figure 8. Tabulation of MBL as a function of abutment height to represent the proportion of implants within each range of MBL (in mm) depending on the height of the abutment (in mm). MBL, marginal bone level.

5. STUDY #4

Title:

The role of KMW as a risk factor for peri-implant disease: a systematic review, meta-analysis and trial sequential analysis[97]

Materials and methods

PECO question

The focused clinical question of this systematic review was formatted according to the PECO (Population, Exposure, Comparison, Outcome) framework:[111]

Is lack of the prespecified ≥2 mm peri-implant KMW a risk factor for peri-implant disease in adult human subjects?

- Population: Systemically healthy adult human subjects undergoing implant therapy
- Exposure: Presence of <2 mm of KMW at the time of implant placement
- Comparison: Presence of ≥2 mm of KMW at the time of implant placement
- Outcomes:
    1. Clinical: Implant survival rate, changes in peri-implant probing depth (PD), REC, CAL, mean gingival index (mGI), mean plaque index score (mPI), incidence of PI (combined clinical and radiographic)
    2. Radiographic: MBL
    3. Patient-reported outcomes (PROMs): Brushing discomfort (assessed immediately following toothbrushing)

Eligibility criteria

Clinical studies must have fulfilled the following inclusion criteria to be considered eligible for inclusion in this systematic review: (i) randomized or non-randomized controlled or non-controlled clinical trials, (ii) ≥1 year of follow-up from restoration delivery, (iii) human subjects

≥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.

Protocol and registration

This review was registered in the online database PROSPERO (International Prospective Register of Systematic Reviews) with the registration number CRD42021233756. Its conduct followed the guidance by the Cochrane Handbook;[112] and the results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[113]

Information sources and search strategies

A comprehensive and systematic search was conducted in the electronic bibliographic databases the National Library of Medicine (MEDLINE via PubMed), Scopus, and Web of Science to identify articles as well as ongoing/unpublished investigations that potentially satisfied the eligibility criteria. The literature search was conducted in an independent manner by two reviewers (A.R. and V.C.A.C.). The protocol for the bibliographic search comprised MESH terms and free text words combined through Boolean operators (AND, OR). The following combination of terms 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, 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, and 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 were requested by emailing the corresponding author(s) of an investigation.

Study selection and data collection

Upon removal of duplicate records, the titles and abstracts were evaluated in duplicate and independently by two reviewers (AR and VCAC). Studies determined to be potentially 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 (GT) 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: name of the 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[59] and no response was received by the other.[114]

Risk of bias assessment

Risk of bias was assessed by two authors (VCAC and CA) independently; disagreements were resolved by open discussion and consensus. Non-RCTs were assessed using the ROBINS-I (Risk Of Bias In Non-randomised Studies - of Interventions) tool.[115] The prospective cohort study were assessed using Newcastle-Ottawa scale (NOS).[116]

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.[117] 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 the online platform developed and recommended by the Cochrane Collaboration Review Manager (RevMan) version 5.4 (https://training.cochrane.org/online-learning/core-software/revman). The pooled mean difference (MD) and 95% CI were the outcomes 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 of .05 as the threshold for statistical significance.

Results

Study selection

Following removal of duplicate records, a total of 1,264 records remained for screening by title and abstract. Results of the number of records identified from each bibliographic database are reported in Table 20.

Table 20. Details of search strings used in the selection process in each online database.

Database	Search Strategy	N Records
PubMed/ Medline	(“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”)	661
Scopus	(“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”)	2,922

Web of Science	(“dental implant” OR “dental implantation” OR “oral implant” OR “implant” OR “dental implants”) (All Fields) AND (“gingival height” OR “tissue thickness” OR “tissue biotype” OR “tissue phenotype” OR “tissue width” OR “keratinized mucosa”) (All Fields)	782

N, number.

A total of 26 reports were then considered for full-text screening. Finally, nine studies fulfilled the eligibility criteria and were selected for data extraction. [59, 84, 114, 118-123] The reasons due to 17 articles were excluded are summarized in Figure 9 and Table 21. Kappa scores for inter-examiner agreement for title and abstract review as well as full-text review were 0.85 and 0.87, respectively. A flowchart of the entire selection process is displayed in Figure 9.

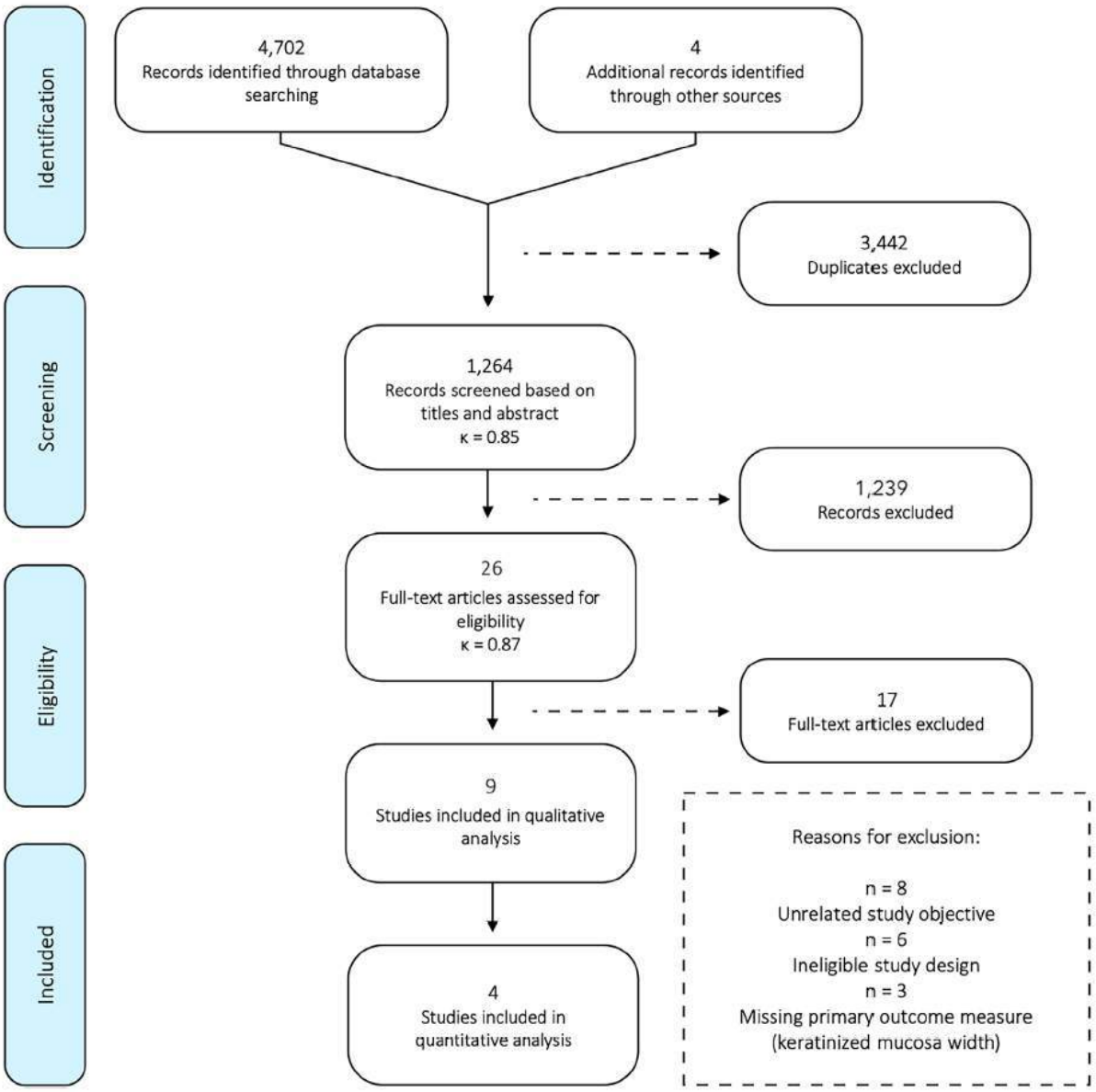

Figure 9. The selection process.

Table 21. Excluded studies with the most important reason for exclusion.

Study	Exclusion Reason
Bhat et al. 2015[124]	The comparison is made on soft tissue thickness
Bittner et al. 2019[125]	The comparison is made on soft tissue thickness
Blanco et al. 2018[57]	Not related to the topic
Bonino et al. 2018[126]	Not related to the topic
Botticelli et al. 2008[127]	Not optimal for the assessment
ElSyad et al. 2018[128]	Not related to the topic
Garaicoa-Pazmino et al. 2021[129]	The comparison is made based on soft tissue thickness
Gallucci et al. 2009[130]	Not optimal for the assessment
Hof et al. 2014[131]	Not optimal for the assessment (retrospective)
Kim et al. 2009[132]	Not optimal for the assessment (retrospective)
Linkevicius et al. 2018[133]	Not related to the topic
Mameno et al. 2019[134]	Not optimal for the assessment
Radaelli et al. 2020[135]	Not related to the topic
Romanos et al. 2015[136]	Not related to the topic
Roos-Jansaker et al.2006[13]	Not optimal for the assessment (retrospective)
Schmidt et al. 2019[137]	Not related to the topic
Schwarz et al. 2018[138]	Not optimal for the assessment (retrospective)
Shimomoto et al. 2021[139]	Not optimal for the assessment
Souza et al. 2016[140]	Not optimal for the assessment (retrospective)
Sukuroglu & Baltacioglu 2019[141]	Not related to the topic
Weber et al. 2006[142]	Not optimal for the assessment

Characteristics of the included studies

Study design

Five of the studies were prospective cohort studies,[84, 114, 118, 121, 122] 3 were non-RCTs,[119, 120, 123]and 1 was an RCT.[59] Seven studies were carried out solely in academic settings,[59, 114, 119-123] while the remaining two were conducted in both academic and private practice settings.[84, 118] All but one

of the studies[84] 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.

Clinical scenarios

Recipient arch distribution and characteristics varied between the included studies Four studies reported having only mandibular implants,[59, 84, 119, 122] and four studies reported(Table 22). having both maxillary and mandibular implants.[114, 118, 120, 123] One study did not report the location of implant placement.[121]

Three studies included partially edentulous arches only,[120, 121, 123] four included completely edentulous arches exclusively,[59, 84, 119, 122] and one study involved treatment of both partially and completely edentulous arches.[118]

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 22.

Observational periods

The follow-up period ranged between 1 and 5 years (Table 22). One study reported a 1-year follow-up period,[119] one study reported a 2-year follow-up period,[118] two studies reported a 4-year follow-up,[120, 123] one study reported a 4.5-year follow-up period,[121] and four studies reported a 5-year follow-up period.[59, 84, 114, 122]

Table 22. Characteristics and qualitative data of the included studies.

	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 of 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
Number of implants 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

Abbreviations: KMW, keratinized mucosa width; NR, not reported.

Quality of the evidence and risk of bias assessment

The results of risk of bias assessment according to the specific assessment tools of included studies are displayed for the prospective studies (Table 23)[116] and for the non-RCTs (Table 24),[115] respectively.

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Table 23. Evaluation of risk of bias in prospective cohort studies using the NOS.[116]

Author Year Reference n	Country	Case Definition Adequacy	Cases Represen-tativeness	Selection of Controls	Defini-tion of Controls	Compa-rability Cases/ Controls	Ascertain -ment of Exposure	Same Method of Ascertain-ment
Mericske-Stern 1994[122]	Switzer-land	A	A	A	A	A	A	A
Bengazi 1996[118]	Sweden	I	A	I	I	I	A	A
Schrott 2009[84]	USA	A	A	A	A	A	A	A
Fernandes-Costa 2019[121]	Brazil	I	A	I	I	I	A	A

A, adequate; I, inadequate; NOS, Newcastle-Ottawa Scale.

Table 24. Risk of bias of included non RCTs withe the ROBINS-I tool. [115]

Author Year	Con-foun-ding	Selection of Partici-pants	Classifi-cation of Interven-tions	Deviation from In-tended Interven-tions	Missing Data	Measure-ment of Outcomes	Selection of the Reported Results		Overall Risk of Bias
Crespi 2010[120]	Low	Low	Low	Low	Low	Low	Low		Low
Boynueğri 2013[119]	Low	Low	Low	Low	Low	Low	Low		Low
Perussolo 2018[123]	Low	Low	Mode-rate	Low	Mode-rate	High	Low		High
De Siqueira 2020[59]	Low	Low	Low	Low	Low	Low	Low		Low
Lim 2018[114]	Low	Low	Low	Low	Mode-rate	Low	Low		Mode-rate

RCT, randomized controlled trial; ROBINS-I, Risk Of Bias In Non-randomised Studies - of Interventions.

When considering the non-randomized included studies, three studies reported low risk of bias,[59, 119, 120] while the studies by Lim et al. and Perussolo et al. were considered at moderate

and high risk of bias,[114, 123] respectively. Finally, half of the prospective cohort studies demonstrated low risk of bias,[84, 122] while two studies,[118, 121] 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 25). 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 mm KMW is associated with either increased MBL or PD, and there is very low-quality evidence to support that the presence of <2 mm KMW is associated with increased REC (Table 25).

Table 25. Summary of findings table with the GRADE approach quality of evidence assessment.

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 (I^2; %)	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 (≥2 mm)	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 (≥2 mm)	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 (≥2 mm)	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 (≥2 mm)	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.[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.
Implant survival rate[c]	See comment	NA	NA	NA	NA	-
Clinical attachment level[c]	See comment	NA	NA	64 (1)	⊕◯◯◯ Very low	One study[29] 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), ($p = 0.319$).

Note: 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.

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.

[a]The GRADE level was changed as follows: Certainty in the evidence downgraded by one level due to serious inconsistency; certainty in the evidence downgraded by two levels due to very serious inconsistency; and certainty in the evidence downgraded by one 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.

Quantitative assessment of outcomes

Results from four publications[59, 120, 122, 123] were statistically comparable and were included for quantitative synthesis. Overall, data from 685 implants were pooled (178 in the KMW <2 mm group, 507 in the KMW ≥2 mm group).

Meta-analysis and TSA for the outcome MBL

Two studies[59, 123] 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 greater 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 10 Panel A). However, such results were not confirmed after adjusting for types 1 and 2 errors in TSA. This absence of statistical significance in TSA can also be graphically noticed in Figure 10 Panel B 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 that such findings were underpowered since the number of included implants (274) was lower than the calculated RIS of 424 implants.

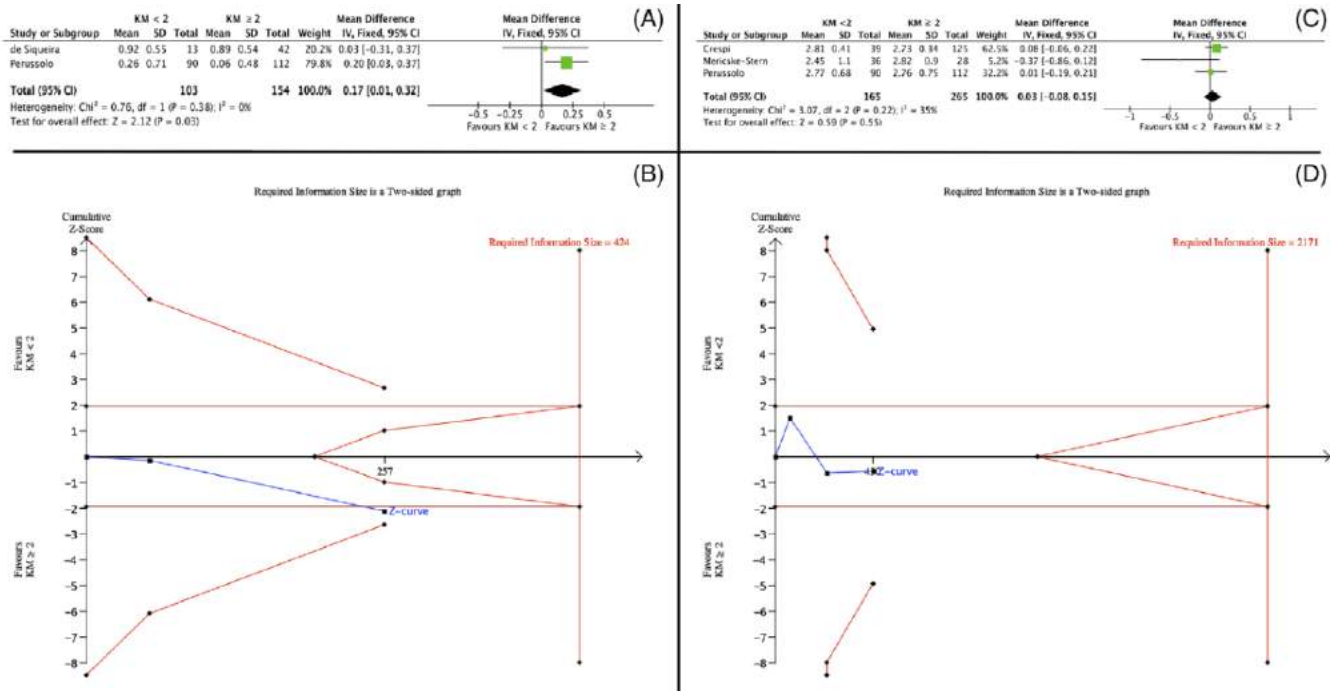

Figure 10. Meta-analysis (A) and TSA (B) of MBL. Meta-analysis (C) and TSA (D) of PD change. MBL, marginal bone loss; PD, peri-implant probing depth; TSA, trial sequential analysis.

Meta-analysis and TSA for the outcome PD reduction

Three studies[120, 122, 123] including a total of 430 implants (265 with KMW ≥2mm and 165 with KMW <2mm) were entered in a meta-analysis of PD reduction. The pooled MD and 95% CI by the 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 10 Panel C). 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 in Figure 10 Panel D 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 (n = 430) of included implants is lower than the calculated RIS of 2,171 implants.

Meta-analysis and TSA for REC

Two studies[59, 120] including a total of 219 implants (52 with KMW ≥2mm and 167 with KMW <2mm) were entered in meta-analysis for REC. The pooled MD and 95% CI at random-effect model showed the absence of a statistically significant difference (overall effect p-value = 0.39) in REC 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 11 Panel A). They were also confirmed after adjusting for types 1 and 2 errors in TSA, the absence of statistically significance results is also graphically shown in Figure 11 Panel B 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 2,525 implants.

Meta-analysis and TSA for the outcome mPI

Three studies[120, 122, 123] 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 11 Panel C). They were also confirmed after adjusting for types 1 and 2 errors in TSA. The statistical significance of the results is also graphically shown in Figure 11 Panel D 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) is greater than the calculated RIS of 310 implants.

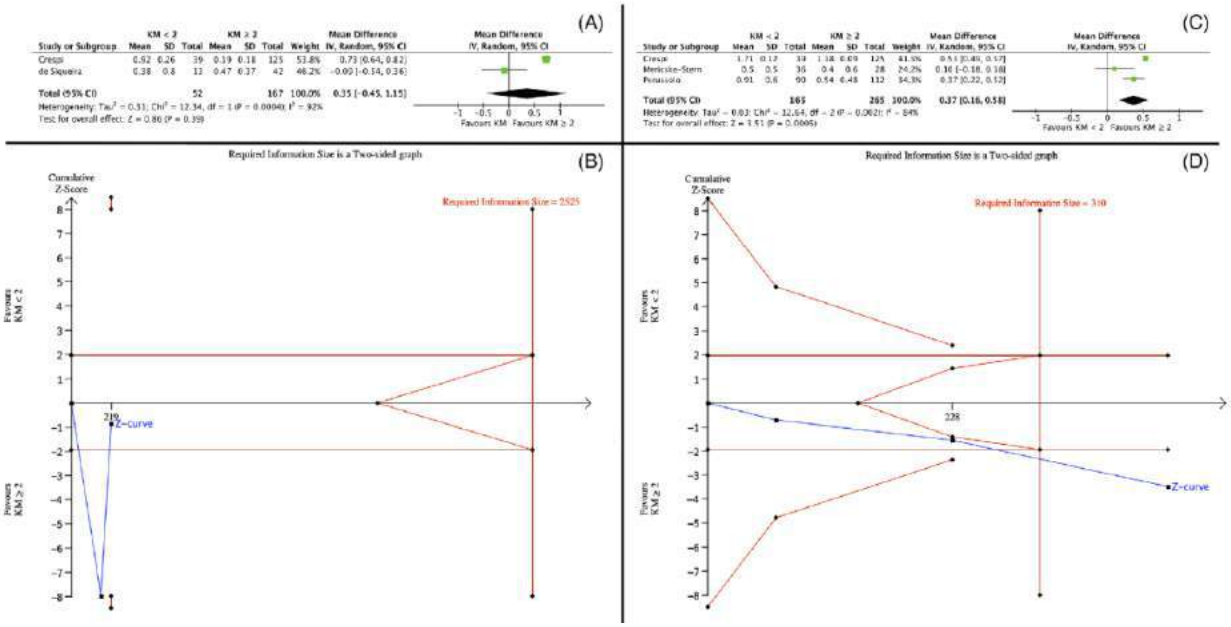

Figure 11. M eta-analysis (A) and TSA (B) of REC; meta-analysis (C) and TSA (D) of mPI.
mPI, mean plaque index score; REC, soft tissue recession; TSA, trial sequential analysis.

Meta-analysis and TSA for the outcomes: Implant survival rate, CAL, GI, and incidence of PI

Comparable articles concerning these four outcome variables were not found.

Brushing discomfort assessment

One study assessed the brushing discomfort in both clinical scenarios.[123] Visual analogue scale (VAS) scores at 4 years of follow-up showed that the level of discomfort experienced was greater 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 mm reported no discomfort while 51.4% of patients with KM<2 mm reported some level of discomfort.

6. DISCUSSION

STUDY #1: Interproximal implant thread exposure after initial bone remodeling as a risk indicator for PI[94]

Main findings

Because PI is difficult to arrest once established, identification of its modifiable risk factors is key for prevention. In the present study, we examined the role of implant threads being radiographically exposed (no BIC) upon physiologic bone remodeling. The results demonstrated an 8-fold increased risk for PI in implants with exposed threads compared to those with non-exposed threads. The risk increased 4-fold with each additional thread exposed. Also, splinting was associated with greater risk for PI (OR=3.49; 95% CI: 1.02 – 12.05; p=0.047). No other confounding patient-level factor (other than age), or implant macro- or micro-design feature was identified as a potential risk factor.

The reason for exploring other potential risk factors was not only to identify them, but to ensure statistically that such confounders might not actually be causing the incident PI instead of the thread exposure. Successful treatment of PI is very challenging. Retaining such success through maintenance has been shown to be challenging as well, as demonstrated by a systematic review and meta-analysis finding that there was merely <5% reduction in the risk of implant loss for patients undergoing periodic maintenance therapy, compared to those who did not. [143] In a recent study, patients without maintenance therapy had 4.25 times greater risk for PI, [19] which was in contrast to the present study in which the mean number of annual maintenance visits was found to not be associated with incident PI.

Our findings suggest that the only modifiable statistically significant patient- and implant-related risk factor for incident PI was the number of implant threads exposed one year after prosthetic implant restorations, and this impact was dose-dependent. To the best of our knowledge, this is the first time such conclusion has been demonstrated by rigorous research, even though this result seems intuitive. Since the body of literature appears to be void of relevant findings, we cannot compare this main finding to prior research results.

Interestingly, severity of PR was not a significant factor for incidence of PI in this study. This finding is in line with the results of the meta-analysis published in 2016, which obviously could not have applied the 2017 World Workshop case definitions for either disease.[143] A systematic review by Doornewaard and co-authors supports our finding that implant surface roughness was not a significant factor for PI.[99] It is noteworthy that we applied the current classification of both PR and PI defined by the 2017 World Workshop, and therefore, any direct comparison to prior research would benefit from reassessing the classification of both diseases in the older studies.

Despite the multitude of operators and potentially changing protocols related to implant placement and restoration at a dental school over a period of 18 years, only 8 (2.9%) implants, from this series, failed. The overall implant level PI rate was 9.6% (and only 4.4% of the implants that did not have any interproximal threads exposed after the initial physiologic bone remodeling), which is well within, actually at the lower end of, the reported prevalence range between 0.4% and 85%.[100, 144-148] Importantly, almost one-fifth (19.4%) of the implants with such thread exposure developed PI. This is the same overall rate as that found for implant placed by general practitioners.[6]

Our stringent eligibility criteria were selected to create the test and comparison groups for comparisons as precise and valid as possible. It requires a large source population to conduct such a study, which can be deducted from including only 165 patients from a pool of 4,325 active patients whose charts were screened. The paucity of such large, well-documented source populations may be a reason for the lack of studies like this. One of the main limitations of this study is the diverse number of implant systems used, some of which were shown to be related to the prevalence of PI. [7] The same applies to the various prosthetic designs included, some of which may be considered risk indicators for PI.[149] The presented results demonstrated that no single implant surface feature was associated with PI. Finally, we suggest that in implant treatment planning, execution, and maintenance, all possible measures to prevent development of exposed threads must be taken.

STUDY #2: The correlation between history of PR according to staging and grading and the prevalence/severity of PI in patients enrolled in maintenance therapy[17]

Main findings

This study investigated the potential association between baseline PR stage and grade and future implant failure as well as PI prevalence and severity. Ninety-nine treated PR patients were subsequently rehabilitated with dental implants (n=221) and followed over a mean period of 10.6 years. Patients were classified according to PR stage and grade at the time of active periodontal therapy. Over the follow-up period, only 6 implants (2.7%) failed. Although the implant failure rate increased from stage I/II (0%) to stage IV (6.5%), this trend was not statistically significant. A statistically significant increase was seen from grade A (0%) to grade C (5.9%). Interestingly, our results showed no correlation between PR staging or grading and increased prevalence/incidence of PI at either implant- or patient-levels. Although the 2017 World Workshop proposed case definitions for PI, these definitions do not facilitate differentiation between severity levels of PI based on the magnitude of MBL.[106, 150] For the current analysis, a MBL severity threshold of 25% of the implant length was chosen to be correlated with PR stage and grade. The present study found that the severity of peri-implant MBL was directly associated with greater grading level. The PR grade (C *versus* A/B) significantly influenced risk of high MBL (>25%) (p=0.022). The risk of severe MBL increased 7.6 times for patients with a history of PR grade C compared to grades A/B.

Overall, these results suggest that staging and grading may not play a role in modulating the probability of PI onset, but once PI pathogenesis is initiated, higher-level grading is associated with increased severity of MBL and higher probability of implant failure, whereas PR staging is not.

Agreement and disagreement with previous studies

There are conflicting findings reported in the literature regarding the association between history of PR and implant failure. Some of the previous studies utilizing the 1999 periodontal classification[151] reported greater long-term implant failure rates in patients who exhibited more severe forms of PR (survival rate range: 88% to 98.4%) compared to those who had moderate/mild PR (survival rate range: 92.8% to 100%).[152-156] However, others did not confirm

this correlation. [157, 158] In the present study, although a greater trend for implant failure was found in patients with a history of severe PR (stages III-IV), no statistically significant differences were found due to the small number of implants lost (only 6).

PR grade is a risk assessment tool composed of a composite of systemic (smoking and diabetes mellitus) and local parameters (RBL/age). To allow for a more precise analysis of the effects of PR grades on implant failure, systemic risk factors were evaluated separately. Implants placed in current heavy smokers were associated with a significantly greater failure rate compared to never-smokers (HR=4.71; p=0.04). A recent systematic review showed that heavy smokers (>20 cigarettes/day) were at a greater risk for implant failure (HR=4; p <0.001) compared with non-smokers.[159] In addition, De Boever and colleagues reported a 17% increased implant failure rate in current smokers with a history of aggressive PR, and a 2% increase in former smokers.[160] In spite of these findings, the 2017 World Workshop recently referred to smoking and diabetes as "inconclusive" risk indicators[8] for PI development due to a lack of conclusive evidence.[28]

Our findings also did not show a significant correlation between PR severity and PI prevalence. It is important to note that the present study population was composed entirely of patients with varying levels of PR severity. Most existing studies investigating the association between PR and PI compared PR patients to those with no history of PR.[29, 160-162] However, very few correlated different levels of PR severity with prevalence and severity of PI.[152, 155, 163] Utilizing stage to categorize patients based on PR severity, results of the present investigation were similar to those from previously published studies that utilized other systems for diagnosing PR severity. Roccuzzo and team reported a PI prevalence of 27% in patients with moderate PR, and 47.2% in patients with severe PR.[163] In a subsequent study, they reported a PI prevalence of 52.2% in patients with moderate PR, and 66.7% in patients with severe PR.[155]

In the current study, patients with mild and moderate severity PR (stages I and II) had a PI prevalence of 33.3%, while patients with severe PR (stages III and IV) had a PI prevalence of 52.7%. In spite of this, the present study did not find any statistically significant association between PI prevalence and PR severity (stage).

The prevalence of PI at both implant- and patient-levels in the present study can be compared to study results by Romandini and team,[164] since that study also applied the 2017 World Workshop

definition of PI in a PR population. Over a mean follow-up of 7.8 years, the authors reported a PI prevalence of 23.2% in healthy *versus* 56.6% in PR patients. At the implant-level, they found the PI prevalence in healthy and PR patients was 12.4% and 27.9%, respectively. In comparison, the prevalence of PI in the present study was lower at a rate of 20.4% at the patient-level, and 15% at the implant-level after 10-years follow-up.

Additional factors that influenced the incidence of PI

Implant diameter and type of abutment-fixture connection were significantly associated with risk of PI development. Each additional 1 mm increase in diameter was associated with a 1.9-fold increased risk of a PI diagnosis (HR=1.90; 95% CI: 1.08 – 3.36; p = 0.027) as displayed in Table 13. Previous studies reported contradictory findings regarding implant diameter and PI risk. The majority of studies reported a greater rate of PI for narrow-diameter implants.[165-167] Others agreed with our study and showed that wider implants were associated with a greater MBL and risk of PI.[168, 169] Overall, the evidence regarding implant diameter as a contributing factor towards PI pathogenesis is limited.

Additionally, implants with external connections were associated with significantly lower prevalence of PI when compared to internal connections (HR=0.11; p=0.018). Further investigation revealed that 100% of the implants with external connection in the current study had a machined surface, which have been associated with lower PI rates.[170, 171] Previous meta-analyses have reported reduced MBL with conical internal connection implants, suggesting that the stability of the abutment-fixture connection is an important determinant of peri-implant bone levels.[172, 173] Prior clinical studies have also demonstrated better bone preservation associated with internal connection implants relative to external connection implants.[174, 175] The low number of external connection implants in our sample (18 fixtures), in conjunction with a machined surface for all of them, can potentially explain this controversial result.

STUDY #3: Limited MBL in implant-supported fixed full-arch rehabilitations after 5 years of follow-up[96]

Summary of main findings

The aim of the present study was to analyze the long-term behavior of a series of implants placed in completely edentulous patients that were restored with fixed full-arch implant-supported screw-retained rehabilitations. For that, 160 Astra Tech TX implants placed in 19 edentulous patients were studied. A mean MBL after 5 years of follow-up of -0.423 (±0.069) mm was found. This MBL is influenced only by abutment height and implant diameter.

Agreement and disagreement with previous studies

As in several previous studies, the height of the abutment was the main factor that influenced the MBL: The taller the abutment, the lesser the MBL. Although the height of the abutment, in our opinion, still does not have the full consideration that it deserves in the prosthetic restoration phases, our data are in accordance with many other studies.[55, 56, 58, 60, 61, 69, 174, 176-180]

Nonetheless, all those previous studies were conducted in single crown restorations,[178, 179] or in 2-unit bridges,[56, 58, 60, 177] 3-unit bridges,[55, 69, 174] fixed cross-arch restorations over 4 or 5 implants,[181] and overdentures.[61] To our knowledge, MBL has not previously been related to abutment height in implants supporting fixed full-arch prosthetic rehabilitations.

Implant survival

In the current study, 100% of implants could be considered as survivors. Only five implants exceeded 3 mm of MBL; thus, if we use the radiographic parameters recommended by the 2017 definition of peri-implant diseases,[9] they could be classified as diseased if accompanied by clinical parameters not evaluated in the current study. However, according to the classic success criteria of 2 mm of MBL, [182] our sample showed a radiographical success of 91.25%.

A majority of studies demonstrate that implant-supported fixed dental prostheses offer a safe and stable solution in the long term, both in terms of survival and MBL.[183-186] Regardless of highly

satisfactory outcomes, independently of the option in use, and even with a high variability of data,[187] many different aspects can be subjected to discussion. For instance, the health status of the patients, history of PR, habits, number of implants, straight or tilted position, type of prosthetic restoration, design of the prosthetic restoration, bone biology, differences between the maxilla and the mandible, one-piece restoration or segmented bridges, etc.

History of PR

In this sense, a good number of studies has reported on the negative influence of history of PR on peri-implant MBL,[163, 188-190] even becoming a highly accepted risk factor.[9] However, the present study was obtained from a pool of edentulous patients as a consequence of severe PR. The mean MBL after five years was -0.423 (0.069) mm. A similar series has recently reported an estimated average MBL after 11 years of -0.307 mm (SE=0.042).[191] In both cases, the reported MBL is in accordance with the higher standards of healthy implants. As commented previously, Francetti and coworkers agree with these results, after 5 and 10 years of follow-up.[183] Guarnieri and Ippoliti also concluded that high survival rates are expected for implants placed in periodontally compromised patients if regular SPT is conducted.[192] Cecchinato's group had also previously claimed in their studies that the percentage of sites with progressive bone loss was small at both implants and teeth and that this was not different in subjects in the "PR" or "non-PR" groups.[193, 194] Some systematic reviews show similar results.[195] Kim and Sung also reported no differences in similar conditions but greater losses when comparing with aggressive PR.[157] Monje's group found a similar tendency, but comparing only with aggressive PR.[196] Thus, there is an increased number of studies claiming that the initial statement is not so valid anymore. Current evidence is pushing the scientific community to re-analyze this concept, taking other variables into consideration.

Number of implants

Regarding the number of implants supporting a full-arch rehabilitation, it was suggested that a minimum of 6 to 8 implants in the mandible and even more in the upper maxilla would be

required.[197] For sure, the number of implants needed to do this kind of restorations depends on many factors. Some of them are biological factors, such as bone nature, density and availability, and anatomical factors, such as the location of the inferior alveolar nerve, or hyper-pneumatized maxillary sinuses. Other factors are related to biomechanics, like the type of prosthetic restoration, the materials, the prosthetic design or if it is conceived as a one-piece restoration or a multiple segmented restoration. All patients in the current series were treated with at least 8 implants per arch, following the Misch and Silc´s golden criteria,[109] as previously described. In addition, segmented restorations were done in all patients in order to improve the overall implant-prosthesis adjustment, and to be able to act only on that specific segment in case of any issue appears in the follow-up. Nevertheless, a recent meta-analysis has stated that the number of implants used in complete-arch prostheses do not influence MBL, implant survival rate, prosthesis survival rate or prosthesis complications in studies with a follow-up period between 5 and 15 years.[198] In the mandible, the number of implants suggested for an implant fixed complete dental prosthesis ranges from four to nine implants. However, Papaspyridakos and colleagues reported a larger number of implant failures in the interforaminal space.[199] This would jeopardize the 4- or 5 implant-supported rehabilitation protocols. In any case, in terms of overall implant survival, they found no statistically significant differences related to the number of implants.[199] There is no evidence in the literature to support this idea in maxilla or mandible either.[198, 200]

De Luna Gomes´ meta-analysis concluded that mean MBL was greater for full-arch prostheses with more than 4 implants per arch (mean, 1.46 mm) than for those with fewer than 5 implants (mean,1.22mm), although without statistical significance.[198] Nevertheless, this mean MBL reported is much greater than that found in our study (-0.423 (+0.069) mm). It is important to keep in mind that in the majority of these meta-analyses there were a plethora of manuscripts reporting all-on-four studies. In some of them, there is not any study with more than 6 implants per arch.[198] Thus, results should not be compared with studies with fixed full-arch rehabilitations supported by 8 implants as the type of prosthesis and treatment concept is completely different.

Implant location and bone grafting

Regarding the location of the implants, the implant survival rate in full-arch rehabilitation has been described as 99% for the maxilla and 98.9% for the mandible[198, 201] or even 100% after 3 years.[202] In the latter study, the authors reported slightly greater bone resorption in implants placed in the anterior mandible, contrary to Maló and collaborators who reported greater marginal bone loss in the posterior segment of the mandible, although those posterior implants were tilted.[184] More recently, Francetti and colleagues reported that 61.5% of the implants affected with PI were in mandibular restorations.[183] In our study, the implants survival was 100% independently of the bone typology and upper or lower location. All implants were in straight position, predominantly in the upper maxilla (61.8%); 20% of them were placed in grafted bone. However, in terms of MBL, as necessary initiation phase of PI, we were not able to find any statistically significant difference associate to location or the nature of the bone substratum. In previous studies, we found a slight significant difference in terms of MBL, it was higher in grafted maxillary sinuses compared to native bone in the posterior maxilla.[188] That study was conducted evaluating implants supporting partial fixed bridges, in contrast to the current study.

Implant type and prosthetic material

Moreover, differences in the type of implants could also explain the disparities. In relation with the type of prosthetic restoration, a recent meta-analysis studied the influence of the prosthetic material on implant survival when they are supporting a full-arch rehabilitation. It was described that metal-ceramic fixed complete dentures are more effective in terms of implant survival than any other type of material, reaching 95% of prosthesis survival and 97% of implant survival.[187] Our study, using the same restoration material, has found a prosthesis survival of 100% and implant survival of 100% in accordance with that meta-analysis.

Prosthetic segmentation

But not only the material is important. Segmentation of the dental prosthesis in smaller bridges, as done in patients included in the current study every time possible, leads to better maintenance, easier retrievability, and easier fabrication and installation.[203] Regardless, a

systematic review on this topic reported that prosthodontic survival rates for 1-piece implant fixed complete dental prostheses ranged from 98.61% (5 years) to 97.25% (10 years).[199]

Biomechanical issues

However, biomechanical issues must also be considered. Some of these biomechanical aspects can be the distribution of the masticatory load through the entire arch, and the horizontal or vertical cantilevers, as crown-to-implant ratios are usually high in these patients.[204] Even though a previous meta-analysis suggested that MBL is not influenced by the presence of horizontal cantilevers,[205] horizontal cantilevers were always avoided in this study.

Regarding the crown-to-implant ratio, our results indicated that this ratio did not play any relevant role in MBL. In fact, this is supported by other studies.[206] It has even been reported that, within the range of 0.6/1 to 2.36/1, the greater the crown-to-implant ratio the less the peri-implant bone loss.[207] None of the other prosthetic factors evaluated in this study played a role in the MBL when the height of the prosthetic abutment was part of the equation (Tables 2 and 3).

Study limitations

This study has some limitations. Firstly, it is a retrospective study with a limited number of patients. However, it reports results in a considerable number of implants in a very specific population of patients. Moreover, this is the longer follow-up study present in the literature reporting the effect of the height of the abutment in the MBL. As in many previous studies, digitalized panoramic radiographies were used. This is similar to many previous studies on fully edentulous patients already referenced throughout the discussion. A potential solution is the internal calibration that is performed for every measurement considering the dimensions of the implant. Also, recent consensus does not include the term “intraoral” examination for the follow-up of this kind of patients.[8, 49] Another potential caveat is the number of implants when categorized by abutment height. In this vein, the minimum number of implants was that of the abutment height 6 (n=17, in 5 patients). But, when we performed the same analysis excluding this abutment category, the results were the same; this is, the significance was obtained for abutment height and implant diameter. In addition, only marginal bone level data at the 5-year

follow-up are presented. It is important to remember that, for the general clinical practice, the progression of marginal bone level change and time at which it occurs (either early or late) are important in the diagnosis of PI. Moreover, clinical parameters could be helpful as supportive diagnostic tools.

STUDY #4: The role of KMW as a risk factor for peri-implant disease: a systematic review, meta-analysis and trial sequential analysis[97]

Summary of main findings

The aim of this systematic review was to assess whether – and to what extent – the current literature supports the need for KMW to achieve and maintain peri-implant health. While there have been investigations that partly address this question, particularly under the umbrella of peri-implant soft tissue augmentation procedures, the level of evidence has not been ideal.

Based on the data from currently available longitudinal studies, the results of 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 errors in TSA), REC, and PD. On the other hand, a lack of keratinized mucosa (KM) was related to increased mPI and more discomfort after brushing.

Level of evidence for KMW as a risk factor

The present study conducted the analysis using the GRADE assessment tool to observe the strength of recommendation for the results of the current review.[208] 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 keratinized mucosa width 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 REC. The imprecision domain was assessed from the sample size and its CIs, 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 underestimation or an overestimation of the beneficial or harmful effect due to the selective publication of studies.[208] 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 review. 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. According to the Cochrane Handbook, *"Although funnel plot asymmetry has long been used to detect publication bias, as a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is low".*[112]

Agreements and disagreements with previous findings

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 by Crespi's group revealed no differences in MBL between "adequate" and "inadequate" KMW.[120] Two of the studies in the current review failed to demonstrate a clinically significant difference.[59, 123] The experimental study by Strub et al. utilizing ligature-induced plaque accumulation in implants bordered by KM supports the same conclusion.[209] Conversely, a recent 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.[81] However, the reported difference of 0.11 to 0.18 mm between test and control cannot be considered clinically significant, and based on the pooled data from 2 to 4 studies, depending on the evaluated outcome. The one soft tissue parameter that seems to play a more significant role in minimizing MBL is the peri-implant STH.[52] This was first demonstrated in an experimental canine model by Berglundh and Lindhe.[11] Multiple clinical studies have also been published in the past decade demonstrating the crucial role this tissue dimension plays in reducing MBL.[62, 65]

Does <2mm of KMW at implant sites influence peri-implant probing depth?

The 2017 World Workshop identified the PD increase as one of the key parameters to establish a diagnosis of PI.[106] Clinically, the progression of the peri-implant condition from peri-implant mucositis to PI was more commonly observed in patients without regular maintenance care, and this was most associated with PD and BOP values.[1] In addition, the prospective study by Bengazi et al. showed that increased PD at baseline was a positive predictor for the amount of early REC expected to ensue.[118]

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 seems to be in agreement with the general body of evidence available as demonstrated by a recent meta-analysis of cohort and cross-sectional studies[210]. Even studies that have correlated increased PI and GI with no KM failed to identify a similar correlation with PD.[119]

While evidence from a recent network meta-analysis indirectly suggests that KMW augmentation results in significant PD reduction (0.78 mm)[211], 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. Based on the evidence at hand today, as well as a dissection of the several analyses within the network meta-analysis, it is more plausible that MT increase is the underlying cause for the reported PD reduction. This speculation is further corroborated by the earlier findings of Thoma and coworkers, who report significantly lower PD values favoring APF plus autogenous tissue versus APF alone.[81]

Does < 2mm of KM at implant sites have an influence on REC?

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. Bengazi and colleagues reported that the lack of KMW was a poor predictor of peri-implant REC.[118] They also suggested that peri-implant REC could merely be a result of soft and hard tissue remodeling to establish peri-implant STH. A non-RCT study by Roccuzzo and team comparing implants with KM versus those with alveolar mucosa reported that REC was significantly more likely at implants with a lack of KM.[76] One of the primary findings from the 3rd EAO Consensus Conference in 2012 was 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.

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 compared to those with KMW ≥2 mm. It is well-established that poor plaque control is considered a risk factor for PI.[8] In a cross-sectional study, Souza and co-workers demonstrated that the presence of KMW results in a more stable seal around the implant, which enhances the plaque removal by self-performed oral hygiene practices. [140] The same study observed that sites with KMW <2 mm had significantly greater mPI scores than implant sites with KMW ≥2 mm.[140] Other cross-sectional studies seem to support the same finding.[90] Possible explanations for these findings could be: 1) the presence of a shallow vestibule that prevents adequate access when KMW is absent; and 2) the increased discomfort when toothbrushing a site with a lack of KM. However, it should be noted that the recommended presence of KM to prevent peri-implant mucositis and future MBL is more critical for erratic maintenance compliers,[52] and that when patients comply with a periodic professional maintenance regime (as was the case for the included studies included in the present meta-analysis), greater mPI values do not necessarily lead to poorer clinical outcomes.

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 in an attempt to maximize the likelihood of conducting a quantitative analysis of the data. However, although 2 mm has been the most utilized cutoff value throughout years of 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 evidence 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.

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 identifying potential risk factors. 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 period 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 are not able 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, greater 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.

One of the weaknesses 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. Moreover, Roccuzzo, like several other authors, suggested that reports of no influence of KMW may be due to selecting 2 mm of KM as the cut-off point, while his study explored KMW *versus* no KMW at all showed a positive influence of KMW.[76] Another limitation 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 approach, and this contributes to the heterogeneity of the data, further warranting future homogenous evidence.

7. CONCLUSIONS

STUDY #1: Interproximal implant thread exposure after initial bone remodeling as a risk indicator for PI[94]

Implant thread exposure defined as no BIC after the initial expected bone remodeling along with splinting were the only statistically significant potential risk indicators for incident PI identified in this study. Implants with >1 thread exposed 1 year after implant restoration were 7.82 times more likely to develop PI than those with no exposed threads. This impact occurred in a dose-response manner, as the risk for PI increased with increasing number of exposed threads, with each additional exposed thread increasing the risk of PI almost 4-fold. Splinting increased the risk of PI by 3.49 times.[94]

STUDY #2: The correlation between history of PR according to the 2017 classification system and the prevalence and severity of PI[17]

No statistically significant association between PR severity (staging) and rate of progression (grading) at baseline, with prevalence of PI was found. However, when PI was present, increased severity of marginal bone loss and probability of implant failure were found for grade C patients. Further studies are needed to confirm these preliminary findings.[17]

STUDY #3: Limited marginal bone loss in implant-supported fixed full-arch rehabilitations in fully edentulous patients with history of PR[96]

Most of the internal conical connection implants supporting fixed full-arch metal-ceramic restorations in patients who lost all their teeth in that dental arch mostly as a consequence of severe PR do not suffer from relevant MBL after 5 years in function. Particularly, those implants with transmucosal abutments longer than 2 mm show, in average, less than 0.5 mm from the implant shoulder to the marginal bone.[96]

STUDY #4: The role of keratinized mucosa width as a risk factor for peri-implant disease: a systematic review, meta-analysis, and trial sequential analysis[97]

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. 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 PI could not be determined due to data scarcity.[97] 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.

8. SUMMARY: CLINICAL SIGNIFICANCE ("THE STORY")

The four studies that make up the basis for this work examine the roles of various factors in MBL around implants and in the development of PI in a variety of clinical scenarios and populations. A multitude of parameters related to the implant and to the patient were assessed.

Firstly, in Study #1 we showed that exposed (with no BIC) implant threads was the main risk factor for PI with the PI risk almost 8 (7.82) times greater than in patients with implants with no exposed threads.[94] This risk increased almost 4-fold (3.77 times) with each additional thread exposed. Splinting increased the risk of PI by 3.49 times.[94] Importantly, no other potentially confounding modifiable risk indicator was identified as statistically significant in incident PI in multivariate and univariate analyses, including a history of PR (yes/no), despite the multitude of macro- or micro-surface design variables included.

Secondly, when the PR present at baseline in these maintenance-compliant patients was classified according to the 2017 World Workshop case definitions,[95, 102] we still found no correlation between PR stages or grades and neither prevalence nor incidence of PI at either implant- nor patient-levels.[17] However, although the implant failure rate increased from stage I/II (0%) to stage IV (6.5%), this trend was not statistically significant, but there was a statistically significant increase in implant failure from grade A (0%) to grade C (5.9%).[17]

Thirdly, we studied patients with at least one completely edentulous arch who had lost their teeth due to severe PR and had received implant-supported fixed full-arch metal-ceramic restorations.[96] We found that the implants performed well and experienced limited MBL, even in patients with prior severe PR. This was even the case in one patient who had full-arch rehabilitation in both edentulous jaws.

Finally, in Study #4 we explored the soft tissue adjacent to the implants via a systematic review and meta-analysis. The approach was necessitated by the lack of sufficient information available for harvest from dental charts in a retrospective study design. Specifically, we focused on KMW and concluded that compared to implants with $\geq$2 mm KMW, implants associated with <2 mm KMW did not exhibit increased MBL; and there is insufficient evidence for KMW <2 mm being a risk factor for incident PI. In a recent systematic review and meta-analysis, <2 mm KMW was found to be associated with increased rates of MBL and PI.[212] Despite the conclusion of an association only, which is not a causal relationship, the authors still state *"Hence, in the cases lacking KT, clinicians might consider soft-tissue grafting to increase KT to promote peri-implant soft- and hard-tissue stability."* [212]

Overall conclusion

Among the multitude of implant- and patient related factors assessed, these four studies conducted among periodontal maintenance-compliant patients showed only one major modifiable risk factor for MBL and incident PI, namely implant thread exposure (no BIC), and splinting was also a risk factor. Among these patients, there was not sufficient evidence for neither a history of (even severe) PR nor for <2 mm KMW being risk factors for MBL and incident PI.

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10. ACRONYMS AND ABBREVIATIONS

Acronyms & Abbreviations	Meaning
2017 World Workshop	2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions
BIC	bone-to-implant-contact
BOP	Bleeding on probing
CAL	clinical attachment level
CI	confidence interval
EAO	European Association of Osseointegration
GEE	generalized estimation equations
GRADE	grading of recommendations, assessment, development & evaluation
HR	hazard ratio
ISFB	implant-supported fixed bridge
KM	keratinized mucosa

KMW	keratinized mucosa width
KW	Kruskal-Wallis test
KT	keratinized tissue
M	mixed
MBL	marginal bone level/loss
MD	mean difference
mGI	mean gingival index
mPI	mean plaque index score
MT	mucosal thickness
n, N	number
ND	natural dentition
NOS	Newcastle-Ottawa Scale
OR	odds ratio
PD	probing depth (around dental implant)
PI	peri-implantitis
PIS	plaque index score
PPD	periodontal probing depth (around natural tooth)
PR	periodontitis
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROMs	patient-reported outcomes
PROSPERO	international prospective register of systematic reviews
PSTDs	peri-implant soft tissue deficiencies
RBL	radiographic bone loss
RCT	randomized controlled trial
RD	removable denture
REC	soft tissue recession
RIS	required information size
ROBINS-I	risk of bias in non-randomised studies - of interventions
SD	standard deviation

SE	standard error
SPT	supportive periodontal therapy
SRP	scaling and root planing
STAd	supracrestal tissue adhesion
STH	supracrestal tissue height
T0	time of initial active periodontal therapy
T1	time of prosthetic restoration
T2	1 year after prosthetic restoration
T3	time of follow-up of ≥2 years after prosthetic restoration
T4	time of the last visit when implant was classified as present or explanted
TSA	trial sequential analysis
VAS	visual analogue scale

APPENDICES

APPENDIX #1.1: STUDY #1 PUBLICATION[94]

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ORIGINAL ARTICLE

Interproximal implant thread exposure after initial bone remodeling as a risk indicator for peri-implantitis

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During data collection for this study, Dr. Ravidà was affiliated with the University of Michigan.

Abstract

Background: Due to the clinical challenges involved in successfully treating peri-implantitis, it is imperative to identify patient- and implant-level risk factors for its prevention. The main goal of this retrospective longitudinal radiographic and clinical study was to investigate whether interproximal radiographic implant thread exposure after physiological bone remodeling may be a risk factor for peri-implantitis. The secondary goal was to evaluate several other potential risk indicators.

Methods: Of 4325 active dental school patients having implants placed, 165 partially edentulous adults (77 men, 88 women) aged 30–91 with ≥2 years of follow-up upon implant restoration were included. Implants with ≥1 interproximal thread exposed (no bone-to-implant contact) (n = 98, 35%) constituted the test group and those without exposed threads (n = 182, 65%) the control group. Descriptive, binary, and multivariate regression analyses were evaluated for goodness of fit. Wald tests were used to evaluate for significance set at 0.05.

Results: Of the 280 implants (98 test, 182 control), 8 (2.9%) failed over a mean follow-up period of 7.67 (±2.63) years, and 27 implants (19 test, 8 control) developed peri-implantitis, with the exposed group having eight-fold (7.82 times) adjusted greater odds than the non-exposed. The risk increased four-fold (3.77 times) with each thread exposed. No other patient- or implant-related potentially confounding risk factors were identified.

Conclusions: Exposed interproximal implant threads after physiologic bone remodeling may be an independent risk indicator for incident peri-implantitis. Hence, clinicians should closely monitor patients with implant threads that have no bone-to-implant contact for incident peri-implantitis.

KEYWORDS
bone resorption, dental implants, periodontics, radiography, tooth loss

1 | INTRODUCTION

Peri-implantitis (PI) is defined as an inflammatory lesion in the tissues surrounding the implant with progressing of bone loss beyond the expected physiologic bone remodeling.[1,2] PI is the most common complication in implant dentistry,[3,4] affecting around 20% of patients[5–7] and 13% of implants,[6,7] with study results ranging widely.

Because successful treatment of PI is so challenging and the outcome unpredictable,[4,8] it is imperative to prevent PI from developing, which necessitates identification of its local and systemic risk factors[3] for potential mitigation.

According to the 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions ("2017 World Workshop"), a history of periodontitis, poor plaque control, and lack of regular maintenance therapy might be considered risk indicators of PI; however, other factors such as smoking, diabetes, width of keratinized tissue, titanium particles, and prosthesis design need to be further evaluated.[1]

It is currently accepted that PI is caused by bacterial challenge in a susceptible host,[9] possibly in combination with a foreign body immune reaction.[10]

Several studies have focused on the roles of the patient (plaque control and compliance with professional maintenance visits) and of the provider (non-surgical or surgical therapies and maintenance) in the development of PI.[8,11–18] Implant design has been discussed extensively regarding osseointegration, but few studies have explored its role in disease onset,[19,20] so the role of the implant topography in PI requires further investigation.[21] Implant topography can be categorized as macro- and microdesign, respectively. The macrodesign pertains to the shape of the implant body as well as the design and number of threads and is an established key factor for osseointegration as a crucial element for primary implant stability and possibly for bone-to-implant contact (BIC).[22–24] Implant macrodesign has also been hypothesized to be a possible factor contributing to peri-implant disease.[21,25–27] In support of this hypothesis, greater PI prevalence was found in implants with triple thread, with a microthreaded collar, and with a cylindric shape.[27]

The microdesign concerns the chemically or mechanically treated implant surface, such as by acid etching, sandblasting, titanium plasma spraying, and hydroxyapatite coating.[28–30] Moderately rough implant surfaces were associated with lower prevalence rates of PI,[7] but due to the limited quality of evidence on the topic, more studies are necessary to evaluate the relationship between implant microdesign and PI.[31] As a potential risk for PI,[32] bone graft was also recorded.[32]

A clinical study observed that small bony buccal dehiscence defects developed greater-than-expected vertical bone loss 6 months after implant placement.[33] However, no study has explored the impact of the interproximal thread exposure on the development of PI.

Thus, the main aim of this retrospective longitudinal study was to investigate whether radiological interproximal implant thread exposure after physiological bone remodeling may be a potential risk indicator for incident PI. The secondary goal was to identify other potential patient- or implant-related risk factors for incident PI.

2 | MATERIALS AND METHODS

The study protocol was approved by the University of Michigan Medical School Institutional Review Board (Study #HUM00194509) and was conducted in accordance with the Helsinki Declaration adopted in 1964 and 1975,[34,35] as revised in 2013.[36] This retrospective investigation included implants placed and restored by graduate students or faculty at the University of Michigan School of Dentistry between January 2000 and September 2017. Eligible participants needed to fulfill the following inclusion criteria: 1) partially edentulous area restored with ≥1 implant with a documented follow-up period of ≥2 years after implant loading; 2) clinical data and high-quality periapical radiographs available at the time of implant placement (T0), prosthetic restoration (T1), 1 year after prosthetic restoration (T2, radiograph exposed at that time as per institutional protocol), and at follow-up of ≥2 years after prosthetic restoration (T3); 3) available information about the implant brand as well as the surface micro- and macrostructure; 4) presence of opposing teeth/restored implants (occlusion); 5) no active periodontitis at the time of implant placement (T0). Exclusion criteria were a) presence of PI in the test group at T2; b) potentially confounding comorbidities, such as a history of uncontrolled diabetes mellitus, radiation or chemotherapy, psychologic or psychiatric issues; and c) receipt of treatment or maintenance visits external to the study institution. Physical and digital records for potentially eligible patients were screened and evaluated by four examiners (A.S., M.Q., M.S., and L.W.) who subsequently extracted the data. Any disagreement that arose during the screening for eligibility and the data collection process was resolved through discussion with the principal investigator (A.R.).

2.1 | Data collection and classification

Relevant patient information was extracted, including age at the time of implant placement (T0), sex, smoking habit (≥1 cigarette/day), diabetes mellitus (validated via the patient's medical records), history of periodontitis,

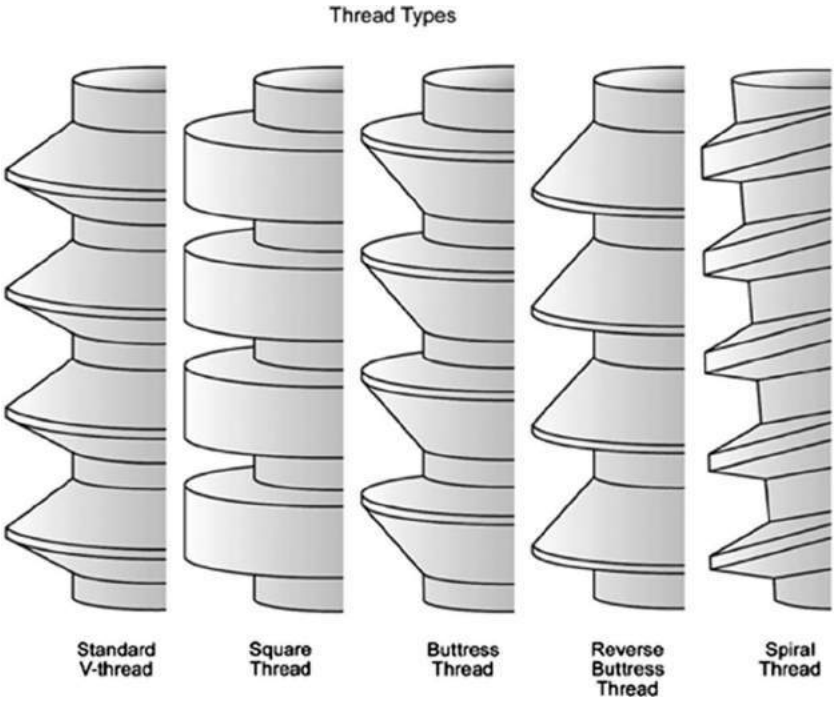

FIGURE 1 Implant thread pattern types: V-thread, square thread, buttress thread, reverse buttress thread, and spiral thread. *Source*: Reprinted with permission from Ref. 24 (Figure 2)

and number of maintenance appointments. A positive history of periodontitis was determined following the case definition for periodontitis proposed by the 2017 World Workshop[37] based on periodontal charts and radiographs. Detailed implant specific data collected included the number of implants and their positions (location in the edentulous jaw area), implant design (bone or soft tissue level), brand, length, diameter, neck design, retention type of restoration (cement or screw), and splinting. Bone grafting (yes/no) was recorded, and the type of implant–abutment connection and neck designs were also collected. Moreover, data were collected on the distance between threads (pitch) and the implant macrosurface, such as thread designs (buttress, reverse buttress, square, progressive square, and V-shaped), which are schematically illustrated in Figure 1.[24] Details about the microsurface recorded included type of surface (microtextured and sandblasted, large-grit, acid-etched). The implants were divided into four different categories according to their roughness (S_a): smooth (S_a < 0.5 μm); minimally rough (S_a 0.5–1.0 μm), moderately rough (S_a > 1.0–2.0 μm), and rough (S_a > 2.0 μm). [38,39]

Implants were divided by radiographic evaluation of interproximal (mesial/distal) BIC 1 year after prosthetic restoration (T2): 1) absence of BIC with ≥1 proximal implant thread (test group, "exposed") and 2) no thread without BIC (control group, "non-exposed"). A thread was regarded radiographically exposed when the adjacent bone did not completely cover its surface.[40] Exposed and non-exposed implant threads are illustrated conceptually in Figure 2 and radiographically in Figures S1 and S2 (in online *Journal of Periodontology*).

2.2 | Definition of outcomes

Based on our predefined outcomes, data analysis for implant failure, prevalence of PI, marginal bone loss, and numbers of threads exposed was performed. Two distinct follow-up periods were defined prior to data acquisition: a) follow-up to assess implant survival and b) follow-up to assess occurrence of PI, marginal bone loss, and number of interproximal (mesial or distal) threads exposed (with no BIC). The follow-up duration based on implant survival was defined as the time between implant placement (T0) and T4, defined as the last visit, during which each implant was classified as present or explanted. The follow-up based on the occurrence of PI, marginal bone loss, and number of threads exposed was defined as the duration of time between T2 and exposure of the last radiograph on which peri-implant bone could be clearly visualized (T3). The time between T2 and T3 is referred to as the "radiograph period." In case of concomitancy between T3 and T4 (the last X-rays available and the last patient visit), the two follow-up durations were identical.

Implant failure was defined as a removed, lost, mobile, or fractured implant.[41] PI was defined as proposed by the 2017 World Workshop[2] and was used to classify cases in a binary fashion as either positive (1) or negative (0) for PI. Because baseline data were available, a PI diagnosis

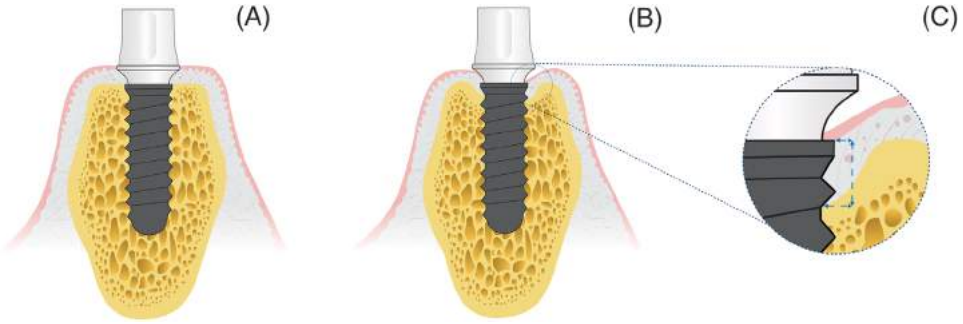

FIGURE 2 Development of marginal bone loss leading to exposed implant thread (no bone-to-implant contact). Implant placed at bone level (T1) (**A**). Bone loss after remodeling 1 year after implant prosthetic restoration (T2) (**B**). Close-up from panel B showing the most coronal implant thread exposed (**C**). (Conceptual model not showing any prosthetic restoration). (Please also see radiographs from study patients with and without interproximal thread exposure in Figures S1 and S2 in the online *Journal of Periodontology*)

was based on 1) progressive bone loss beyond initial bone remodeling, 2) increased probing depth, and 3) presence of bleeding and/or suppuration on gentle probing. Marginal bone level (MBL) was defined as the distance between the most coronal portion of the implant expected to present radiographic bone contact (for tissue-level implants, the interface between the polished collar and rough surface, and for bone-level implants, the platform level) to the most coronal point of the implant body in contact with bone. The MBL and the count of the exposed threads at T2 and T3 were radiographically assessed by two authors (A.R., M.S.) at the mesial and distal aspects of the affected implants using commercially available image software.[*] If significant differences arose (>0.5 mm for bone loss and >1 thread for the thread count), a third reviewer (H.L.W.) was included for reassessing the radiographs in a joint session to reach a final judgment. Repeated measurements of 15 implants were initially conducted to quantify mean interexaminer agreement measurement errors for MBL, which was 0.32 (±0.2) mm.

2.3 | Statistical analysis

The statistical analysis included descriptive analyses of categorical (absolute and relative frequencies) and continuous (mean, standard deviation, range, and median) variables for the total sample and stratified by study group (exposed/non-exposed threads) using dedicated statistical software.[†] The outcome PI diagnosis (yes/no) was related to all independent variables using multilevel binary logistic regression with generalized estimation equations (GEE). Raw odds ratios (OR) and 95% confidence intervals (CI) were obtained from the Wald chi-square statistic. Then, multivariate models were applied to adjust by potential confounding factors. The goodness of fit of different GEE estimates (for different matrix correlations) was assessed by QIC (quasi-likelihood under the independence model criterion) statistic. Significance level in all analyses was set to 5% ($\alpha = 0.05$). A post hoc power analysis was conducted. A sample size of 280 independent implants would provide 90.9% power with a confidence level of 95% to detect an OR of 3 as significant, using logistic regression models. Since the implants were not independent due to the two-level (patient and implant) data structure, this power needed correction. With each patient providing 1.75 implants on average and assuming a within-subject correlation of 0.5 (moderate), the correcting coefficient (D) was 1.35. Therefore, 280 dependent implants provide the same power as 207 independent implants, estimated at 80.4% under the mentioned conditions.

3 | RESULTS

3.1 | Clinical characteristics and demographic profiles

Records from a total of 4325 active patients who had received implant therapy at the University of Michigan School of Dentistry were screened for potential inclusion. A total of 1287 patients were excluded due to <2 years postimplant restoration follow-up period, 2423 patients due to absence of ≥1 radiograph or periodontal chart, 352 patients due to lack of information about brand and other implant characteristics, 53 patients due to presence of fixed full-arch restorations, and 45 due to ambiguous or incomplete charts. Hence, 165 patients were included in the study, including 77 males (46.7%) and 88 females (53.3%) with a mean age of 62.5 (±11.7) years ranging from 30 to 91 years at baseline (T0). A total of 280 implants were

[*] ImageJ, US National Institutes of Health, Bethesda, Maryland.
[†] SPSS, Chicago, Illinois.

included (n = 98 in the test group; n = 182 in the control group). Characteristics of the sample at patient and implant levels are displayed in Table 1.

3.2 | PI and marginal bone loss

Overall, the PI rate was 9.6% (27/280) in the total sample of implants. About one-fifth (19.4%) of the implants in the test group and 4.4% in the control group developed PI. Results from simple binary logistic regression using GEE (Table 2) show that an increasing number of threads exposed and the square thread design significantly increased the probability of developing PI. Moreover, increasing patient age significantly decreased this probability. No other confounder obtained statistically significant effect in the bivariate analyses.

A multivariate model (Table 3) considering these findings and adjusting for potential confounders (duration of and mean annual number of maintenance visits during the radiographic period [T2 to T3]) showed that thread exposure remained a significant factor for increasing the likelihood of PI, with the risk of PI increasing almost eight-fold with each additional exposed thread (OR 7.82; 95% CI, 1.91–32.03; p = 0.004). Splinting was also associated with greater risk for PI (OR 3.49; 95% CI, 1.02–12.05; p = 0.047). Each year of increased age was associated with 5% lower risk of a PI diagnosis (OR 0.95; 95% CI, 0.92–0.99; p = 0.016).

No association was found between PI and any other implant macro- or microsurface design nor a history of periodontitis. The mean annual crestal bone loss between T2 to T3 was 0.26 (±0.65) mm in the exposed (test group) versus 0.11 (±0.31) mm per year in the non-exposed (control) group (p = 0.05). Each additional exposed thread significantly increased the odds of PI almost four-fold (OR 3.77; 95% CI, 1.82–7.82; $p < 0.001$) (Figure 3A; see also Table S1 in online *Journal of Periodontology*).

3.3 | Implant failure

Each group lost four implants. The failure rate was at 2.9% (8/280) in the total sample (4.1% in the test group and 2.2% in the control group), a statistically non-significant difference (p = 0.470) (see Table S2 in online *Journal of Periodontology*). The probability of failure increased with the number of exposed threads, with each additional thread increasing the probability of failure about three times (OR 3.13; 95% CI, 1.01–9.66; $p < 0.001$) (Figure 3B; see also Table S3 in online *Journal of Periodontology*). Other than older age (OR 0.97; 95% CI, 0.94–1.00; p = 0.049), there were no other variables identified to potentially prevent implant failure.

4 | DISCUSSION

Because PI is difficult to arrest once established, identification of its modifiable risk factors is key for prevention. In implant treatment planning, execution, and maintenance, all possible measures to prevent development of exposed threads must be taken. Indeed, the results demonstrated an eight-fold increased risk for PI in implants with exposed threads compared to those with non-exposed threads. The risk increased four-fold with each additional thread exposed, and splinting was associated with 3.49 times greater risk for incident PI, whereas no other confounding patient-level factor (except for age) or implant macro- or microdesign feature was identified.

The reasons for exploring other potential risk factors were to not only identify them but to ensure statistically that such confounders might not actually be causing the incident PI instead of the thread exposure. Successful treatment of PI is very demanding. Retaining such success through maintenance proved to be challenging as well as shown by a systematic review and meta-analysis, where there was merely <5% reduction in the risk of implant loss for patients undergoing periodic maintenance therapy compared to those who did not.[42] In a recent study, patients without maintenance therapy had 4.25 times greater risk for PI.[16] Nonetheless, in the present study, the mean number of annual maintenance visits was found to not be associated with incident PI.

Splinting was found to present a 3.49 times greater risk for PI in multivariate analyses adjusted for duration and mean annual number of maintenance visits (Table 3). This finding is in contrast to the conclusions of a systematic review that a) there was no difference in MBL between splinted and non-splinted implant restorations[43] and b) splinting was associated with lower risk for implant failure.[43] On the contrary, our finding was in agreement with another study that also found greater risk of PI in splinted individual implant restorations, although three-unit bridges supported by two implants had significantly less risk for PI.[44] It should be noted that our study was not able to assess the accessibility for cleaning the implants and their restorations.

Our findings suggest that apart from splinting, the only modifiable statistically significant patient- and implant-related risk factor for incident PI was the number of implant threads exposed 1 year after prosthetic implant restorations, and the latter impact was dose-dependent. To the best of our knowledge, this is the first time such

TABLE 1 Patient- and implant-level characteristics of the implants placed in the 165 patients ($N = 280$ implants)

Characteristic	Total, mean ± SD or *n* (%)	Non-exposed (0 threads exposed), mean ± SD or *n* (%)	Exposed (≥1 thread exposed), mean ± SD or *n* (%)
Number of implants	280	182 (65.0)	98 (35.0)
Patient age at T0, years	63.0 ± 11.3	62.7 ± 11.1	63.3 ± 11.5
Sex			
Male	123 (43.9)	76 (41.8)	47 (48.0)
Female	157 (56.1)	106 (58.2)	51 (52.0)
Smoking (≥1 cigarette/day)			
No	241 (86.1)	161 (88.5)	80 (81.6)
Yes	39 (13.9)	21 (11.5)	18 (18.4)
Diabetes			
No	245 (87.5)	155 (85.2)	90 (91.8)
Yes	35 (12.5)	27 (14.8)	8 (8.2)
History of periodontitis			
No	185 (66.1)	122 (67.0)	63 (64.3)
Yes	95 (33.9)	60 (33.0)	35 (35.7)
Duration of follow-up period			
T0–T1, months	8.81 ± 4.72	8.41 ± 4.57	9.55 ± 4.94
T2–T3 (radiograph period), years	4.60 ± 2.52	4.51 ± 2.66	4.78 ± 2.25
T0–T4, years	7.67 ± 2.63	7.53 ± 2.45	7.91 ± 2.93
Edentulous site			
Incisor/canine	20 (7.2)	12 (6.6)	8 (8.2)
Premolar	110 (39.3)	70 (38.5)	40 (40.8)
Molar	150 (53.6)	100 (54.9)	50 (51.0)
Arch			
Maxilla	99 (35.4)	65 (35.7)	34 (34.7)
Mandible	181 (64.6)	117 (64.3)	64 (65.3)
Bone graft			
No	212 (76.0)	138 (76.2)	74 (75.5)
Yes	67 (24.0)	43 (23.8)	24 (24.5)
Implant surface			
MTX	105 (37.5)	87 (47.8)	18 (18.4)
TiUnite	103 (36.8)	32 (17.6)	71 (72.4)
SLA	43 (15.4)	42 (23.1)	1 (1.0)
SLA active	2 (0.7)	2 (1.1)	0
Friadent plus	7 (2.5)	7 (3.8)	0
Nanotite	9 (3.2)	6 (3.3)	3 (3.1)
RBT	10 (3.6)	6 (3.3)	4 (4.1)
CMI	1 (0.4)	0 (0.0)	1 (1.0)
Roughness (S_a)			
Smooth/minimally rough ($S_a \leq 1.0\ \mu m$)	7 (2.5)	7 (3.8)	0
Moderate ($S_a > 1.0$–$2.0\ \mu m$)	170 (60.7)	143 (78.6)	27 (27.6)
Rough ($S_a > 2.0\ \mu m$)	103 (36.8)	32 (17.6)	71 (72.4)

(Continues)

TABLE 1 (Continued)

Characteristic	Total, mean ± SD or *n* (%)	Non-exposed (0 threads exposed), mean ± SD or *n* (%)	Exposed (≥1 thread exposed), mean ± SD or *n* (%)
Connection			
Internal hexagon	124 (44.4)	99 (54.4)	25 (25.8)
External hexagon	52 (18.6)	8 (4.4)	44 (45.4)
Morse taper	45 (16.1)	44 (24.2)	1 (1.0)
Internal hexagon with Morse taper	20 (7.2)	12 (6.6)	8 (8.2)
Internal trilobe	31 (11.1)	12 (6.6)	19 (19.6)
Morse taper cone connection	7 (2.5)	7 (3.8)	0
Neck design			
0.5 machined collar (Zimmer)	25 (9.0)	17 (9.3)	8 (8.2)
0.5 MTX collar	67 (24.0)	58 (31.9)	9 (9.3)
1.0 machined collar (Zimmer)	13 (4.7)	12 (6.6)	1 (1.0)
Fine micron feature	9 (3.2)	6 (3.3)	3 (3.1)
Laser-Lok collar	10 (3.6)	6 (3.3)	4 (4.1)
Misc. machined collar (Nobel)	22 (7.9)	8 (4.4)	14 (14.4)
Microrough shoulder	7 (2.5)	7 (3.8)	0
Microthreads	29 (10.4)	16 (8.8)	13 (13.4)
Smooth collar	44 (15.8)	43 (23.6)	1 (1.0)
Threaded	53 (19.0)	9 (4.9)	44 (45.4)
Thread design			
Buttress	46 (16.4)	44 (24.2)	2 (2.0)
Progressive square	7 (2.5)	7 (3.8)	0
Reverse buttress	93 (33.2)	26 (14.3)	67 (68.4)
Square	20 (7.1)	12 (6.6)	8 (8.2)
V-shaped	114 (40.7)	93 (51.1)	21 (21.4)
Implant level			
Bone level	197 (70.6)	110 (60.4)	87 (89.7)
Tissue level	82 (29.4)	72 (39.6)	10 (10.3)
Length			
<11 mm	79 (28.3)	52 (28.6)	27 (27.8)
11–12 mm	131 (47.0)	88 (48.4)	43 (44.3)
>12 mm	69 (24.7)	42 (23.1)	27 (27.8)
Diameter			
<4 mm	52 (22.4)	34 (20.0)	18 (29.0)
4–4.5 mm	81 (34.9)	63 (37.1)	18 (29.0)
>4.5 mm	99 (42.7)	73 (42.9)	26 (41.9)
Retention			
Cemented	201 (72.0)	134 (73.6)	67 (69.1)
Screwed	75 (26.9)	45 (24.7)	30 (30.9)
Overdenture	3 (1.1)	3 (1.6)	0
Splinted			
No	204 (72.9)	144 (79.1)	60 (61.2)
Yes	76 (27.1)	38 (20.9)	38 (38.8)

(Continues)

TABLE 1 (Continued)

Characteristic	Total, mean ± SD or *n* (%)	Non-exposed (0 threads exposed), mean ± SD or *n* (%)	Exposed (≥1 thread exposed), mean ± SD or *n* (%)
Number of annual maintenance visits during radiograph period (T2–T3)			
≤1	63 (23.1)	41 (22.8)	22 (23.7)
>1–≤2	104 (38.1)	73 (40.6)	31 (33.3)
>2–≤3	77 (28.2)	47 (26.1)	30 (32.3)
>3	29 (10.6)	19 (10.6)	10 (10.8)
Number of annual maintenance visits (T0–T4)			
≤0.5	61 (22.4)	43 (24.0)	18 (19.4)
>0.5–≤1	59 (21.7)	45 (25.1)	14 (15.1)
>1–≤1.5	91 (33.5)	54 (30.2)	37 (39.8)
>1.5	61 (22.4)	37 (20.7)	24 (25.8)

Abbreviations: MTX, microtextured; RBT, resorbable blast texturing; SLA, sandblasted, large-grit, acid-etched; T0, time of implant placement; T1, time of prosthetic restoration; T2, 1 year after prosthetic restoration; T3, time of exposure of last radiograph on which peri-implant bone could be clearly visualized; T4, time of last patient visit.

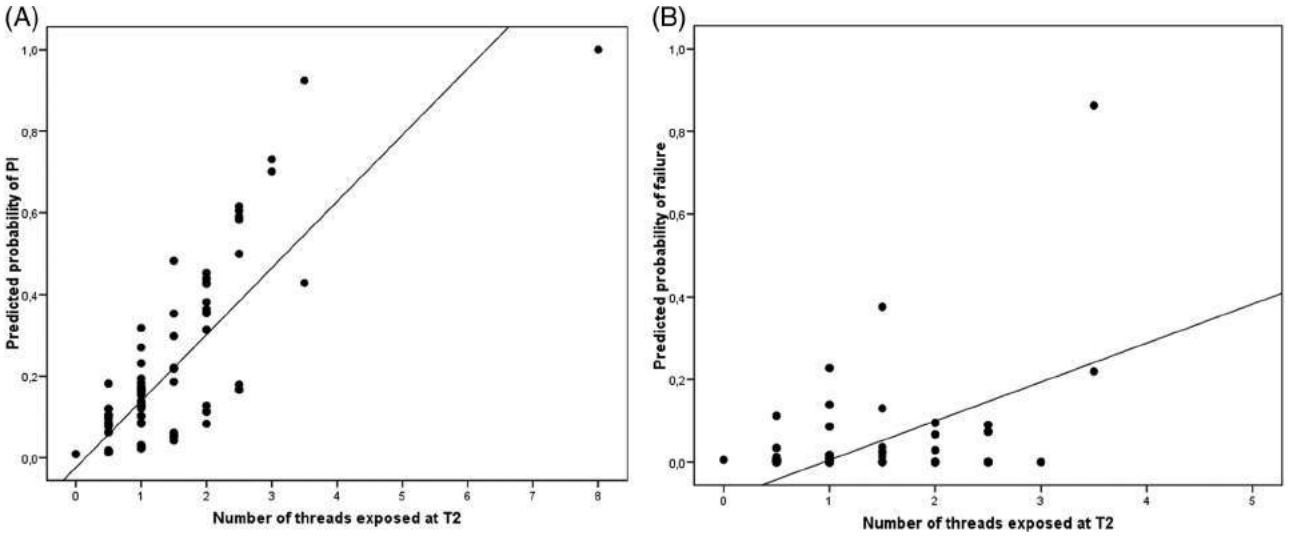

FIGURE 3 Predicted probability of peri-implantitis (PI) (**A**) and of implant failure (**B**) by the number of exposed threads ($N = 280$ implants). Implant failure is defined as removed, lost, mobile, or fractured implant.[41] T2, 1 year after implant prosthetic restoration

conclusion has been demonstrated by rigorous research, even though this result seems intuitive. Since the body of literature appears to be void of relevant findings regarding the number of exposed threads, we cannot compare this main finding to prior research results.

Interestingly, severity of periodontitis was not a significant factor for incidence of PI, which is in accord with our group's earlier findings in another study population among patients at the same institution, where only periodontitis Grade C was associated with incident PI.[15] This finding is also in line with the results of the meta-analysis published in 2016, which obviously could not have applied the 2017 World Workshop case definitions for either disease.[42] A systematic review by Doornewaard and coworkers supports our findings that implant surface roughness was not a significant factor in PI.[39] It is noteworthy that we applied the current classification of both periodontitis and PI defined by the 2017 World Workshop, and therefore any direct comparison to prior research would benefit from reassessing the classification of both diseases in the older studies.

Despite the multitude of operators and potentially changing protocols related to implant placement and restoration at a dental school over a period of 18 years,

TABLE 2 Risks of incident peri-implantitis by patient, implant, and prosthesis characteristics during the total study period (T0–T4). Results from unadjusted binary logistic regression analyses with generalized estimation equations ($N = 280$ implants)

Characteristic	Total, mean ± SD or *n* (%)	Peri-implantitis, *n* (%)	OR	95% CI	*p* value
Number of implants	280	27 (9.6)			
Study group					
Non-exposed (0 threads exposed)	182 (65.0)	8 (4.4)	1		
Exposed (≥1 thread exposed)	98 (35.0)	19 (19.4)	5.23	2.10–13.0	**<0.001*****
Patient age at T0, years	63.0 ± 11.3		0.95	0.92–0.99	**0.008****
Sex					
Male	123 (43.9)	16 (13.0)	1		
Female	157 (56.1)	11 (7.0)	0.50	0.18–1.40	0.190
Smoking (≥1 cigarette/day)					
No	241 (86.1)	26 (10.8)	1		
Yes	39 (13.9)	1 (2.6)	0.22	0.03–1.77	0.154
Diabetes					
No	245 (87.5)	23 (9.4)	1		
Yes	35 (12.5)	4 (11.4)	1.25	0.26–5.93	0.783
History of periodontitis					
No	185 (66.1)	15 (8.1)	1		
Yes	95 (33.9)	12 (12.6)	1.64	0.61–4.43	0.331
Duration of follow-up period					
T0–T1, months	8.81 ± 4.72		1.05	0.93–1.18	0.458
T2–T3 (radiograph period), years	4.60 ± 2.52		1.08	0.84–1.39	0.546
T0–T4, years	7.67 ± 2.63		1.03	0.79–1.33	0.841
Edentulous site					0.552
Incisor/canine	20 (7.2)	1 (5)	1		
Premolar	110 (39.3)	12 (10.9)	2.33	0.42–12.9	0.334
Molar	150 (53.6)	14 (9.3)	1.96	0.26–15.0	0.519
Arch					
Maxilla	99 (35.4)	9 (9.1)	1		
Mandible	181 (64.6)	18 (9.9)	1.10	0.38–3.21	0.856
Bone graft					
No	212 (76.0)	22 (10.4)	1		
Yes	67 (24.0)	5 (7.5)	0.70	0.23–2.13	0.525
Implant surface					0.194
MTX	105 (37.5)	6 (5.7)	1		
TiUnite	103 (36.8)	15 (14.6)	2.81	0.82–9.61	0.099
SLA	43 (15.4)	2 (4.7)	0.81	0.15–4.37	0.801
SLA active	2 (0.7)	0	n/a	n/a	n/a
Friadent plus	7 (2.5)	0	n/a	n/a	n/a
Nanotite	9 (3.2)	1 (11.1)	2.06	0.18–23.9	0.563
RBT	10 (3.6)	3 (30.0)	7.07	0.77–64.9	0.084
CMI	1 (0.4)	0	n/a	n/a	n/a
Roughness (S_a)					
Smooth/minimally rough (S_a <1.0 μm)	7 (2.5)	0	n/a	n/a	n/a
Moderate (S_a 1.0–2.0 μm)	170 (60.7)	12 (7.1)	1		
Rough (S_a > 2.0 μm)	103 (36.8)	15 (14.6)	2.24	0.82–6.13	0.115

(Continues)

TABLE 2 (Continued)

Characteristic	Total, mean ± SD or *n* (%)	Peri-implantitis, *n* (%)	OR	95% CI	*p* value
Connection					0.275
Internal hexagon	124 (44.4)	10 (8.1)	1		
External hexagon	52 (18.6)	6 (11.5)	1.49	0.40–5.47	0.550
Morse taper	45 (16.1)	2 (4.4)	0.53	0.11–2.62	0.437
Internal hexagon with Morse taper	20 (7.2)	5 (25.0)	3.80	0.82–17.7	0.089
Internal trilobe	31 (11.1)	4 (12.9)	1.69	0.37–7.72	0.499
Morse taper cone connection	7 (2.5)	0	n/a	n/a	n/a
Neck design					0.308
0.5 machined collar (Zimmer)	25 (9.0)	3 (12.0)	1		
0.5 MTX collar	67 (24.0)	3 (4.5)	0.34	0.04–2.78	0.317
1.0 machined collar (Zimmer)	13 (4.7)	0	n/a	n/a	n/a
Fine micron feature	9 (3.2)	1 (11.1)	0.92	0.06–13.5	0.317
Laser-Lok collar	10 (3.6)	3 (30.0)	3.14	0.27–36.9	0.362
Machined collar (Zimmer)	22 (7.9)	2 (9.1)	0.73	0.10–5.62	0.765
Microrough shoulder	7 (2.5)	0	n/a	n/a	n/a
Microthreads	29 (10.4)	7 (24.1)	2.33	0.37–14.9	0.309
Smooth collar	44 (15.8)	2 (4.5)	0.35	0.05–2.65	0.309
Threaded	53 (19.0)	6 (11.3)	0.94	0.16–5.66	0.943
Thread design					0.080
Buttress	46 (16.4)	2 (4.3)	1		
Progressive square	7 (2.5)	0	n/a	n/a	n/a
Reverse buttress	93 (33.2)	13 (14.0)	3.58	0.77–16.6	0.105
Square	20 (7.1)	5 (25.0)	7.33	1.16–46.4	**0.034***
V-shaped	114 (40.7)	7 (6.1)	1.44	0.28–7.39	0.663
Implant level					
Bone level	197 (70.6)	22 (11.2)	1		
Tissue level	82 (29.4)	5 (6.1)	0.52	0.16–1.69	0.274
Length					0.280
<11 mm	79 (28.3)	5 (6.3)	1		
11–12 mm	131 (47.0)	17 (13.0)	2.21	0.76–6.41	0.146
>12 mm	69 (24.7)	5 (7.2)	1.16	0.29–4.67	0.838
Diameter					0.978
<4 mm	52 (22.4)	4 (7.7)	1		
4–4.5 mm	81 (34.9)	7 (8.6)	1.14	0.19–6.63	0.888
>4.5 mm	99 (42.7)	9 (9.1)	1.20	0.21–6.81	0.837
Retention					0.409
Cemented	201 (72.0)	22 (10.9)	1		
Screwed	75 (26.9)	5 (6.7)	0.58	0.16–2.11	0.409
Overdenture	3 (1.1)	0	n/a	n/a	n/a
Splinted					
No	204 (72.9)	14 (6.9)	1		
Yes	76 (27.1)	13 (17.1)	2.80	0.98–8.02	0.055

(Continues)

TABLE 2 (Continued)

Characteristic	Total, mean ± SD or *n* (%)	Peri-implantitis, *n* (%)	OR	95% CI	*p* value
Number of annual maintenance visits during radiograph period (T2–T3)					0.079
≤1	63 (23.1)	5 (7.9)	1		
>1–≤2	104 (38.1)	4 (3.8)	0.46	0.11–1.96	0.296
>2–≤3	77 (28.2)	12 (15.6)	2.14	0.56–8.22	0.267
>3	29 (10.6)	5 (17.2)	2.42	0.44–13.2	0.309
Number of annual maintenance visits (T0–T4)					0.280
≤0.5	61 (22.4)	5 (8.2)	1		
>0.5–≤1	59 (21.7)	4 (6.8)	0.82	0.17–3.92	0.798
>1–≤1.5	91 (33.5)	6 (6.6)	0.79	0.16–3.95	0.775
>1.5	61 (22.4)	11 (18.0)	2.46	0.64–9.44	0.188

Note: p value by Wald test.

Abbreviations: CI, confidence interval; MTX, microtextured; OR, odds ratio; RBT, resorbable blast texturing; SLA, sandblasted, large-grit, acid-etched; T0, time of implant placement; T1, time of prosthetic restoration; T2, 1 year after prosthetic restoration; T3, time of exposure of last radiograph on which peri-implant bone could be clearly visualized; T4, time of last patient visit.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

TABLE 3 Risk of incident peri-implantitis by patient, implant, and prosthesis characteristics during the radiograph period (T2–T3). Results from multivariate logistic regression with generalized estimation equations adjusting for duration and mean annual number of maintenance visits ($N = 280$ implants)

Characteristic	Total, mean ± SD or *n* (%)	Peri-implantitis, *n* (%)	OR	95% CI	*p* value
Number of implants	280	27 (9.6)			
Study group					
Non-exposed (0 threads exposed)	182 (65.0)	8 (4.4)	1		
Exposed (≥1 thread exposed)	98 (35.0)	19 (19.4)	7.82	1.91–32.0	**0.004****
Patient age at T0, years	63.0 ± 11.3		0.95	0.90–0.99	**0.016***
Thread design					0.205
Buttress	46 (16.4)	2 (4.3)	1		
Progressive square	7 (2.5)	0	n/a	n/a	n/a
Reverse buttress	93 (33.2)	13 (14.0)	0.35	0.04–3.11	0.348
Square	20 (7.1)	5 (25.0)	2.02	0.26–15.9	0.506
V-shaped	114 (40.7)	7 (6.1)	0.23	0.20–2.28	0.211
Splinted					
No	204 (72.9)	14 (6.9)	1		
Yes	76 (27.1)	13 (17.1)	3.49	1.02–12.0	**0.047***
Duration of radiograph period (T2–T3), years	4.60 ± 2.52		1.19	0.95–1.50	0.136
Number of annual maintenance visits during radiograph period (T2–T3)					0.052
≤1	63 (23.1)	5 (7.9)	1		
>1–≤2	104 (38.1)	4 (3.8)	0.84	0.20–3.52	0.811
>2–≤3	77 (28.2)	12 (15.6)	3.23	0.57–13.9	0.114
>3	29 (10.6)	5 (17.2)	5.16	0.73–36.4	0.101

Note: *p* values by Wald test.

Abbreviations: CI, confidence interval; OR, odds ratio; T2, 1 year after prosthetic restoration; T3, time of exposure of last radiograph on which peri-implant bone could be clearly visualized.

*$p < 0.05$; **$p < 0.01$.

only eight (2.9%) implants from this series failed. The overall implant level PI rate was 9.6% (and only 4.4% of the implants that did not have any interproximal threads exposed after the initial physiologic bone remodeling), which is well within, actually at the lower end of, the reported range between 0.4% and 85%.[5,7,40,45–47] Importantly, almost one-fifth (19.4%) of the implants with such thread exposure developed PI. This is the same overall rate as that found for implants placed by general practitioners.[48]

Our stringent eligibility criteria were selected to create the test and comparison groups for comparisons as precise and valid as possible. It requires a large source population to conduct such a study, which can be deducted from including only 165 patients from a pool of 4325 active patients whose charts were screened. The low eligibility rate of 3.8% also leads to potential bias in representing any real-life population. Hence, this study could be perceived as a proof-of-concept study, although the prevalence of PI corresponds to findings from non-academic studies. The paucity of such large, well-documented source populations may be a reason for the lack of studies like this. A main limitation of this study is the high number and great diversity in skill levels of various categories of providers as well as the variety of implant systems used, some of which have been associated with the prevalence of PI.[26] The same applies to the various prosthetic designs included, some of which may be considered risk indicators for PI.[49]

Furthermore, with this study being primarily based on radiographic assessment, the observed correlation between implant threads not embedded in bone and an increased risk for the onset of PI could not consider soft tissue variables, such as keratinized mucosa width, mucosal thickness, or peri-implant soft tissue height. Moreover, we could not assess the presence/absence of buccal thread exposure due to the utilization of two-dimensional radiographs allowing only assessment of the interproximal aspects. Finally, inherent in the study design are the limitations of any retrospective study, such as no new data being collected and the data having been recorded for purposes other than this study with no possibility for randomization and recording of prospective observations.

5 | CONCLUSION

Within the limitations of this retrospective study, and age being the only non-modifiable risk factor identified, splinting and implant thread exposure (no BIC) after the expected initial bone remodeling were the only statistically significant potentially modifiable risk indicators for incident PI that were identified in this study. Implants with ≥1 thread exposed 1 year after implant restoration were 7.82 times more likely to develop PI than those with no exposed threads. This impact occurred in a dose–response manner, as the risk for PI increased with increasing number of exposed threads, with each additional exposed thread increasing the risk of PI almost four-fold.

AUTHOR CONTRIBUTIONS

Study conception and design: Andrea Ravidà, Hom-Lay Wang, and Pablo Galindo-Moreno. Data collection: Andrea Ravidà, Ankita Samal, Musa Qazi, and Liana Preto Webber. Analysis and interpretation of the data: Hom-Lay Wang, Pablo Galindo-Moreno, Wenche S. Borgnakke, and Muhammad H. A. Saleh. Drafting of the manuscript: Andrea Ravidà, Liana Preto Webber, Wenche S. Borgnakke, and Muhammad H. A. Saleh. All authors gave their final approval and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest related to this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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SUPPORTING INFORMATION

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

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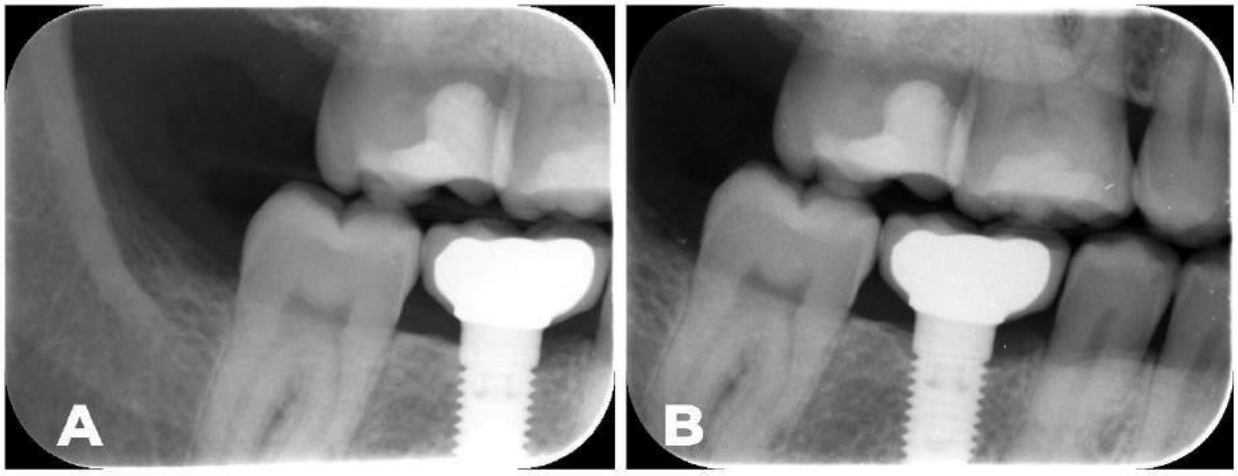
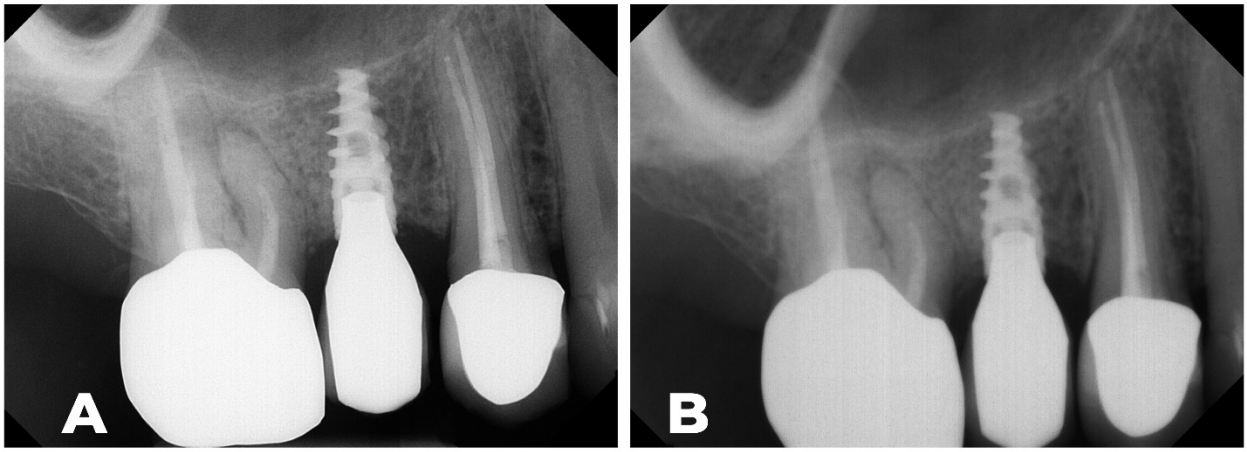


Supplementary Figure 1. Radiographs from study patient without exposed mesial or distal implant threads both at 1 year after prosthetic restoration (T2) **(Panel A)** and at the time of the last radiograph (T3) **(Panel B).**



Supplementary Figure 2. Radiographs from study patient with an exposed mesial implant thread at 1 year after prosthetic restoration (T2) **(Panel A),** but with exposed mesial and distal implant threads at time of the last radiograph (T3) **(Panel B).**

Supplementary Table 1. Risk for peri-implantitis in test group at 1 year after prosthetic restoration (T2) by thread exposure and duration and mean annual number of maintenance visits during the radiograph period (T2 to T3), respectively (N=98 implants).

Characteristic	OR	95% CI	p-value
Number of exposed threads	3.77	1.82 – 7.82	**<0.001*** **
Radiograph period (T2 to T3), years	0.92	0.73 – 1.15	0.454
Number of annual maintenance visits during radiograph period (T2 to T3)			0.184
≤1	1		
>1 - ≤2	0.20	0.03 – 1.29	0.092
>2 - ≤3	1.18	0.29 – 4.86	0.818
>3	2.24	0.37 – 13.7	0.384

N, number; CI, confidence interval; OR, odds ratio; T2, 1 year after prosthetic restoration; T3, time of last radiograph.
***p<0.001

Supplementary Table 2. Risk for incident implant failure (removed, lost, mobile, or fractured) by patient, implant, and prosthesis characteristics during the total study period (T0 to T4): Results from unadjusted binary logistic regression analyses with generalized estimation equations (GEE) (N=280 implants).

Characteristic	Total Mean (±SD) or n (%)	Implant Failure n (%)	OR	95% CI	p-value
Number of implants	280	8 (2.9)			
Study group					
Non-exposed (0 threads exposed)	182 (65.0)	4 (2.2)	1		
Exposed (≥1 threads exposed)	98 (35.0)	4 (4.1)	1.89	0.34 – 10.7	0.470
Patient age at T0, years	63.0 ± 11.3		0.97	0.94 – 1.00	**0.049***
Sex					
Male	123 (43.9)	5 (4.1)	1		
Female	157 (56.1)	3 (1.9)	0.46	0.08 – 2.77	0.396
Smoking (≥1 cigarette/day)					
No	241 (86.1)	8 (3.3)	1		
Yes	39 (13.9)	0	n/a	n/a	n/a
Diabetes					
No	245 (87.5)	6 (2.4)	1		
Yes	35 (12.5)	2 (5.7)	2.41	0.26 – 22.2	0.436
History of periodontitis					
No	185 (66.1)	6 (3.2)	1		
Yes	95 (33.9)	2 (2.1)	0.64	0.11– 3.60	0.614
Duration of follow-up period					
T0-T1, months	8.81 ± 4.72	n/a	0.74	0.42 – 1.30	0.295
T2-T3 (radiograph period), years	4.60 ± 2.52	n/a	1.29	0.97 – 1.71	0.078
Edentulous site					0.552
Incisor/Canine (I/C)	20 (7.2)	0 (0)	n/a	n/a	n/a
Premolar (PM)	110 (39.3)	3 (2.7)	1		
Molar (M)	150 (53.6)	5 (3.3)	1.23	0.31 – 4.95	0.771
Arch					
Maxilla	99 (35.4)	2 (2.0)	1		
Mandible	181 (64.6)	6 (3.3)	1.66	0.28 – 9.76	0.573
Bone graft					
No	212 (76.0)	8 (3.8)	1		
Yes	67 (24.0)	0 (0)	n/a	n/a	n/a
Implant surface					0.886
MTX	105 (37.5)	3 (2.9)	1		
TiUnite™	103 (36.8)	4 (3.9)	1.37	0.20 – 9.27	0.744
SLA	43 (15.4)	1 (2.3)	0.81	0.07 – 9.01	0.864
SLA active	2 (0.7)	0	n/a	n/a	n/a
Friadent® plus	7 (2.5)	0	n/a	n/a	n/a
Nanotite®	9 (3.2)	0	n/a	n/a	n/a
RBT	10 (3.6)	0	n/a	n/a	n/a
CMI	1 (0.4)	0	n/a	n/a	n/a
Roughness (S_a)					
Smooth/Minimally rough (S_a <1.0 µm)	7 (2.5)	0	n/a	n/a	n/a
Moderate (S_a 1.0-2.0 µm)	170 (60.7)	4 (2.4)	1		
Rough (S_a >2.0 µm)	103 (36.8)	4 (3.9)	1.68	0.30 – 9.28	0.554

Connection					0.492
Internal hexagon	124 (44.4)	3 (2.4)	1		
External hexagon	52 (18.6)	0	n/a	n/a	n/a
Mores taper	45 (16.1)	1 (2.2)	0.92	0.08 – 10.2	0.944
Internal hexagon with Morse taper	20 (7.2)	1 (5.0)	2.12	0.17 – 26.3	0.558
Internal tri-lobe	31 (11.1)	3 (9.7)	4.32	0.52 – 35.8	0.175
Morse taper cone connection	7 (2.5)	0	n/a	n/a	n/a
Neck Design					0.514
0.5 Machined collar (Zimmer)	25 (9.0)	2 (8.0)	1		
0.5 MTC collar	67 (24.0)	1 (1.5)	0.47	0.03 – 7.97	0.604
1.0 Machined collar (Zimmer)	13 (4.7)	0	n/a	n/a	n/a
Fine micron feature	9 (3.2)	0	n/a	n/a	n/a
Laser-Lok® collar	10 (3.6)	0	n/a	n/a	n/a
Machined collar (Nobel)	22 (7.9)	1 (4.5)	1.49	0.09 – 24.8	0.781
Micro-rough shoulder	7 (2.5)	0	n/a	n/a	n/a
Micro-threads	29 (10.4)	3 (10.3)	3.61	0.29 -44.6	0.316
Smooth collar	44 (15.8)	1 (2.3)	0.73	0.05 – 11.8	0.823
Threaded	53 (19.0)	0	n/a	n/a	n/a
Thread design					0.937
Buttress	46 (16.4)	1 (2.2)	1		
Progressive square	7 (2.5)	0	n/a	n/a	n/a
Reverse buttress	93 (33.2)	3 (3.2)	1.50	0.13 – 16.8	0.742
Square	20 (7.1)	1 (5.0)	2.37	0.14 – 38.9	0.550
V-shaped	114 (40.7)	3 (2.6)	1.22	0.11 – 13.6	0.874
Implant level					
Bone level	197 (70.6)	5 (2.5)	1		
Tissue level	82 (29.4)	3 (3.7)	1.46	0.24 – 8.90	0.683
Length					0.994
<11mm	79 (28.3)	3 (3.8)	1		
11-12mm	131 (47.0)	5 (3.8)	1.01	0.26 – 3.92	0.994
>12mm	69 (24.7)	0	n/a	n/a	n/a
Diameter					0.625
<4mm	52 (22.4)	1 (1.9)	1		
4-4.5mm	81 (34.9)	3 (3.7)	1.96	0.20 – 19.5	0.566
>4.5mm	99 (42.7)	2 (2.0)	1.05	0.09 – 12.0	0.968
Retention					0.253
Cemented	201 (72.0)	4 (2.0)	1		
Screwed	75 (26.9)	4 (5.3)	2.78	0.48 – 15.9	0.253
Overdenture	3 (1.1)	0	n/a	n/a	n/a
Splinted					
No	204 (72.9)	4 (2.0)	1		
Yes	76 (27.1)	4 (5.3)	2.78	0.48 – 15.9	0.253
Number of annual maintenance visits during radiograph period (T2 to T3)					0.210
≤1	63 (23.1)	1 (1.6)	1		
>1 - ≤2	104 (38.1)	1 (1.0)	0.60	0.04 – 9.51	0.602
>2 - ≤3	77 (28.2)	3 (3.9)	2.51	0.21 – 29.6	0.464
>3	29 (10.6)	3 (10.3)	7.15	0.58 – 87.7	0.124

Number of annual maintenance visits (T0 to T4)					0.453
≤0.5	61 (22.4)	1 (1.6)	1		
>0.5 - ≤1	59 (21.7)	0	n/a	n/a	n/a
>1 - ≤1.5	91 (33.5)	3 (3.3)	2.05	0.18 – 23.7	0.567
>1.5	61 (22.4)	4 (6.6)	4.21	0.41 – 42.9	0.225

N or n, number; CI, confidence interval; MTX, Microtextured surface; OR, odds ratio; T0, time of implant placement; T1, time of prosthetic restoration; T2, 1 year after prosthetic restoration; T3, time of exposure of last radiograph on which peri-implant bone could be clearly visualized; T4, time of last patient visit.
p-value by Wald´s test; *p<0.05

Supplementary Table 3. Risk of implant failure (removed, lost, mobile, or fractured) by number of exposed threads and duration and mean annual number of maintenance visits during the radiograph period (T2 to T3) (N=280 implants).

Characteristic	OR	95%CI	p-value
Number of exposed threads	3.13	1.01 – 9.66	**0.048***
Duration of radiograph period (T2 to T3), years	0.77	0.30 – 2.02	0.595
Number of annual maintenance visits during radiograph period (T2 to T3)	2.21	0.37 – 13.1	0.381

CI, confidence interval; OR, odds ratio; T2, 1 year after prosthetic restoration; T3, time of exposure of the last radiograph on which peri-implant bone could be clearly visualized.
*$p<0.05$.

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To: Dr. Hom-Lay Wang

From:

Michael	Geisser
Alan	Sugar
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Matthew Simon-Peter	Galli
Alice	Ou
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Hom-Lay	Wang
Ankita	Samal
Nathalia	Paiva De Andrade

Subject: Notice of Exemption for [HUM00194509]

SUBMISSION INFORMATION:
Title: Influence of implant thread exposure after bone remodelling on subsequent marginal bone loss, peri-implantitis and implant failure. A retrospective case-control study
Full Study Title (if applicable):
Study eResearch ID: HUM00194509
Date of this Notification from IRB: 2/17/2021
Date of IRB Exempt Determination: 2/17/2021
UM Federalwide Assurance: FWA00004969 (For the current FWA expiration date, please visit the UM HRPP Webpage)
OHRP IRB Registration Number(s):

Additional Supporting Documents:

IRB EXEMPTION STATUS:
The IRBMED has reviewed the study referenced above and determined that, as currently described, it is exempt from ongoing IRB review, per the following exemption category:

EXEMPTION 4(iii) at 45 CFR 46.104(d):

Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(iii)The research involves only information collection and analysis involving the investigator's use of **identifiable health information when that use is regulated under 45 CFR parts 160 and 164,**

subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b)

Note that the study is considered exempt as long as any changes to the use of human subjects (including their data) remain within the scope of the exemption category above. Any proposed changes that may exceed the scope of this category, or the approval conditions of any other non-IRB reviewing committees, must be submitted as an amendment through eResearch.

Although an exemption determination eliminates the need for ongoing IRB review and approval, you still have an obligation to understand and abide by generally accepted principles of responsible and ethical conduct of research. Examples of these principles can be found in the Belmont Report as well as in guidance from professional societies and scientific organizations.

HIPAA REVIEW:
The IRB has reviewed the project referenced above and has granted a Waiver of HIPAA Authorization. The IRB has determined that the proposed project conforms with applicable regulations and policies. This project must be conducted in accordance with the description and information provided in the application and associated documents.

Note: This project is regulated under the HIPAA Privacy Rule, which requires you to account for certain disclosures of Protected Health Information (PHI).

SUBMITTING AMENDMENTS VIA eRESEARCH:
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ACCESSING EXEMPT STUDIES IN eRESEARCH:
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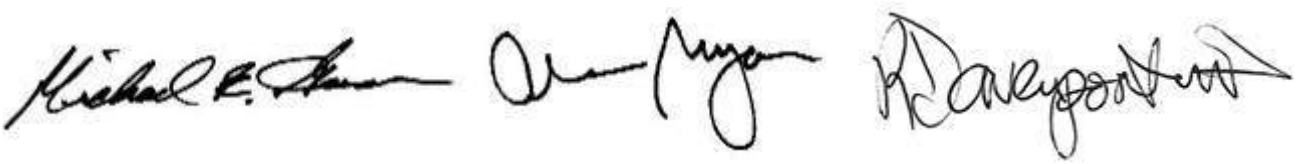

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APPENDIX #2.1: STUDY #2 PUBLICATION[17]

Complete citation

Ravidà A, Rodriguez MV, Saleh MHA, Galli M, Qazi M, Troiano G, Wang HL, Moreno PG. The correlation between history of periodontitis according to staging and grading and the prevalence/severity of peri-implantitis in patients enrolled in maintenance therapy. *J Periodontol* 2021;92(11):1522-1535. doi: 10.1002/JPER.21-0012. PMID: 33720410.[17]

The 14-page publication and its online-only 7-page supplement are inserted after this page.

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JOURNAL OF Periodontology

ORIGINAL ARTICLE

The correlation between history of periodontitis according to staging and grading and the prevalence/severity of peri-implantitis in patients enrolled in maintenance therapy

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Abstract

Background: The aim of this study was to determine if a previous history of periodontitis according to the preset definitions of the 2017 World Workshop is correlated with increased implant failure, and occurrence and severity of peri-implantitis (PI).

Methods: A retrospective analysis of patients with a history of periodontitis who received nonsurgical and, if indicated, surgical corrective therapy prior to implant placement was performed. Periodontitis stage and grade were determined for each included patient based on data from the time of initiation of active periodontal therapy. Cox Proportional Hazard Frailty models were built to analyze the correlation between stage and grade of periodontitis at baseline with implant failure, as well as occurrence and severity of PI.

Results: Ninety-nine patients with a history of periodontitis receiving 221 implants were followed for a mean duration of 10.6 ± 4.5 years after implant placement. Six implants (2.7%) failed and a higher rate of implant failure due to PI was found for Grade C patients ($P < 0.05$), whereas only an increased trend was seen for Stages III and IV compared with I and II. Grading significantly influenced the risk of marginal bone loss (MBL) >25% of the implant length ($P = 0.022$) in PI-affected implants. However, a direct correlation between higher-level stage and grade and PI prevalence was not recorded.

Conclusion: No statistically significant association between periodontitis stage or grade and the prevalence of PI was found. However, when PI was diagnosed, there was a relationship between periodontitis grade and severity of PI or the occurrence of implant failure.

KEYWORDS
dental implants, periodontal diseases, periodontitis

1 | INTRODUCTION

Peri-implantitis (PI) is a highly prevalent and asymptomatic complex chronic inflammatory disease culminating in progressive loss of supporting bone around dental implants.[1–3] The etiologies of both PI and periodontitis (PR) are believed to be microbially-mediated.[4] One of the principal articles of the recent 2017 World Workshop indicated that there is a strong level of evidence that patients with a previous history of PR, inadequate biofilm control, and a lack of regular maintenance care are at an increased risk for developing PI.[1] PI etiology, risk factors, and management are less well-understood compared to PR.

PR, much like PI, is a chronic inflammatory disease caused by a biologically destructive interaction between the host immunoinflammatory response and subgingival microbial biofilm which may lead to both oral (e.g., tooth loss) and systemic sequelae.[5–8] Several studies included in a recent narrative review showed a greater risk (in between 2.2 and 19 times) of PI in patients with a history of treated PR.[9] A meta-analysis demonstrated that PR patients had a 2.3-fold greater risk of developing PI compared to periodontally healthy patients.[10] In addition, implants placed in patients with prior tooth loss because of PR were significantly more likely to develop PI and exhibited 0.5 mm more marginal bone loss (MBL) on average after 5 years.[11] Possible theories for a linkage between PR and PI include that PR patients might harbor more pathogenic bacterial species, a higher bacterial load, or an impaired host immune response.[12]

Aoki and co-workers demonstrated that periodontal pathogens that reside in deeper pockets such as *Aggregatibacter actinomycetemcomitans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Treponema denticola*, and *Fusobacterium nucleatum* can be transmitted from affected teeth to adjacent implants.[13] Pjetursson and co-workers also illustrated that PR patients with residual periodontal probing depths (PPDs) ≥5 mm had a significant higher risk for the development of PI and implant loss.[14] Residual PPD≥ 6 mm involving >10% of sites after treatment in severe periodontitis patients was shown to be a significant risk indicator for development of PI.[15] Daubert et al.[16] reported that severe PR was the strongest risk indicator for PI of all examined variables. In addition, Ong et al.[17] found that PR patients had an overall higher percentage of biologic complications, including implant failures, than non-PR patients.

However, it should be noted that conflicting findings exist regarding the association of PR and subsequent development of PI, where an association with moderate and severe, but not mild, periodontitis was found.[18–20] Different findings can possibly be attributed to the use of different case definitions in previous studies.[9] Adoption of the 2017 World Workshop case definitions of PR and PI to investigate potential associations can lead to more accurate interstudy analyses and comparisons. Hence, the primary aim of this study was to determine if a previous history of periodontitis associated with higher-level stage (severity) and grade (rate of progression) increases the risk of implant failure or PI according to the 2017 World Workshop case definitions. Secondary aims were to investigate whether PR stage and grade have an influence on the severity of subsequent PI.

2 | MATERIALS AND METHODS

The present study was conducted in compliance with the Helsinki Declaration of 1975, as revised in 2013. The protocol of this study was approved by the University of Michigan, School of Dentistry, Institutional Review Board for Human Studies (HUM00157260).

Data were acquired from the physical and electronic charts of patients who received nonsurgical and, if indicated, surgical corrective therapy between January 1996 and January 2018 at the University of Michigan, School of Dentistry, Ann Arbor, MI, USA. Patients treated for periodontal disease (scaling and root planing [SRP] and/or surgical therapy) with a complete medical history, baseline periodontal charting, and full-mouth radiographs were included in the present study. All included patients were maintained after active periodontal therapy with at least one session of supportive periodontal therapy (SPT) per year at the University of Michigan, School of Dentistry. Furthermore, the following exclusion criteria were implemented: non-periodontal patients, patients receiving implant-related or periodontal care outside the School of Dentistry, periodontal patients that did not receive a dental implant or received an implant with a follow-up period of <1 year, and patients with incomplete or unclear data.

Staging and grading algorithms published by Tonetti and Sanz[21] were used to classify patient periodontal status. Determination of baseline periodontal staging and grading was conducted by a single investigator (MS) using clinical and radiographic data collected at the time of initial active periodontal therapy (T0).[22] Data on pertinent patient characteristics, the number of SPT visits per year, and relevant medical history (history of diabetic status and self-reported smoking history at baseline) were collected. Radiographic bone loss (RBL, % of root length) at baseline was measured from periapical radiographs to assess PR stage and grade.[23] Tooth-specific data on clinical parameters including periodontal probing depth (PPD), clinical attachment level (CAL) calculated as the difference between PPD and the distance from the free gingival margin to the

cemento-enamel junction, bleeding on probing (BOP), and furcation involvement were also recorded. Information about masticatory dysfunction, drifting, flaring, bite collapse, and plaque accumulation were retrieved from patient records where available. As part of the data collection process, additional information was gathered at the time of implant placement including: age, tobacco usage and diabetic history, the number of implants placed and their locations, implant characteristics (brand, length, diameter, soft tissue/bone level), mechanism of crown retention (screw or cement-retained), number of follow-up visits and maintenance appointments, type of implant-abutment connection, as well timing of bone grafting (prior/during implant placement).

2.1 | Survival rate and PI definition

Based on the goal of conducting data analyses for both implant survival rates as well as PI prevalence/severity, two distinct follow-up periods were defined prior to data acquisition. These were a) follow-up based on implant survival, and b) follow-up based on the occurrence of PI. Follow-up based on implant survival was defined as the time period between implant placement and the last follow-up of the implant. At this date, each individual implant was classified as present or explanted.[24] Follow-up based on the occurrence of PI was defined as the duration of time between implant-supported prosthetic placement and the last radiograph in which peri-implant bone could clearly be visualized. The definition for PI proposed by the American Academy of Periodontology/European Federation of Periodontology 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions guidelines[25] was used to classify cases in a binary fashion as either positive or negative for PI (0 for peri-implant health, 1 for PI). Because baseline data were available, PI diagnosis was based on: 1) progressive bone loss beyond initial bone remodeling, 2) increased probing depth, and 3) presence of bleeding and/or suppuration on gentle probing.[25] The marginal bone level changes were radiographically examined by two authors (AR, MV) at the mesial and distal aspects of the affected implants using commercially available software (ImageJ, U. S. National Institutes of Health, Bethesda, MD, USA). If significant differences arose, a third reviewer (HLW) was included for reassessing the radiographs in a joint session and to give a final judgment. Interproximal marginal bone levels were radiographically calculated as a percentage of implant length, utilizing the most coronal bone-implant contact point to represent the marginal bone level to classify implants based on the severity of bone loss (<25%; 25% to 50%; or >50% of the implant length). For implants with a polished collar, the length was measured from the smooth-rough interface to the apex. For bone level implants, the platform level was used as the coronal demarcation point when evaluating implant length for calculation of radiographic peri-implant bone levels.

2.2 | Statistical analysis

Descriptive statistics were employed for analysis of categorical (absolute and relative frequencies) and continuous (mean, standard deviation, range, and median) variables taking into account both implant failure events and PI diagnosis. At the implant-level, time-to-event "implant failure" and time-to-event "PI diagnosis" were analyzed using Kaplan-Meier survival methodology. Cumulative survival functions were plotted and compared between different patient profiles and clinical factors using a Log-rank test. In order to consider dependence between observations (implant-level data clustered by patients), univariate Cox regression frailty models were performed analyzing the influence of individual factors and covariates on failures and PI diagnosis. Hazard ratio estimations and corresponding 95% confidence intervals (CIs) were obtained. Wald test was used to consider within-patient correlations. Then, multiple Cox regression frailty models were used to adjust for potential confounders. Schoenfeld's tests for proportional hazard and residual analysis were carried out to validate theoretical hypotheses.

For non-failed PI-afflicted implants, severity of bone loss (<25% or ≥25%) was related to stage and grade, adjusting by radiographic follow-up duration using logistic regression with generalized estimation equations (GEE). Odds ratios and 95% CIs were obtained using the Wald's Chi2 statistic. The significance level for statistical analyses was set at 5% ($\alpha = 0.05$). Regarding the power analysis, a post-hoc estimation was obtained.

A sample size of 221 independent implants provided 96.5% power at 95% confidence to detect a relative risk (RR) of 3.0 as significant using a Cox multiple regression model to assess the influence of a two-level factor (e.g., maxillary or mandibular implant location), assuming that 80% of observations were censored (the proportion of no PI diagnosis was roughly 80%). In the power calculation, correction was performed to account for the two-level structure of the data. Each patient provided 2.23 implants on average and within-subject correlation CCI = 0.5 (moderate) was assumed, leading to a correcting coefficient D = 1.62. Therefore, 221 dependent implants provided the same power as 137 independent implants, calculated at 84% under the described conditions (RR = 3.0; 95% confidence).

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TABLE 1 Demographic characteristics of the sample and periodontitis status at baseline, as well as results of Kruskal-Wallis test (KW) for comparison between different levels of stage and grade

		N of maintenances per year	*P* (KW)	Follow-up since IP (years)	Follow-up since CP (years)
Number of patients	99	2.2 ± 1.0		10.6 ± 4.5	10.0 ± 4.5
Mean age (years)	60.6 ± 10.2				
Sex					
Male	49 (49.5)				
Female	50 (50.5)				
Smoking					
No	63 (63.6)				
Former smoker	20 (20.2)				
Yes (<10 c/d)	8 (8.1)				
Yes (>10 c/d)	8 (8.1)				
Diabetes					
No	90 (90.9)				
Yes	9 (9.1)				
Stage					
1	7 (7.1)	2.7 ± 2.0	0.515	6.8 ± 3.4	6.1 ± 3.5
2	27 (27.3)	1.9 ± 0.8		9.8 ± 4.8	9.2 ± 4.8
3	56 (56.6)	2.2 ± 0.9		11.3 ± 4.0	10.7 ± 4.0
4	9 (9.1)	2.2 ± 1.3		12.1 ± 5.5	11.1 ± 5.7
Grade					
A	5 (5.1)	2.2 ± 1.0	0.526	10.0 ± 2.9	9.4 ± 3.0
B	68 (66.7)	2.2 ± 1.0		10.1 ± 4.6	9.5 ± 4.6
C	26 (26.3)	2.2 ± 1.0		12.2 ± 4.1	11.5 ± 4.2
Extent					
Localized	78 (78.8)				
Generalized	21 (21.2)				

3 | RESULTS

3.1 | Characteristics of the patient cohort

In total, 99 patients composed of 49 males (49.5%) and 50 females (50.5%), with a mean age of 60.6 ± 10.2 years at the time of implant placement (range 38 to 86 years) were included in the present study. Overall, 221 implants were followed for a mean duration of 10.6 ± 4.5 years from implant placement, and 10.0 ± 4.5 years from prosthetic insertion. The loading protocol for all included implants followed a delayed approach (≥4 months after placement). Demographic characteristics of the included cohort are reported in Table 1.

3.2 | Correlation between stage and grade and implant failure

Analysis at the patient-level revealed that five patients (5.1%) experienced implant failure at least at one site (one patient experienced two failures). At the implant-level, a mean survival rate of 97.3% was found at the end of the follow-up period, and six implants (2.7%) failed. The cumulative survival rate (Kaplan Mayer analysis) was 99% at 5-years, 98% at 10-years, 94% at 15-years, and 92% at 20-years follow-up (Figure S1A). In the present study, the only cause of implant failure found was PI (Figure S1B). Table 2A shows Kaplan Meier univariate implant survival analysis according to clinical variables related to the patient,

TABLE 2 Results of Kaplan Meier survival analysis of time-to-event data implant survival and peri-implantitis diagnosis

A: Kaplan Meier survival analysis of time-to-event data based on clinical variables related to the patient, implant position, characteristics, and surgery			
	Total (%)	**Failure rate (%)**	***P***
Number of implants	221	6 (2.7)	
Mean age (years)	60.3 ± 9.3		
Sex			0.516
Male	110 (49.8)	2 (1.8)	
Female	111 (50.2)	4 (3.6)	
Smoking			0.141
No	121 (54.8)	2 (1.7)	
Former smoker	48 (21.7)	0 (0.0)	
Yes (<10 c/d)	18 (8.1)	1 (5.6)	
Yes (>10 c/d)	34 (15.4)	3 (8.8)	
Diabetes			0.104
No	204 (92.3)	5 (2.5)	
Yes	17 (7.7)	1 (5.9)	
Stage			p=0.411 (STAGE 1+2 versus 3 versus 4)
1	8 (3.6)	0 (0.0)	p=0.226 (STAGE 1+2 versus 3+4)
2	48 (21.7)	0 (0.0)	p=0.267 (STAGE 1+2 versus 3)
3	134 (60.6)	4 (3.0)	p=0.131 (STAGE 1+2 versus 4)
4	31 (14.0)	2 (6.5)	
Grade			0.048* (GRADE A+B versus C)
A	5 (2.3)	0 (0.0)	
B	131 (59.3)	1 (0.8)	
C	85 (38.5)	5 (5.9)	
Extent			0.465
Localized	171 (77.4)	4 (2.3)	
Generalized	50 (22.6)	2 (4.0)	
Arch			0.172
Maxilla	122 (55.2)	5 (4.1)	
Mandible	99 (44.8)	1 (1.0)	
Position			0.223
Anterior	37 (16.7)	0 (0.0)	
Posterior	184 (83.3)	6 (3.3)	
Prosthesis type			0.956 (Single versus Splinted)
Single	153 (69.2)	3 (2.0)	
Splinted	59 (26.7)	2 (3.4)	
Overdenture	9 (4.1)	1 (11.1)	–
Level			0.806
Soft	48 (21.7)	1 (2.1)	
Bone	173 (78.3)	5 (2.9)	
Connection			0.769 (Internal versus External)
Internal	200 (90.5)	5 (2.5)	
External	18 (8.1)	1 (5.6)	
Locator	3 (1.4)	0 (0.0)	–
Retention			<0.001‡ (Cemented versus Screw)
Cemented	204 (92.3)	4 (2.0)	
Screwed	14 (6.3)	1 (7.1)	

(Continues)

TABLE 2 (Continued)

A: Kaplan Meier survival analysis of time-to-event data based on clinical variables related to the patient, implant position, characteristics, and surgery			
	Total (%)	**Failure rate (%)**	***P***
Ball attachment	3 (1.4)	1 (33.3)	–
Implant length			0.110
<=11 mm	66 (29.9)	1 (1.5)	
11.5 mm	45 (20.4)	3 (6.7)	
12 mm	34 (15.4)	1 (2.9)	
>=13 mm	76 (34.4)	1 (1.3)	
Implant diameter			0.183
<4 mm	52 (23.5)	0 (0.0)	
4-4.5 mm	90 (40.7)	3 (3.3)	
>4.5 mm	79 (35.7)	3 (3.8)	
Bone graft			0.755
No	149 (68.3)	4 (2.7)	
Yes	69 (31.7)	2 (2.9)	
FAILURE			
No	215 (97.3)		
Yes	6 (2.7)		
Peri-implantitis			<0.001‡
No	176 (79.6)	0 (0.0)	
Yes	45 (20.4)	6 (13.3)	
B: Kaplan Meier survival analysis of time-to-event peri-implantitis diagnosis according to clinical variables related to the patient, implant position, characteristics, and surgery.			
	Total (%)	**PI rate (%)**	***P***
Number of implants	221	45 (20.4)	
Age (years)	60.3 ± 9.3		
Sex			0.825
Male	110 (49.8)	21 (19.1)	
Female	111 (50.2)	24 (21.6)	
Smoking			0.723
No	121 (54.8)	23 (19.0)	
Former smoker	48 (21.7)	11 (22.9)	
Yes (<10 c/d)	18 (8.1)	6 (33.3)	
Yes (>10 c/d)	34 (15.4)	5 (14.7)	
Diabetes			0.094
No	204 (92.3)	40 (19.6)	
Yes	17 (7.7)	5 (29.4)	
Stage			0.411 (STAGE 1+2 versus 3 versus 4)
1	8 (3.6)	1 (12.5)	
2	48 (21.7)	10 (20.8)	
3	134 (60.6)	23 (17.2)	
4	31 (14.0)	11 (35.5)	
Grade			0.990 (GRADE A+B versus C)
A	5 (2.3)	2 (40.0)	
B	131 (59.3)	25 (19.1)	
C	85 (38.5)	18 (21.2)	
Extent			0.650
Localized	171 (77.4)	33 (19.3)	

(Continues)

TABLE 2 (Continued)

B: Kaplan Meier survival analysis of time-to-event peri-implantitis diagnosis according to clinical variables related to the patient, implant position, characteristics, and surgery.			
	Total (%)	**PI rate (%)**	***P***
Generalized	50 (22.6)	12 (24.0)	
Time since 1st SRP to IP (years)	12.9 ± 8.1		
Total follow up (years)	10.7 ± 5.1		
RX follow up (years)	9.6 ± 5.1		
Number of maintenances per year	2.3 ± 1.0		
Arch			0.546
Maxilla	122 (55.2)	22 (18.0)	
Mandible	99 (44.8)	23 (23.2)	
Position			0.110
Anterior	37 (16.7)	8 (21.6)	
Posterior	184 (83.3)	37 (20.1)	
Prosthesis type			0.409 (Single versus splinted)
Single	153 (69.2)	20 (13.1)	
Splinted	59 (26.7)	18 (30.5)	
Overdenture	9 (4.1)	7 (77.8)	–
Level			0.120
Soft	48 (21.7)	5 (10.4)	
Bone	173 (78.3)	40 (23.1)	
Connection			0.008† (Internal versus External)
Internal	200 (90.5)	41 (20.5)	
External	18 (8.1)	3 (16.7)	
Locator	3 (1.4)	1 (33.3)	–
Retention			0.002‡ (Cemented versus Screw)
Cemented	204 (92.3)	39 (19.1)	
Screwed	14 (6.3)	3 (21.4)	
Ball attachment	3 (1.4)	3 (100)	–
Implant length			0.009†
<=11 mm	66 (29.9)	10 (15.2)	
11.5 mm	45 (20.4)	12 (26.7)	
12 mm	34 (15.4)	2 (5.9)	
>=13 mm	76 (34.4)	21 (27.6)	
Implant diameter			0.009†
<4 mm	52 (23.5)	7 (13.5)	
4-4.5 mm	90 (40.7)	22 (24.4)	
>4.5 mm	79 (35.7)	16 (20.3)	
Bone graft			0.551
No	149 (68.3)	29 (19.5)	
Yes	69 (31.7)	14 (20.3)	
Failure			
No	215 (97.3)	39 (18.1)	
Yes	6 (2.7)	6 (100.0)	
Peri-implantitis			
No	176 (79.6)		
Yes	45 (20.4)		

*$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

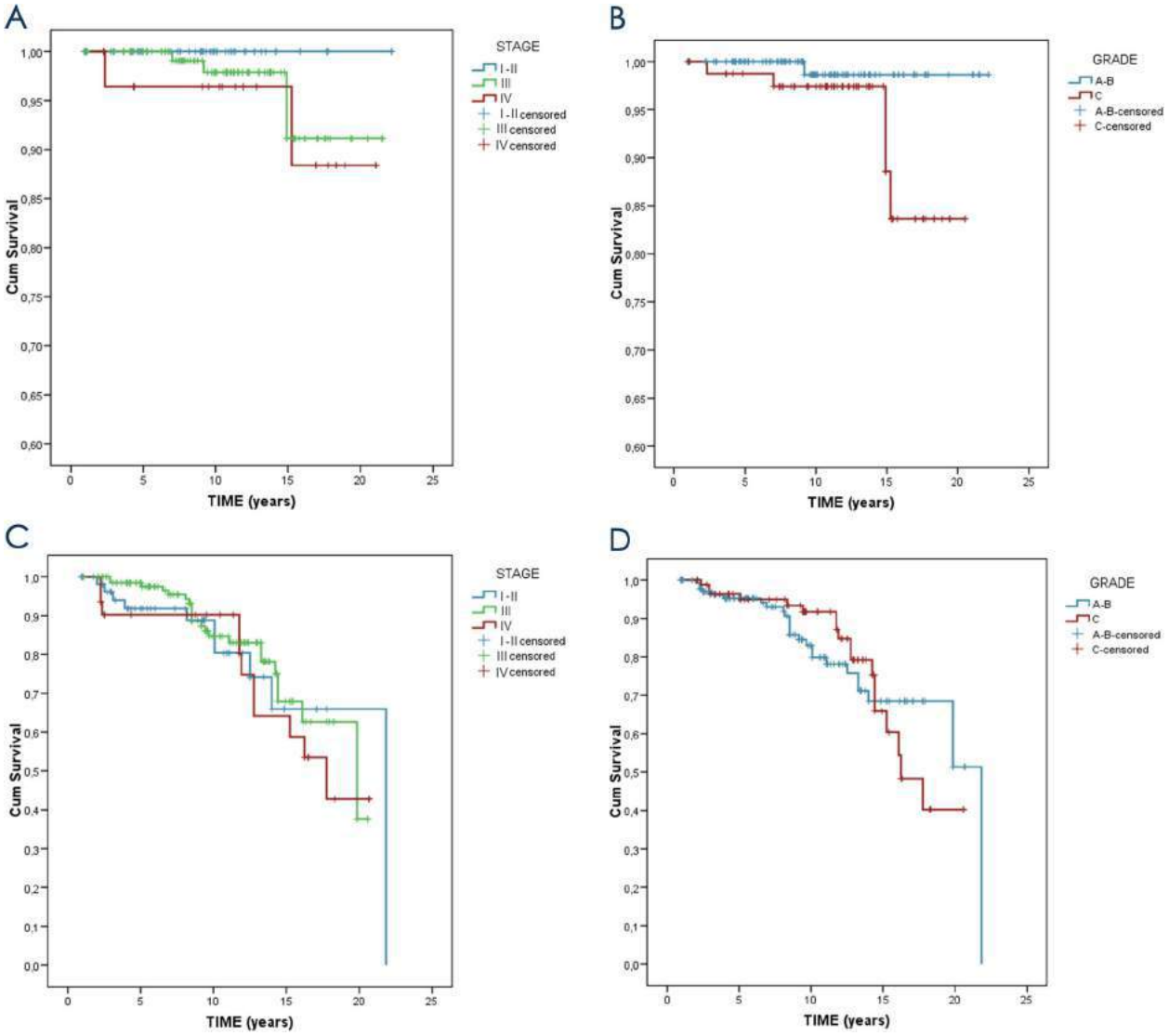

FIGURE 1 (**A**) Implant failure survival analysis by stage; (**B**) implant failure survival analysis by grade; (**C**) peri-implantitis (PI) prevalence survival analysis by stage; the drop of the blue curve (represents Stages I/II) at 23 years follow-up is because of the reduced sample size at that time (**D**) PI prevalence survival analysis by grade. The drop of the blue curve (represents Grades A/B) at 23 years follow-up is because of the small sample size at that time

implant position, characteristics, and surgery. Similarly, Table 2B illustrates Kaplan Meier survival analysis of time-to-event PI diagnosis based upon above scenarios.

Regarding PR staging, four implant failures were recorded in patients with Stage III PR at baseline, whereas the remaining two failures occurred in patients with a previous history of Stage IV disease ($P > 0.05$). Mean implant failure rates were 0% for Stages I-II, 3% for Stage III, and 6.5% for Stage IV. Cumulative implant survival rates are shown in Figure 1A and Table S1.

In terms of grading, one failure was recorded in a patient with a previous history of Grade B PR, whereas the remaining five failures occurred in patients with a history of Grade C disease. The mean failure rate was 0% for Grade A, 0.8% for Grade B, and 5.9% for Grade C ($P < 0.05$) (Figure 1B and Table S2). Cox proportional hazard regression analysis showed that implants placed in Grade C patients were associated with a trend towards a higher failure rate than those placed in Grade A/B patients (HR = 6.57; $P = 0.075$) (Table 3). The same model demonstrated that implants placed in current heavy smokers were associated with a significantly higher failure rate compared to never-smokers (HR = 4.71; $P = 0.04$). Six implants were lost in patients with a history of Stage III/IV PR, whereas no implants were lost in those with a history of Stage I and II PR. Stage was not a significant predictor of implant

TABLE 3 Cox proportional hazard regression model illustrating time-to-event failure by clinical variables related to the patient, implant position, characteristics, and surgery

	HR	95% CI	*P*
Age (years)	1.02	0.95–1.10	0.538
Sex			
Male	1		
Female	1.75	0.36–8.60	0.491
Smoking			0.102
No	1		
Former smoker	–	–	–
Yes (<10 c/d)	1.82	0.21–15.6	0.578
Yes (>10 c/d)	4.71	1.08–20.6	0.040*
Diabetes			
No	1		
Yes	5.79	0.63–53.5	0.122
Stage			
1-2	–	–	–
3	1		
4	1.54	0.26–9.17	0.635
Grade			
A-B	1		
C	6.57	0.82–52.4	0.075
Extent			
Localized	1		
Generalized	1.86	0.40–8.58	0.429
Arch			
Maxilla	1		
Mandible	0.25	0.03–2.18	0.209
Prosthesis type			
Single	1		
Splinted	1.04	0.10–10.5	0.971
Overdenture	–	–	–
Level			
Soft	1		
Bone	1.31	0.16–10.9	0.801
Connection			
Internal	1		
External	0.72	0.07–7.29	0.777
Locator	–	–	–
Retention			
Cemented	1		
Screwed	51.9	4.89–550.4	0.001†
Ball attachment	–	–	–
Implant length	1.05	0.79–1.39	0.743
Implant diameter	2.23	0.79–6.26	0.128
Bone graft			
No	1		
Yes	1.30	0.25–6.94	0.756

*$P < 0.05$; †$P < 0.01$.

failure ($P = 0.635$) when Stage IV was compared to Stage III (Table 3). It should be noted that Stages I-II were excluded from the model because of a lack of convergence because these categories were both associated with 0% implant failure rates.

3.3 | Analysis of the association between stage and grade with the onset and severity of PI

A total of 45 implants (20.4%) were diagnosed with PI during the follow-up period. At the implant-level, the cumulative probability of PI occurrence (based on Kaplan Mayer analysis) was 5% at 5-years, 15% at 10-years, 35% at 15-years, and 54% at 20-years follow-up (Figure S2A). At the patient-level, the cumulative probability of PI occurrence is shown in Figure S2B. Univariate survival analysis of PI diagnosis according to clinical variables (implant position, implant characteristics, as well as patient-specific and surgical-related parameters) is shown in Table 2B. Overall, no correlation was found between increased staging and grading and increased prevalence of PI at both the implant- (Table 2B, Figures 1C and 1D) and patient-levels (Figures S3A and S3B). Cox proportional hazard regression analysis (Table S3) demonstrated a HR of 1.90 ($P = 0.027$) based on implant diameter, such that each additional 1 mm increase in diameter was associated with a 1.9-fold increased risk of PI diagnosis. Furthermore, external connections were associated with a lower risk of PI compared to internal connections (HR = 0.11; $P = 0.018$). Distribution of implants diagnosed with PI ($n = 45$) according to the severity of bone loss is shown in Figure 2A. Severity of MBL was associated with increased grading (A-B versus C), but not with increased staging (Figure 2B). Results from the binary logistic regression model using GEE with fixed follow-up, showed that grading significantly influenced the risk of high MBL (>25%) ($P = 0.022$). Risk of severe MBL increased roughly 7.6 times for patients with a previous history of Grade C PR compared to the reference Grades A/B. Furthermore, there was no significant difference in risk of severe MBL according to stage ($P = 0.399$) (Table 4).

4 | DISCUSSION

4.1 | Main findings

This study investigated the potential association between baseline PR stage and grade and future implant failure as well as PI prevalence and severity. Ninety-nine treated PR patients were subsequently rehabilitated with dental

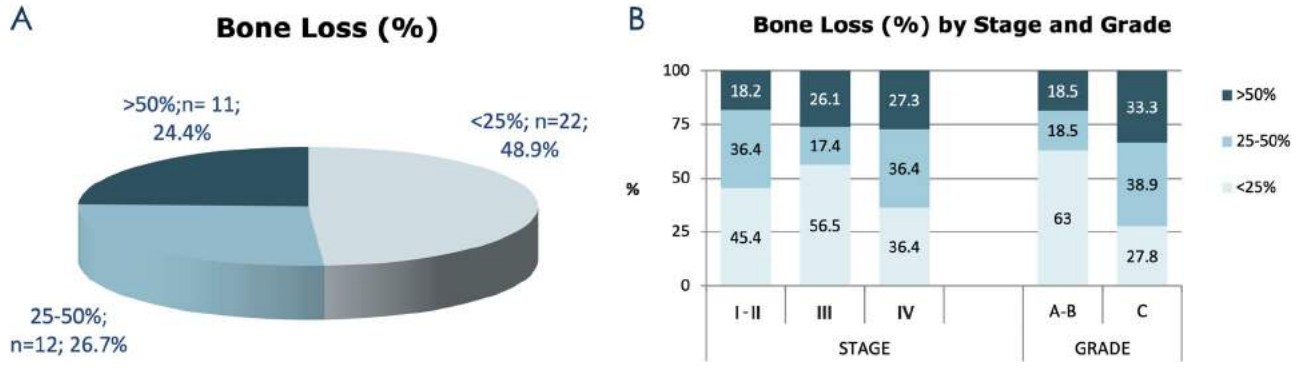

FIGURE 2 (**A**) Distribution of implants diagnosed with peri-implantitis (PI) ($n = 45$) according to marginal bone loss severity (<25%/25% to 50%/>50% of implant length); (**B**) categorization of implants diagnosed with PI according to baseline staging/grading and severity of MBL

TABLE 4 Risk of ≥25% bone loss according to periodontal diagnosis (stage and grade) adjusted by time since crown placement to radiographic analysis (RX)

	OR	95% CI	*P*
Stage			0.399
1-2	1		
3	0.26	0.04–1.93	0.186
4	0.25	0.03–2.16	0.209
Grade			
A-B	1		
C	7.61	1.35–43.1	0.022*
RX follow up (years)	1.11	0.97–1.28	0.127

The results of the binary logistic regression model were evaluated using GEE, adjusted odds ratio (OR), and 95% CI.
*$P < 0.05$.

implants (n = 221) and followed over a mean period of 10.6 years. Patients were classified according to periodontal stage and grade at the time of active periodontal therapy. Over the follow-up period, only six implants (2.7%) failed. Although the implant failure rate increased from Stage I/II (0%) to Stage IV (6.5%), this trend was not statistically significant. A statistically significant increase was seen from Grade A (0%) to Grade C (5.9%). Interestingly, our results showed no correlation between PR staging or grading and increased prevalence/incidence of PI at either implant- or patient-levels. Although the 2017 World Workshop proposed case definitions for PI, these definitions do not facilitate differentiation between severity levels of PI based on the magnitude of MBL.[25,26] For the current analysis, a MBL severity threshold of 25% of the implant length was chosen to be correlated with PR stage and grade. The present study found that the severity of peri-implant MBL was directly associated with higher-level of grading. The periodontitis grade (C versus A-B) significantly influenced risk of high MBL (>25%) ($P = 0.022$). Risk of severe MBL increased 7.6 times for patients with a previous history of periodontal Grade C compared to Grades A/B.

Overall, these results suggest that staging and grading may not play a role in modulating probability of PI onset, but once PI pathogenesis is initiated, higher-level grading is associated with increased severity of MBL and higher probability of implant failure, whereas staging is not.

4.2 | Agreement and disagreement with previous studies

There are conflicting results in the literature regarding the association between history of periodontitis and implant failure. Some of the previous studies utilizing the 1999 periodontal classification[27] reported higher long-term implant failure rates in patients who exhibited more severe forms of PR (survival rate range: 88% to 98.4%) compared to those who had moderate/mild PR (survival rate range: 92.8% to 100%).[28–32] However, others did not confirm this correlation.[33,34] In the present study, although a higher trend for implant failure was found in patients with a previous history of severe PR (Stages III-IV), no statistically significant differences were found because of the small number of implants lost (only six).

Grade is a risk assessment tool composed of a composite of systemic (smoking and diabetes mellites) and local parameters (radiographic bone loss/age). To allow for a more precise analysis of the effects of grading on implant failure, systemic risk factors were evaluated separately. Implants placed in current heavy smokers were associated with a significantly higher failure rate compared to never-smokers (HR = 4.71; $P = 0.04$). A recent systematic review showed that heavy smokers (>20 cigarettes/d) were

at a higher risk for implant failure (HR = 4; $P < 0.001$) compared with non-smokers.[35] In addition, De Boever et al.[36] reported a 17% increased implant failure rate in current smokers with a history of aggressive periodontitis, and a 2% increase in former smokers. In spite of these findings, the 2017 World Workshop recently referred to smoking and diabetes as "inconclusive" risk indicators[1] for PI development because of a lack of conclusive evidence.[9]

Our findings also did not show a significant correlation between PR severity and PI prevalence. It is important to note that the present study population was entirely composed of PR patients with varying levels of severity. Most existing studies investigating the association between PR and PI compared PR patients to those with no previous history of PR.[10,36–38] However, very few correlated different levels of PR severity with prevalence and severity of PI.[28,31,39] Utilizing stage to categorize patients based on PR severity, results of the present investigation were similar to those from previously published studies which used other systems for diagnosing PR severity. Roccuzzo and coworkers reported a PI prevalence of 27% in patients with moderate PR, and 47.2% in patients with severe PR.[39] In a subsequent study, they reported a PI prevalence of 52.2% in patients with moderate PR, and 66.7% in patients with severe PR. In the current study, patients with mild and moderate severity PR (Stage I and II) had a PI prevalence of 33.3%, whereas patients with severe PR (Stage III and IV) had a PI prevalence of 52.7%. Despite this, the present study did not find any statistically significant association between PI prevalence and PR severity (stage).

The prevalence of PI at both the implant- and patient-levels in the present study can be compared to the results of Romandini et al., because this study also used the 2017 World Workshop definition of PI in a PR population.[3] Over a mean follow-up of 7.8 years at the patient-level, the authors reported a PI prevalence of 23.2% in healthy versus 56.6% in PR patients. At the implant-level, they found PI prevalence in healthy and PR patients was 12.4% and 27.9%, respectively. In comparison, the prevalence of PI in the present study was lower at a rate of 20.4% at the patient-level, and 15% at the implant-level after 10-years follow-up.

4.3 | Additional factors which influenced incidence of PI

Implant diameter and type of abutment-fixture connection were significantly associated with risk of PI development. Each additional 1 mm increase in diameter was associated with a 1.9-fold increased risk of PI diagnosis (HR = 1.90; $P = 0.027$) (Table S3). Previous studies reported contradictory findings regarding implant diameter and PI risk. The majority of studies reported a higher rate of PI for narrow diameter implants.[40–42] Others agreed with our study and showed that wider implants were associated with a higher MBL and risk of PI.[43,44] Overall, the evidence regarding implant diameter as a contributing factor towards PI pathogenesis is limited.

Additionally, implants with external connections were associated with significantly lower prevalence of PI when compared to internal connections (HR = 0.11; $P = 0.018$). Further investigation revealed that 100% of the implants with external connection in the current study had a machined surface, which have been associated with lower PI rates.[45,46] Previous meta-analyses have reported reduced MBL in conical internal connection implants, suggesting that the stability of the abutment-fixture connection is an important determinant of peri-implant bone levels.[47,48] Prior clinical studies have also demonstrated better bone preservation associated with internal connection implants relative to external connection implants.[49,50] The low number of external connection implants in our sample (18 fixtures), in conjunction with a machined surface for all of them, can potentially explain this controversial result.

4.4 | Limitations

The present study is not exempt from limitations. First of all, severe forms of PR may have reduced available bone quality and quantity, which in turn may potentially influence PI prevalence and severity.[15] Although this statement cannot be validated from our findings, our results did not show any significant difference in PI rates between different levels of PR staging or grading. Secondly, the small sample size in lower severity classes (Stage I and Grade A), which was dictated by their lower prevalence in the population[26] and by the exclusion of non-compliant patients (<1 maintenance/y) could have influenced the strength of the relationships evaluated during statistical analysis. For instance, Grade C PR patients were associated with a much higher implant failure rate (HR = 6.57; $P = 0.075$), but the difference did not reach a level of statistical significance. The same can be seen for the stage; although all failed implants were found in patients with a history of Stage III and IV PR, the comparison with Stages I and II did not reach significance. Finally, factors contributing to PI were not totally accounted for, including but not limited to: implant (mal)positioning, residual cement, and prosthetic considerations (emergence profile and abutment height). Future studies should consider these factors to have a better understanding of how they may interact with a previous history of periodontitis in order to influence PI prevalence and severity.

5 | CONCLUSIONS

In a well-maintained compliant population with a history of periodontitis, no statistically significant association between staging or grading and prevalence of PI was found. However, when PI was diagnosed, increased severity of MBL and probability of implant failure were associated with a previous history of Grade C periodontitis. Further studies are needed to confirm these preliminary findings.

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CONFLICTS OF INTEREST

The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the paper.

AUTHOR CONTRIBUTIONS

Andrea Ravidà: Contributed to the conception and design of the study, acquisition of the data and drafting of the article. Musa Qazi: contributed to the acquisition of data. Maria Vera: contributed to the acquisition of data. Matthew Galli: contributed to the conception and design of the study and drafting of the article. Muhammad H. A. Saleh: contributed to the drafting of the article. Giuseppe Troiano: Contributed to the conception and design of the study, data analysis and interpretation. Hom-Lay Wang: contributed to the conception, critical revision of the article and final approval of the version to be published. Pablo Galindo Moreno: contributed to the conception, critical revision of the article and final approval of the version to be published.

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SUPPORTING INFORMATION

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

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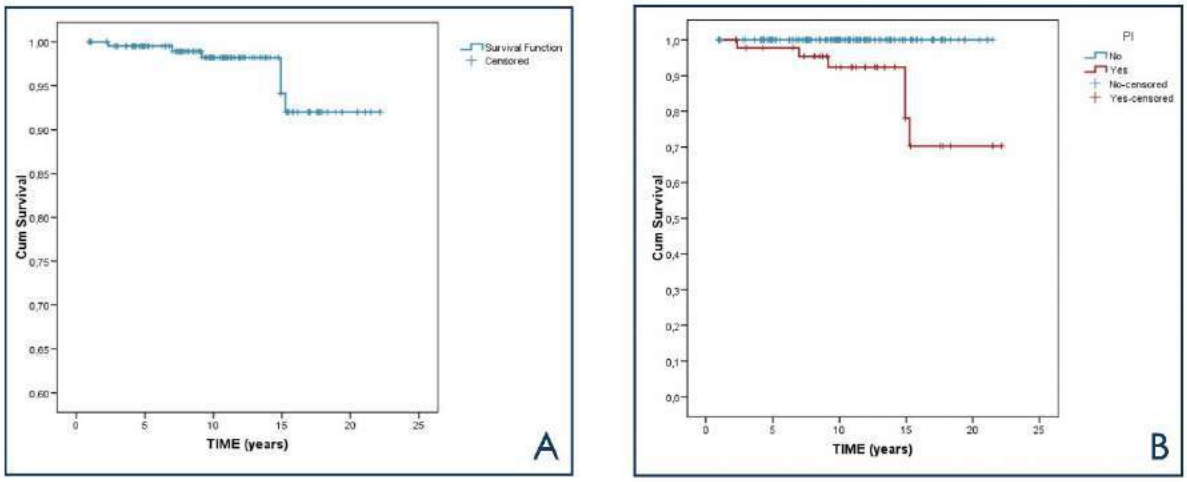

Figure S1.

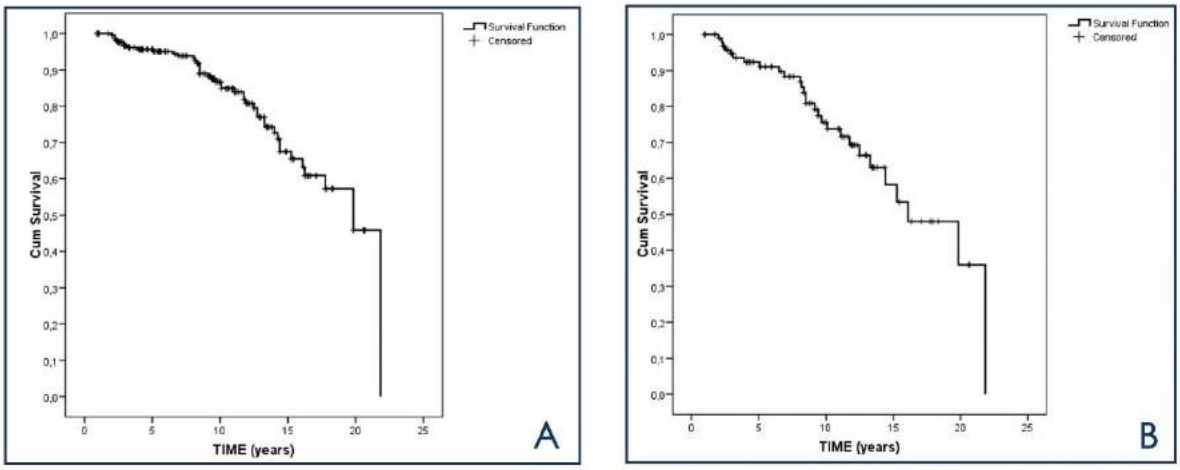

Figure S2.

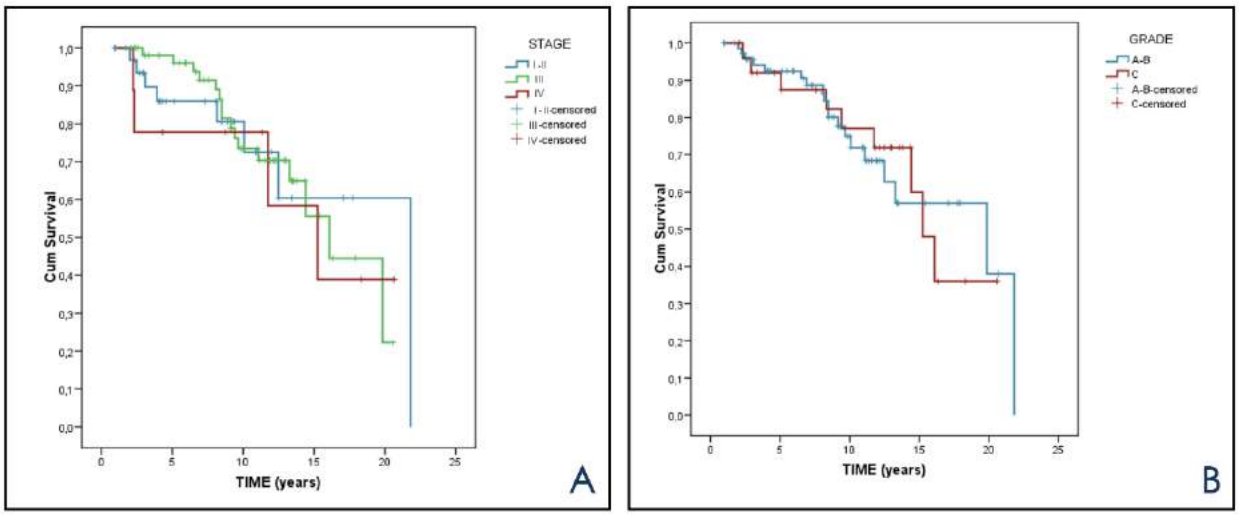

Figure S3.

Supplementary Table 1: Survival analysis of time-to-event failure by stage: cumulative survival probability at different time-point (years)

	STAGE 1-2		STAGE 3		STAGE 4	
Time	**Survival**	**SE**	**Survival**	**SE**	**Survival**	**SE**
1 y	1.000	0.000	1.000	0.000	1.000	0.000
2.5 y	1.000	0.000	1.000	0.000	0.964	0.035
5 y	1.000	0.000	1.000	0.000	0.964	0.035
10 y	1.000	0.000	0.979	0.015	0.964	0.035
15 y	1.000	0.000	0.911	0.048	0.884	0.083
20 y	1.000	0.000	0.911	0.048	0.884	0.083

*SE: Standard error

Supplementary Table 2: Survival analysis of time-to-event failure by grade: Cumulative survival probability at different time-point (years)

	GRADE A-B		GRADE C	
Time	**Survival**	**SE**	**Survival**	**SE**
1 y	1.000	0.000	1.000	0.000
2.5 y	1.000	0.000	0.988	0.012
5 y	1.000	0.000	0.988	0.012
10 y	0.986	0.014	0.974	0.018
15 y	0.986	0.014	0.886	0.062
20 y	0.986	0.014	0.836	0.076

*SE: Standard error

Supplementary Table 3: Results of Cox proportional hazard regression model illustrating time-to-event PI by clinical variables related to the patient, implant position, characteristics, and surgery.

	HR	95% CI	p-value
AGE (years)	1.03	0.99 – 1.08	0.145
GENDER			
Male	1		
Female	1.07	0.49 – 2.32	0.874
SMOKING			0.820
No	1		
Former smoker	1.17	0.44 – 3.07	0.763
Yes (<10c/d)	0.71	0.25 – 2.06	0.531
Yes (>10c/d)	0.68	0.22 – 2.14	0.513
DIABETES			
No	1		
Yes	2.21	0.72 – 6.82	0.166
STAGE			0.805
1-2	1		
3	0.90	0.35 – 2.28	0.819
4	1.23	0.30 – 5.05	0.776
GRADE			
A-B	1		
C	1.00	0.46 – 2.17	0.996
EXTENSION			
Localized	1		
Generalized	1.16	0.48 – 2.82	0.740
ARCH			
Maxilla	1		
Mandible	1.20	0.59 – 2.45	0.607
POSITION			
Anterior	1		
Posterior	2.19	0.41 – 11.8	0.359
PROSTHESIS TYPE			
Single	1		
Splinted	1.33	0.56 – 3.11	0.518
Overdenture	--	--	**--**
LEVEL			
Soft	1		
Bone	2.07	0.54 – 7.92	0.289
CONNECTION			
Internal	1		
External	0.11	0.02 – 0.68	**0.018***
Locator	--	--	--
RETENTION			
Cemented	1		
Screwed	5.43	1.15 – 25.8	**0.033***
Ball atachment	--	--	--
IMPLANT LENGTH	1.16	0.92 – 1.48	0.223
IMPLANT DIAMETER	1.90	1.08 – 3.36	**0.027***
BONE GRAFT			
No	1		
Yes	1.22	0.56 – 2.67	0.624

p<0.05; †p<0.01; ‡p<0.001

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Alice Ou
Kenneth Kornman
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Hom-Lay Wang
Wenche Borgnakke
Musa Qazi

Subject: Notice of Exemption for [HUM00157260]

SUBMISSION INFORMATION:
Title: Long-term tooth retention after stage and grade assessment-results after more than 10 years of a conservative periodontal treatment regimen in a university setting
Full Study Title (if applicable):
Study eResearch ID: HUM00157260
Date of this Notification from IRB: 3/11/2019
Date of IRB Exempt Determination: 2/27/2019
UM Federalwide Assurance: FWA00004969 (For the current FWA expiration date, please visit the UM HRPP Webpage)
OHRP IRB Registration Number(s): IRB00001999

Additional Supporting Documents:

IRB EXEMPTION STATUS:
The IRBMED has reviewed the study referenced above and determined that, as currently described, it is exempt from ongoing IRB review, per the following exemption category:

EXEMPTION 4(iii) at 45 CFR 46.104(d):

Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(iii)The research involves only information collection and analysis involving the investigator's use of **identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E**, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b)

Note that the study is considered exempt as long as any changes to the use of human subjects (including their data) remain within the scope of the exemption category above. Any proposed changes that may exceed the scope of this category, or the approval conditions of any other non-IRB reviewing committees, must be submitted as an amendment through eResearch.

Although an exemption determination eliminates the need for ongoing IRB review and approval, you still have an obligation to understand and abide by generally accepted principles of responsible and ethical conduct of research. Examples of these principles can be found in the Belmont Report as well as in guidance from professional societies and scientific organizations.

HIPAA REVIEW:
The IRB has reviewed the project referenced above and has granted a Waiver of HIPAA Authorization. The IRB has determined that the proposed project conforms with applicable regulations and policies. This project must be conducted in accordance with the description and information provided in the application and associated documents.

Note: This project is regulated under the HIPAA Privacy Rule, which requires you to account for certain disclosures of Protected Health Information (PHI).

SUBMITTING AMENDMENTS VIA eRESEARCH:
You can access the online forms for amendments in the eResearch workspace for this exempt study, referenced above.

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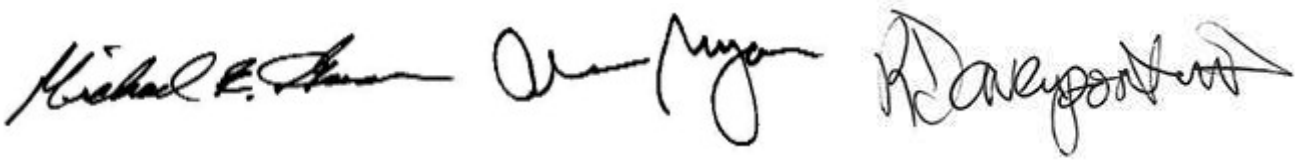
TERMINATION:
You will receive an annual message reminding you of your responsibilities to manage this research application. Terminate the application once you only hold or are analyzing deidentified data, or the research has ended.



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APPENDIX #3.1: STUDY #3 PUBLICATION[96]

Complete citation

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ORIGINAL ARTICLE

CLINICAL ORAL IMPLANTS RESEARCH WILEY

Limited marginal bone loss in implant-supported fixed full-arch rehabilitations after 5 years of follow-up

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Abstract

Purpose: The aim of the present study was to evaluate the 5-year results in terms of marginal bone level (MBL) around implants supporting fixed full-arch metal-ceramic restorations in a series of cases of patients who had lost their teeth in that dental arch because of severe periodontal disease.

Material and Methods: A retrospective cohort study was designed to evaluate the 5-year MBL results of OsseoSpeed™ Astra Tech TX implants with internal tapered conical connection. Age, gender, bone substratum, smoking habits, history of periodontitis, and prosthetic features were recorded. Mixed linear model was used to determine the influence of the different variables on MBL.

Results: In this series, a total of 160 implants placed in 19 patients were evaluated. No implant failure was reported during the 5 years of follow-up. Only 14 (8.75%) implants had more than 2 mm of MBL. Abutment height, $F(3,142) = 6.917$, $p < .001$, and implant diameter, $F(1,141) = 15.059$, $p < .001$, were determined to be statistically associated with MBL. No other effect was significant. Pairwise comparisons showed that MBL was larger for abutment height = 1 (MBL = −0.987, SE = 0.186) compared with the remaining heights [−0.335 (0.171), −0.169 (0.192) and −0.247 (0.267), 2, 4 and 6 mm, respectively]. MBL was larger for narrow (−0.510, SE = 0.169) than for wide implants (−0.364, SE = 0.190).

Conclusion: The current study demonstrates that the vast majority of internal conical connection implants supporting fixed full-arch metal-ceramic restorations do not suffer from relevant MBL after 5 years in function. Particularly, those implants with transmucosal abutments longer than 2 mm show less than 0.5 mm from the implant shoulder to the marginal bone.

KEYWORDS
alveolar bone loss, dental implants, marginal bone level, peri-implantitis, periodontitis

1 | INTRODUCTION

Edentulism is a problem that affects a high percentage of the world's population, especially those in an elderly range. These patients suffer different oral pathologies such as cavities, dry mouth, masticatory dysfunction, and, above all, periodontitis (Eke et al., 2012). According to the American Academy of Prosthodontists, 30 million Americans suffer from edentulism; this is around 10% of the population. Edentulism has been associated with other systemic pathologies so that toothless patients are more likely to develop systemic pathologies of different kinds, such as gastrointestinal, cardiovascular, nutritional, or neurodegenerative disorders (Emami et al., 2013).

The possibilities for occlusal rehabilitation are multiple. Even if only the possibility of rehabilitating these patients through implant-supported prosthesis is considered, the options described in the literature are still varied. Among those, three major modalities can be highlighted: overdentures, implant-supported hybrid prostheses, and fixed implant-supported full-arch rehabilitations. Undoubtedly, each of these options has its particular indications and contraindications. All of them have reported high success rates both in terms of survival of the prosthesis, and in terms of maintenance and survival of the implants that support them. Even, the most advanced option, the fixed implant-supported full-arch rehabilitation, is reported in the literature with a wide variety of options, such as all-on-four and all-on-six techniques, rehabilitation on zygomatic implants, or screw-retained or cemented fixed prosthesis on 6–8 implants. This last option would be highly dependent on bone availability, anatomical accidents, or the need to perform complementary graft techniques (Stacchi et al., 2020). These different prosthetic solutions condition the long-term success of the restorations and the implants supporting them. The long-term success mainly depends on the type of bone where the implants are located, the inclination of the implants under functional load, the number, geometry, design and size of the implants, the possibility of hygiene of the prosthesis and implants or the type of restoration and materials that are used. It should not be forgotten that patients who had lost all their teeth usually have concomitant pathologies like an altered response to stress such as that induced by the periodonto-pathogenic bacterial footprint.

The final decision of which option to apply to one specific patient is usually due to factors that, in most cases, are not supported on scientific criteria: economic costs (number of implants or restoration materials, such as resins vs. ceramics o zirconium), surgical and prosthetic skills (complex grafting procedures vs. zygomatic implants, etc.) or training schools (all-on-four, zygomatic implants, maxillary sinus floor elevation, transposition of the inferior alveolar nerve, etc.).

In any case, the disparity of implant-supported prosthetic options in the treatment of the completely edentulous patient is so large that there is a lack of comparable and comparative long-term studies. Thus, meta-analysis cannot be properly conducted, and this is why all these techniques can be recommended with adequate clinical success in the medium- and long-term but without truly knowing if one or another is better. In any case, our treatment philosophy in these clinical situations is supported by the golden rules advocated by Misch and Silc (2009): placement of eight implants spread across the edentulous arch to support a fixed implant-supported full-arch screw-retained rehabilitation.

Long-term marginal bone loss, as a fundamental parameter to predict future bone loss and peri-implantitis (Galindo-Moreno et al., 2015), needs to be evaluated in the aforementioned treatment option, as studies on this specific type of restorative option are limited. Thus, we initiated the present study aimed at analyzing the long-term marginal bone level (MBL) of implants placed in completely edentulous patients with fixed full-arch rehabilitation after 5 years.

2 | MATERIALS AND METHODS

2.1 | Study population

This retrospective cohort study was presented and approved by the Ethics Committee for Human Research of the University of Granada, that waived the obtaining of informed consent (487CEIH2018). The study is reported following the recommendations of the STROBE guidelines.

Patients ($n = 19$, number of implants = 160) for the current study were selected from a pool of edentulous subjects due to severe periodontal disease restored with fixed implant-supported full-arch screw-retained rehabilitations, who have been in function for at least 5 years. Only those who attended at least one follow-up visit per year in which radiographic evaluation was performed were included. Type of implants and prosthesis, as described below, also defined inclusion. All those patients had been treated in a faculty clinic of the Department of Oral Surgery and Implant Dentistry of the University of Granada. If the patient's records indicated that the subject had gone under any kind of bone augmentation procedure except sinus floor elevation when vertical bone in the posterior maxilla was less than 8 mm (Galindo-Moreno et al., 2007), or taken any kind of medications known to affect bone metabolism, data from that subject would not be included in the analysis. If the patient's records indicated an uncontrolled progression of periodontal disease in the opposing arch within the follow-up period of the study according to the definition by López et al. (2002), data from that subject would not be included in the analysis either.

2.2 | Surgical procedures

An experienced surgeon (P.G.-M.) performed all the surgeries under local anesthesia (Ultracain®; Aventis, Inc.) with a regular implant placement protocol. No bone augmentation was needed in any case except maxillary sinus floor elevation. All implants included in the current study were of the same type (OsseoSpeed™ Astra Tech TX implants with internal tapered conical connection; Dentsply Implants).

TABLE 1 Frequency distribution of the variables analyzed in the study.

Variable					*p*
Gender	Women = 10	Men = 9			.819
Implant location	Mandible = 61	Maxilla = 99			.003
Maxillary sinus floor augmentation	No = 128	Yes = 32			.001
Implant diameter	3.5 mm = 42	4 mm or + = 118			.001
Abutment height	1 = 31	2 = 78	4 = 34	6 = 17	.001
Opposing arch	ND = 36	M = 66	ISFB = 51	RD = 7	.001

Note: For abutment height and opposing arch, proportions tests were done for the lowest category.
Abbreviations: ISFB, implant-supported fixed bridge; M, mixed; ND, natural dentition; RD, removable denture.

The position of each implant was prosthetically driven with the following criteria (Misch & Silc, 2009): (1) Implants on occlusal guides. So, for anterior disocclusion, implants were placed in the central incisors; for lateral group function or canine guide, implants were placed in the canine and the first premolars; finally, for molar occlusion, implants were placed in the position of each first molar. (2) No more than two pontics. (3) In addition, horizontal cantilevers were avoided by the appropriate bucco-lingual emergence of the implant. All implants were placed at the level of the bone crest.

After the implant surgery, amoxicillin/clavulanic acid tablets (875/125 mg, TID for 7 days) or, if allergic to penicillin, clindamycin tablets (300 mg, TID for 7 days) were prescribed to all patients. In addition, anti-inflammatory drugs (Ibuprofen 600 mg every 4–6 h as needed to a maximum of 3600 mg/day) and pain killers (metamizole 550 mg every 4–6 h only if needed) were also indicated.

2.3 | Restorative procedure

Eight weeks or 6 months if maxillary sinus floor elevation was conducted the restorative process was initiated by experienced Implantologists (M.P.-M. and P.G.-M.) with the necessary second surgical stage. In all cases, uni-abutments (Dentsply Implants) were interposed between the implants and the prosthesis for the design of metal-ceramic screw-retained restorations. Segmented restorations were fabricated in all cases. Only in one patient, both arches were restored simultaneously and, thus, considered for this study.

2.4 | Radiographic evaluation of MBL

Marginal bone level after 5 years was evaluated by importing the panoramic radiographs to an image analysis platform (Image J; NIH) in anonymous DICOM format. An experienced examiner (M.P.-M.) analyzed all the radiographs. Linear measures were obtained from the shoulder of the implant to the most coronal aspect of the supporting crestal bone, assigning a negative value when it was apically located with respect to the implant shoulder. Measurements on both the mesial and distal aspects of the implants were recorded, so that average could be calculated. Each measure was calibrated against the diameter of the implant.

Before the analysis of any of the study images, the examiner (M.P.-M.) conducted an intra-examiner calibration exercise following the same methodology described above. Briefly, 16 implant positions were evaluated twice with a time window of 7 days between measurements. The intraclass correlation coefficient for single measures was calculated with a two-way mixed model. The calculated intraclass correlation was 0.892.

2.5 | Additional data recorded

Additional data included age, gender, dental arch, the need of sinus graft and location, length, and diameter of each implant. Prosthetic variables included in this study were as follows: (1) Abutment height: 1, 2, 4, or 6 mm. (2) Prosthesis height defined as the distance from the connection between the prosthesis and the abutment to the most occlusal aspect of the ceramic. (3) Prosthesis-to-implant ratio, calculated as the ratio between the length of the implant and the sum of the prosthesis and the abutment heights. (4) Implants per bridge, that included how many implants were supporting each particular bridge. (5) Crowns per bridge, considering how many crowns were included in each bridge. (6) Bridge ratio, defined as the ratio between the number of implants and crowns per bridge. (7) Opposing arch, to describe the type of dentition in the other arch, considering the whole arch as a unit: natural dentition, implant-supported full-arch screw-retained restoration, mixed, or removable denture (either implant-retained or conventional).

2.6 | Statistical analysis

A total of 160 implants placed in 19 patients were analyzed in this retrospective study. When data beyond the 5-year follow-up was available, it was not considered in order to homogenize the analysis. To this end, we used a mixed linear model to estimate the effects of graft, abutment height, and opposing arch on average MBL (distal and mesial), controlling for gender, age, implant location, implant length and diameter, and the remaining additional data (crowns per bridge, prosthesis-to-implant ratio, implants per bridge, bridge ratio, and prosthesis height), while controlling for subjects clustering. The covariance matrix was selected (compound symmetry)

using the Schwarz Bayesian Criterion. We used the IBM SPSS v23 for Windows (IBM Corp.).

3 | RESULTS

From the initial pool of patients whose records were retrieved from the database according to the criteria defined earlier, no patient was excluded.

Table 1 displays the distribution of non-metric variables in the sample. It can be seen that except for gender, all the other variables were significantly distributed using proportion test. Table 2 describes the metric variables, including the MBL.

Results of the mixed linear model demonstrate a main effect on MBL of abutment height, $F(3,142) = 6.917$, $p < .001$, and implant diameter, $F(1,141) = 15.059$, $p < 0.001$. The size of the random effect was 32.6%. As it can be seen in Table 3, no other effects were significant. MBL was larger for narrow (−0.510, standard error [SE] = 0.169) than for wide implants (−0.364, SE = 0.190). Regarding abutment height, Bonferroni corrected pairwise comparisons showed that MBL was larger for abutment height = 1 (MBL = −0.987, SE = 0.186) compared with the remaining heights: −0.335 (0.171), −0.169 (0.192) and −0.247 (0.267), 2, 4 and 6, respectively (Figure 1). Table 4 displays the adjusted and unadjusted MBL averages per abutment height.

In addition, we performed a tabulation of the MBL as a function of abutment height (Table 5; Figure 2) in order to compare with the stratification proposed by Derks et al. (2016). As it can be observed, most implants have less than 1.00 mm of MBL in all abutment heights; MBL higher than 3.00 mm are only present in five implants that were restored with abutments of 1.00 mm of height. Furthermore, according to the criterion of 2 mm of MBL to distinguish between success or survival implants from the Pisa Consensus (Misch et al., 2008), only 14 (8.75%) implants can be considered as survival implants while the others can be considered successful in terms of bone maintenance. No failure was reported after 5 years of follow-up.

TABLE 2 Descriptive statistics of the study population.

Variable	Mean	SE	95% CI
Age	55.625	0.613	54.414, 58.836
Implant length	11.809	0.192	11.429, 12.189
Prosthesis height	12.849	0.279	12.299, 13.400
Prosthesis-to-implant ratio	1.380	0.048	1.286, 1.475
Implants per bridge	4.694	0.189	4.302, 5.067
Crowns per bridge	7.956	0.324	7.317, 8.595
Bridge ratio	1.695	0.022	1.652, 1.739
MBL average	−0.423	0.069	−0.559, −0.288

Abbreviations: CI, confidence interval; MBL, marginal bone level; SE, standard error.

4 | DISCUSSION

The aim of the present study was to analyze the long-term behavior of a series of implants placed in completely edentulous patients that were restored with fixed full-arch implant-supported screw-retained rehabilitations. For that, 160 Astra Tech TX implants placed in 19 edentulous patients were studied. A mean MBL after 5 years of follow-up of −0.423 (0.069) mm was found. This MBL is influenced only by abutment height and implant diameter.

As in many previous studies, the height of the abutment was the capital factor that influenced the MBL: the taller the abutment the lesser the MBL. Although the height of the abutment, in our opinion, still does not have the full consideration that it deserves in the prosthetic restoration phases, our data are in accordance with many other studies (Borges et al., 2018, 2019; Galindo-Moreno et al., 2015, 2016; Galindo-Moreno, León-Cano, et al., 2014; Nóvoa et al., 2017; Pico et al., 2019; Spinato et al., 2018, 2019, 2020; Vervaeke et al., 2014, 2016). Nevertheless, all those previous studies were conducted in single crown restorations (Spinato et al., 2018, 2020), or in 2-unit bridges (Borges et al., 2018; Nóvoa et al., 2017; Pico et al., 2019; Spinato et al., 2019), 3 unit bridges (Galindo-Moreno et al., 2015, 2016; Galindo-Moreno, León-Cano, et al., 2014), fixed cross-arch restorations over four or five implants (Collaert & De Bruyn, 2002) and overdentures (Vervaeke et al., 2014). To our knowledge, MBL has not been previously related to abutment height in implants supporting fixed full-arch prosthetic rehabilitations.

In the current study, 100% of implants could be considered as survivors. Only five implants overpassed 3 mm of MBL; thus, if we use the radiographic parameters recommended by the 2017 definition of Peri-implant diseases, they could be classified as diseased if accompanied by clinical parameters (Berglundh et al., 2018), not evaluated in the current study. However, according to the classic success criteria of 2 mm of MBL (Albrektsson et al., 1986), our sample showed a radiographical success of 91.25%.

A majority of studies demonstrate that implant-supported fixed dental prostheses offer a safe and stable solution in the long term, both in terms of survival and MBL (Francetti et al., 2019; Maló et al., 2018; Papaspyridakos et al., 2019; Pera et al., 2018). Regardless highly satisfactory outcomes, independently of the option in use, and even with a high variability of data (Bagegni et al., 2019), many different aspects can be subjected to discussion. For instance, health status of the patients, previous history of periodontitis, habits, number of implants, straight or tilted, type of prosthetic restoration, design of the prosthetic restoration, bone biology, differences between maxilla and mandible, one-piece restoration or segmented bridges, etc. (Morton et al., 2018).

In this sense, a good number of studies have reported on the negative influence of history of periodontitis in the peri-implant MBL (Galindo-Moreno, Fernández-Jiménez, et al., 2014; Matarasso et al., 2010; Roccuzzo et al., 2012; Saaby et al., 2016), even becoming a highly accepted risk factor (Berglundh et al., 2018). However, the present study was obtained from a pool of edentulous patients as a consequence of severe periodontitis. The mean MBL after 5 years

TABLE 3 Estimates of the mixed linear model.

Parameter	Regression coefficient	Standard error	95% CI (LL)	95% CI (UL)
Abutment height 1	−0.740	0.271	−1.276	−0.205
Abutment height 2	−0.098	0.218	−0.529	0.333
Abutment height 4	0.078	0.216	−0.349	0.505
Opposing arch 1	0.155	0.606	−1.104	1.414
Opposing arch 2	−0.015	0.597	−1.260	1.230
Opposing arch 3	0.740	0.700	−0.719	2.200
Maxillary sinus floor augmentation	−0.147	0.138	−0.419	0.126
Implant diameter	0.487	0.125	0.238	0.736
Gender	0.108	0.208	−0.343	0.559
Age	0.029	0.020	−0.013	0.072
Implant location	−0.117	0.184	−0.483	0.249
Implant length	0.021	0.059	−0.097	0.139
Crown height	0.010	0.037	−0.062	0.083
Crown/implant ratio	0.318	0.349	−0.373	1.008
Implant per bridge	0.410	0.238	−0.061	0.881
Crown per bridge	−0.243	0.140	−0.521	0.034
Bridge ratio	0.543	0.505	−0.456	1.542

Note: Abutment height, opposing arch, and maxillary sinus floor augmentation were considered as factor, and the reference was the last category.

Abbreviations: LL, lower limit; UL, upper limit.

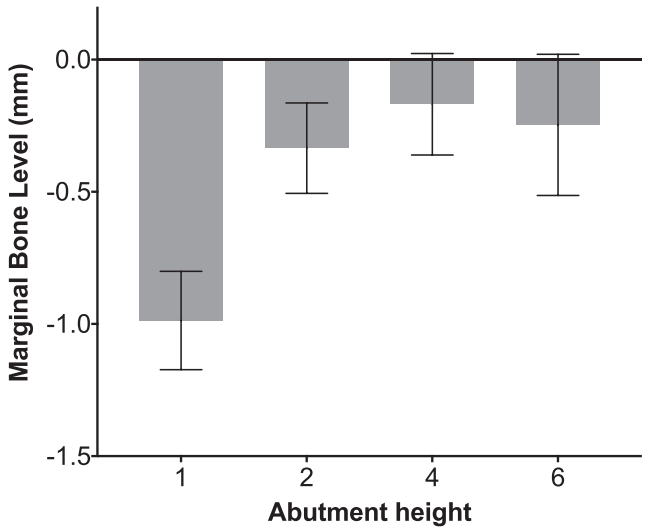

FIGURE 1 Average marginal bone level (MBL, in mm) for the different abutment heights. MBL for the abutment height 1 mm was significantly larger than for the other three abutment heights.

was −0.423 (0.069) mm. A similar series has recently reported an estimated average MBL after 11 years of −0.307 (SE = 0.042) (Galindo-Moreno et al., 2022). In both cases, the reported MBL is in accordance with the higher standards of healthy implants. As commented previously, Francetti et al. (2019) agree with these results, after 5 and 10 years of follow-up. Guarnieri and Ippoliti (2019) also concluded that high survival rates are expectable in implants in periodontally compromised patients if a regular supportive periodontal therapy is conducted. Cecchinato had also previously claimed in their studies that the percentage of sites with progressive bone loss was small at both implants and teeth and that this was not different in subjects in the "periodontitis" or "non-periodontitis" groups (Cecchinato et al., 2017, 2018). Some systematic reviews show similar results (Theodoridis et al., 2017). Kim and Sung (2012) reported no differences in similar conditions but higher losses when comparing with aggressive periodontitis. Monje et al. (2014) found a similar tendency, but comparing only with aggressive periodontitis. Thus, there is an increased number of studies claiming that the initial statement is not so valid anymore. Current evidence is pushing the scientific community to re-analyze this concept, taking other variables into consideration.

Regarding number of implants supporting a full-arch rehabilitation, it was suggested that a minimum of 6–8 implants in the mandible and even more in the upper maxilla would be required (Brånemark et al., 1995). For sure, the number of implants needed to do this kind of restorations depends on many factors. Some of them are biological factors, such as bone nature, density and availability, and anatomical factors, such as the location of the inferior alveolar nerve, or hyper-pneumatized maxillary sinuses. Other factors are related to biomechanics, like the type of prosthetic restoration, the materials, the prosthetic design or if it is conceived as a one-piece restoration or a multiple-segmented restoration. All patients in the current series were treated with at least eight implants per arch, following the Misch and Silc's golden

TABLE 4 Adjusted and unadjusted MBL averages (standard errors of the mean) according to abutment height.

Abutment height	1	2	4	6
Adjusted	−0.987 (0.186)	−0.335 (0.171)	−0.169 (0.192)	−0.247 (0.267)
Unadjusted	−1.241 (0.188)	−0.295 (0.077)	−0.202 (0.076)	0.045 (0.024)

Abbreviation: MBL, marginal bone level.

TABLE 5 Frequency distribution of MBL as a function of implant abutment height.

Abutment height	<−4	≥−4, <−3	≥−3, <−2	≥−2, <−1	≥−1, <0	≥0	No. of implants
1	0	5	7	3	13	3	31
2	1	0	0	5	40	32	78
4	0	0	1	1	22	10	34
6	0	0	0	0	4	13	17
N patients	0	0	0	3	11	5	19
Worst case (mm)	−4.28	−3.06	−2.67	−1.91	−0.96	0	

Note: The patient's frequency data is based on patient's averages. The worst case is the worst MBL for the set of patients showing each category of MBL.

Abbreviation: MBL, marginal bone level.

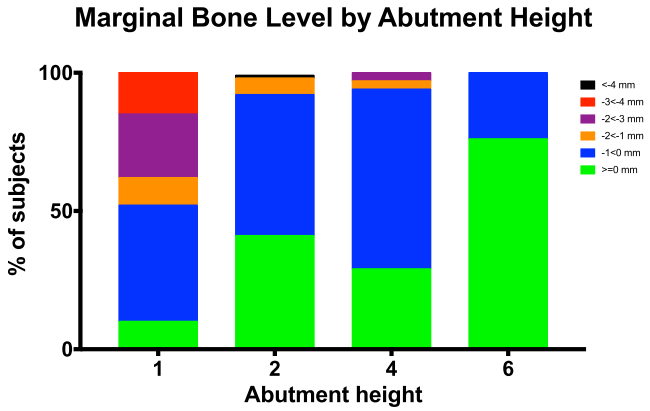

FIGURE 2 Tabulation of the marginal bone level (MBL) as a function of abutment height to represent the % of implants within each range of MBL (in mm) depending on the height of the abutment.

criteria, as previously described. In addition, segmented restorations were done in all patients in order to improve the overall implant-prosthesis adjustment, and to be able to act only on that specific segment in case of any issue appears in the follow-up. Nevertheless, a recent meta-analysis has stated that the number of implants used in complete-arch prostheses do not influence MBL, implant survival rate, prosthesis survival rate or prosthesis complications in studies with a follow-up period between 5 and 15 years (de Luna Gomes et al., 2019). In the mandible, the number of implants suggested for an implant-fixed complete dental prosthesis ranges from four to nine implants. However, Papaspyridakos et al., (2014) reported a larger number of implant failures in the interforaminal space. This would jeopardize the four or five implant-supported rehabilitation protocols. In any case, in terms of overall implant survival, they found no statistically significant differences related to the number of implants (Papaspyridakos et al., 2014). There is no evidence in literature to support this idea in maxilla or mandible either (Daudt Polido et al., 2018; de Luna Gomes et al., 2019).

de Luna Gomes' meta-analysis stated that mean MBL was higher for full-arch prostheses with more than four implants per arch (mean, 1.46 mm) than for those with fewer than five implants (mean, 1.22 mm), although without statistical significance (de Luna Gomes et al., 2019). Nevertheless, this mean MBL reported is much higher than that found in our study [−0.423 (0.069) mm]. It is important to keep in mind that in the majority of these meta-analyses there were a plethora of manuscripts reporting all-on-four studies. In some of them, there is not any study with more than six implants per arch (de Luna Gomes et al., 2019). Thus, results should not be compared with studies with fixed full-arch rehabilitations supported by eight implants as the type of prosthesis and treatment concept is completely different.

Regarding the location of the implants, the implant survival rate in full-arch rehabilitation has been described as 99% for the maxilla and 98.9% for the mandible (Agliardi et al., 2010; de Luna Gomes et al., 2019) or even 100% after 3 years (Francetti et al., 2012). In the latter study, the authors reported a slightly higher bone resorption in implants placed in the anterior mandible, contrary to Malo and coworkers that reported a higher marginal bone loss in the posterior segment of the mandible, although those posterior implants were tilted (Maló et al., 2018). More recently, Francetti et al., (2019) have reported that 61.5% of the implants affected with peri-implantitis were in mandibular restorations. In our study, the implants survival was 100% independently of the bone typology and upper or lower location. All implants were in straight position, predominantly in the upper maxilla (61.8%); 20% of them were placed in grafted bone. However, in terms of MBL, as necessary initiation phase of peri-implantitis, we were not able to find any statistically significant difference associated with location or the nature of the bone substratum. In previous studies, we found a slight significant difference

in terms of MBL, it was higher in grafted maxillary sinuses compared with native bone in the posterior maxilla (Galindo-Moreno, Fernández-Jiménez, et al., 2014). That study was conducted evaluating implants supporting partially fixed bridges, in contrast to the current study. Moreover, differences in the type of implants could also explain the disparities.

In relation with the type of prosthetic restoration, a recent meta-analysis studied the influence of the prosthetic material on implant survival when they are supporting a full-arch rehabilitation. It was described that metal-ceramic fixed complete dentures are more effective in terms of implant survival than any other type of material, reaching 95% of prosthesis survival and 97% of implant survival (Bagegni et al., 2019). Our study, using the same restoration material, has found a prosthesis survival (100%) and implant survival (100%) in accordance with that meta-analysis.

But, not only the material is important. Segmentation of the dental prosthesis in smaller bridges, as done in patients included in the current study every time possible, leads to better maintenance, easier retrievability, and easier fabrication and installation (Gallucci et al., 2005). Regardless, a systematic review on this topic reported that prosthodontic survival rates for 1-piece implant fixed complete dental prostheses ranged from 98.61% (5 years) to 97.25% (10 years) (Papaspyridakos et al., 2014). However, biomechanical issues have also to be considered. Some of these biomechanical aspects can be the distribution of the masticatory load through the entire arch, and the horizontal or vertical cantilevers, as crown-to-implant ratios are usually high in these patients (Misch et al., 2005). Even though previous meta-analysis suggested that marginal bone loss is not influenced by the presence of horizontal cantilevers (Torrecillas-Martínez et al., 2014), but in our current study, horizontal cantilevers were always avoided.

Regarding the crown-to-implant ratio, our results indicated that this ratio did not play any relevant role in the MBL. In fact, this is supported by other studies (Blanes, 2009). It has even been reported that, within the range of 0.6/1 to 2.36/1, the higher the crown-to-implant ratio the lesser the peri-implant bone loss (Garaicoa-Pazmiño et al., 2014). None of the other prosthetic factors evaluated in this study (Tables 2 and 3) played a role in the MBL when the height of the prosthetic abutment was part of the equation.

This study has some limitations. Firstly, it is a retrospective study with a not very large number of patients. However, it reports results in a considerable number of implants in a very specific population of patients. Moreover, this is the longer follow-up study present in the literature reporting the effect of the height of the abutment in the MBL. As in many previous studies, digitalized panoramic radiographies were used. This is similar to many previous studies on fully edentulous patients already referenced throughout the discussion. A potential solution is the internal calibration that is performed for every measurement considering the dimensions of the implant. Also, recent consensus (Jepsen et al., 2019; Schwarz et al., 2018) does not include the term "intraoral" examination for the follow-up of this kind of patients. Another potential caveat is the number of implants when categorized by abutment height. In this vein, the minimum number of implants was that of the abutment height 6 ($n = 17$, in five patients), but, when we performed the same analysis excluding this abutment category, the results were the same; this is, the significance was obtained for abutment height and implant diameter. In addition, for this study, only MBL data at the 5-year follow-up is presented. It is important to remember that, for the general clinical practice, the progression of MBL change and when it occurs (either early or late) is important in the diagnosis of peri-implantitis. Moreover, clinical parameters could be helpful as supportive diagnostic tools.

5 | CONCLUSION

Within the limitations of the current study, it was found that the vast majority of internal conical connection implants supporting fixed full-arch metal-ceramic restorations in patients who lost all their teeth in that dental arch mostly as a consequence of severe periodontitis do not suffer from relevant MBL after 5 years in function. Particularly, those implants with transmucosal abutments longer than 2 mm show, in average, less than 0.5 mm from the implant shoulder to the marginal bone.

AUTHOR CONTRIBUTIONS

Pablo Galindo-Moreno: Conceptualization (lead); investigation (equal); writing – original draft (lead). **Andrea Ravidà:** Data curation (equal); formal analysis (equal); validation (equal); writing – review and editing (equal). **Andrés Catena:** Data curation (equal); formal analysis (lead); validation (equal); visualization (equal); writing – review and editing (equal). **Francisco O'Valle:** Formal analysis (equal); writing – review and editing (equal). **Miguel Padial-Molina:** Data curation (equal); investigation (equal); writing – original draft (equal). **Hom-Lay Wang:** Conceptualization (equal); writing – review and editing (equal).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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COMITE DE ETICA EN INVESTIGACION DE LA UNIVERSIDAD DE GRANADA

La Comisión de Ética en Investigación de la Universidad de Granada, visto el informe preceptivo emitido por la Presidenta del Comité en Investigación Humana, tras la valoración colegiada del Comité en sesión plenaria, en el que se hace constar que la investigación propuesta respeta los principios establecidos en la legislación internacional y nacional en el ámbito de la biomedicina, la bioteconología y la bioética, así como los derechos derivados de la protección de datos de carácter personal,
Emite un Informe Favorable en relación a la investigación titulada: 'ESTUDIO RETROSPECTIVO DE PéRDIDA óSEA MARGINAL A LARGO PLAZO ALREDEDOR DE IMPLANTES DENTALES' que dirige D./Dña. PABLO GALINDO MORENO, con NIF 26.211.833-K, quedando registrada con el nº: 487/CEIH/2018.

Granada, a 15 de Febrero de 2018.

EL PRESIDENTE
Fdo: Enrique Herrera Viedma

EL SECRETARIO
Fdo: Fernando Cornet Sánchez del Águila

APPENDIX #4: STUDY #4 PUBLICATION[97]

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REVIEW

WILEY

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

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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 noncontrolled 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 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system guide.

Results: Nine studies were included in the qualitative analysis and four 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 <2 mm or ≥ 2 mm) 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.

KEYWORDS
alveolar bone loss, dental implants, gingival recession, meta-analysis, oral mucosa

What is known

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

- 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 <2 mm or ≥2 mm) 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.

1 | INTRODUCTION

Peri-implant phenotype comprises 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 ≥2 mm since this is the amount that requires to prevent soft-tissue recession, bone resorption and to facilitate adequate oral hygiene measures.[3–7] It was hence advocated to develop adequate KMW at planned implant sites.[8] 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).[9] On the other hand, some studies have demonstrated that implants with lining mucosa can also possess high long-term success[3,10] and have no association between peri-implant mucosal inflammation and the lack of a certain amount of KMW.[4,5]

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 shown the association between "inadequate" KMW and higher plaque index in well-maintained populations.[6] The same was also found for gingival inflammation as measured via gingival index and soft-tissue recession. In the sixth EAO Conference Consensus Report suggested that mucosal recession, gingival index, and plaque control are improved when KMW is increased via soft-tissue augmentation procedures.[7] 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 whether a minimum amount of KMW is required for peri-implant health and stability; for such reasons, the aim of this 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

This 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 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), and 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 nonrandomized controlled or noncontrolled 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 <2 mm versus ≥2 mm (to enable data pooling).

The exclusion criteria of the study were as follows: (i) case reports, case series, retrospective cohort, and cross-sectional clinical studies; and (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. Table S1 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 the 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*, and *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 were 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 (AR and VCAC). 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 (GT) 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, and 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 (VCAC and CA) 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 was 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 Data S1. 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 (MDs) 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 value of p < 0.05 as the threshold of statistical significance.

3 | RESULTS

3.1 | Study selection

Following duplicate removal, a total of 1264 records remained for screening by title and abstract. Results of the number of records obtained for each database are reported in Table S1. A total of 26 articles were then considered for full-text screening. Finally, nine studies fulfilled the eligibility criteria and were selected for data extraction.[4,20,21,25–30] The reasons due to 17 articles were excluded, as summarized in Figure 1 and Table S2. 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 in Figure 1.

3.2 | Characteristics of the included studies

3.2.1 | Study design

Five of the studies were prospective cohort studies,[4,21,25,28,29] three were non-RCTs,[26,27,30] and one was an RCT.[20] Seven studies were carried out solely in academic settings,[20,21,26–30] while the remaining two were conducted in both academic and private practice

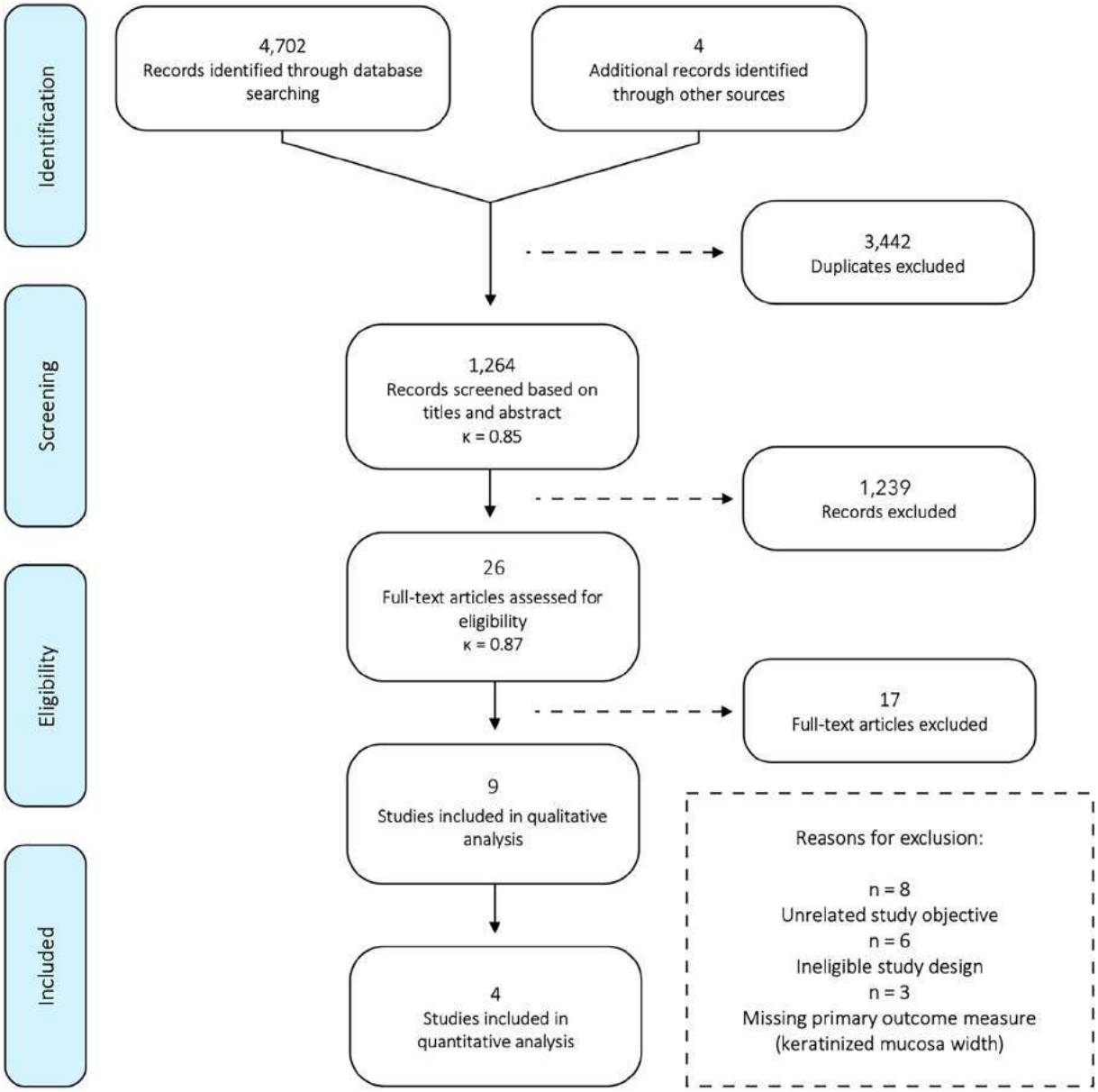

FIGURE 1 PRISMA flowchart of the selection process

TABLE 1 Characteristics and qualitative data of the included studies

	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 of 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
Number of implants 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

Abbreviations: KMW, keratinized mucosa width; NR, not reported.

settings.[4,25] All but one of the studies[4] 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[4,20,26,29] and four 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] four included completely edentulous arches exclusively,[4,20,26,29] and one 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] one study reported a 2-year follow-up period,[25] two studies reported a 4-year follow-up,[27,30] one study reported a 4.5-year follow-up period,[28] and four studies reported a 5-year follow-up period.[4,20,21,29]

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 Tables S3 and S4. When considering the nonrandomized included studies, three studies reported low risk of bias[20,26,27]; however, 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,[4,29] 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 2). 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 2).

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 are shown in Table 3. Overall, 685 implants were analyzed (178 in the KMW < 2 mm group and 507 in the KMW ≥ 2 mm group).

3.4.1 | Meta-analysis and TSA for the outcome MBL

Two studies[20,30] including a total of 257 implants (103 with KMW < 2 mm and 154 with KMW ≥ 2 mm) were entered in meta-analysis for MBL. The pooled MD and 95% CI showed a lower MBL rate when a higher KMW (≥2 mm) 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 in 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) was lower than the calculated RIS of 424 implants.

3.4.2 | Meta-analysis and TSA for the outcome PD reduction

Three studies[27,29,30] including a total of 430 implants (265 with KMW ≥ 2 mm and 165 with KMW < 2 mm) 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 (≥2 mm) 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 significant results is also graphically shown in Figure 2D since the final value of z-curve (blue line) did not 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.

TABLE 2 Summary of findings table with the GRADE approach quality of the evidence assessment

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 (I^2; %)	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 (≥2 mm)	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 (≥2 mm)	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 (≥2 mm)	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 (≥2 mm)	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.[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.
Implant survival rate[c]	See comment	NA	NA	NA	NA	-
Clinical attachment level[c]	See comment	NA	NA	64 (1)	⨁◯◯◯ Very low	One study[29] 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), ($p = 0.319$).

Note: 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.

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.

[a]The GRADE level was changed as follows: Certainty in the evidence downgraded by one level due to serious inconsistency; certainty in the evidence downgraded by two levels due to very serious inconsistency; and certainty in the evidence downgraded by one 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.

TABLE 3 Quantitative data of the included studies

Author (year/country)	Results						
	Baseline variables		Multiple regression with ΔREC: baseline 2 years as the dependent variable				
			Estimate		Sign		
Bengazi, (1996, Italy and Sweden)	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		
			BL	*p* value	1 year	*p* value	
Boynuegri (2013, Turkey)	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)		
	Width of keratinized mucosa at baseline (buccal sites)						
Crespi (2010, Italy)			<2 mm		≥2 mm	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	ns	
	Bone level		1.0 mm		0.9 mm	ns	
	Drecession		1.3 mm		0.2 mm	$p < 0.01$	
	Width of keratinized mucosa at baseline						
			<2 mm		≥2 mm		
de Siqueira, (2020, Brazil)	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 and 60 months evaluation evaluations						
			Vertical mucosa thickness >2 mm		Vertical mucosa thickness <2 mm		
	Implant surface	Time	Mean + SD	Median (Min; Max)	Mean + SD	Median (Min; Max)	*p* value
	Buccal and lingual	T4	0.29 + 0.28	0.30 (−0.25; 0.75)	0.50 + 0.41	0.50 (−0.17; 1.25)	0.445
		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)	

		PD				BoP			
		Worsening	Improvement	RR (CI 95%)	*p*	Worsening	Improvement	RR (CI 95%)	*p*
Fernandes-Costa, (2019, Brazil)	<2 mm	18 (50.0)	18 (50.0)	0.94 (0.61–1.44)	0.934	16 (44.4)	20 (55.6)	0.80 (0.51–1.25)	0.435
	>2 mm	23 (53.5)	20 (46.5)			24 (55.8)	19 (44.2)		

TABLE 3 (Continued)

		Width of keratinized mucosa					
		Buccal sites			Lingual sites		
	Year 5	<2 mm	≥2 mm	Sign.	<2 mm	>2 mm	Sign.
Mericske-Stern, (1994, Switzerland)	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	$p < 0.05$

	Width of keratinized mucosa						
		BI			4 years		
		≥2 mm	<2 mm	*p* value	≥2 mm	<2 mm	*p* value
Perussolo (2018, Brazil)	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

	Year 5	Width of keratinized mucosa at baseline					
		Buccal sites			Lingual sites		
		<2 mm	≥2 mm	Sign.	<2 mm	≥2 mm	Sign.
Schrott (2009, USA)	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	-	-	-

Abbreviations: BoP, bleeding on probing; CAL, clinical attachment level; NS, nonspecified; PD, Pocked depth; PI, Plaque index.

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 ≥ 2 mm and 167 with KMW < 2 mm) 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 (≥2 mm) 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 significant results is also graphically shown in 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 mPI

Three studies[27,29,30] including a total of 430 implants (265 with KMW ≥ 2 mm and 165 with KMW < 2 mm) 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 (≥2 mm) 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 in Figure 3D since the final value of *z*-curve (blue line) crosses

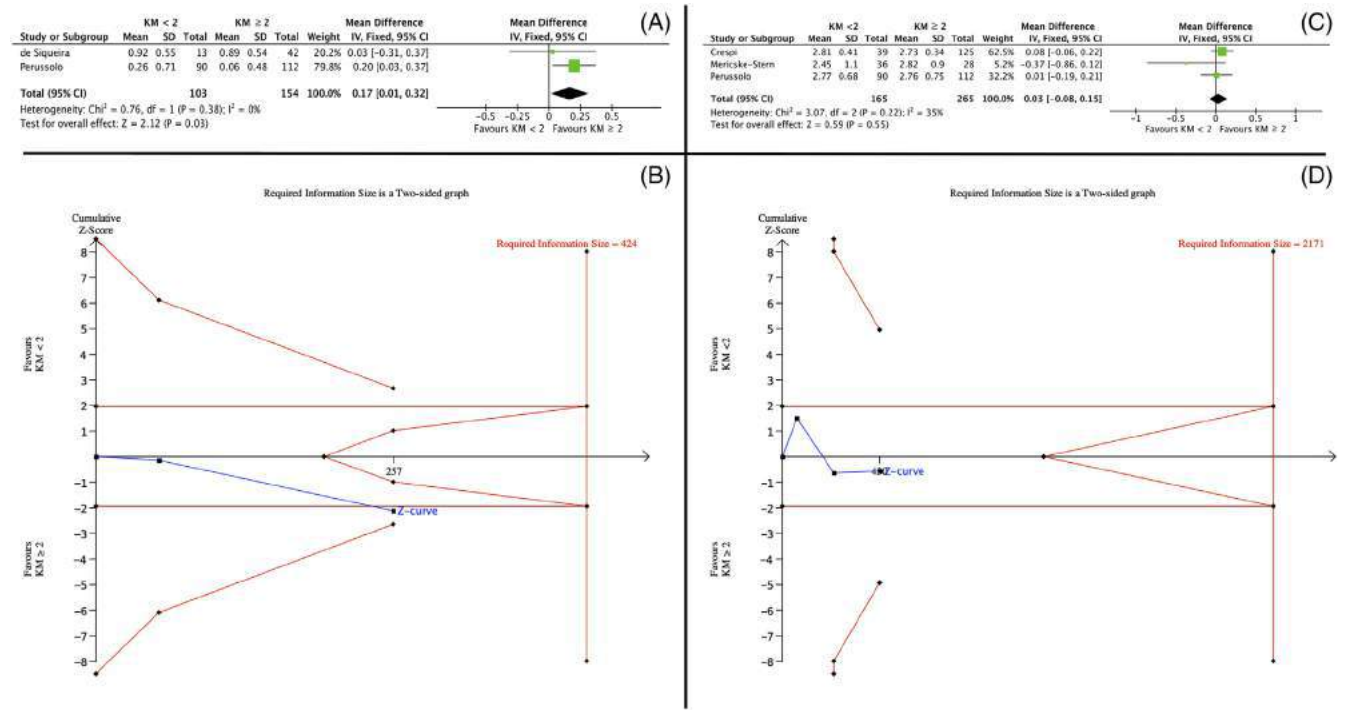

FIGURE 2 Meta-analysis (A) and trial sequential analysis (B) of marginal bone loss; meta-analysis (C) and trial Sequential Analysis (D) of probing depth change

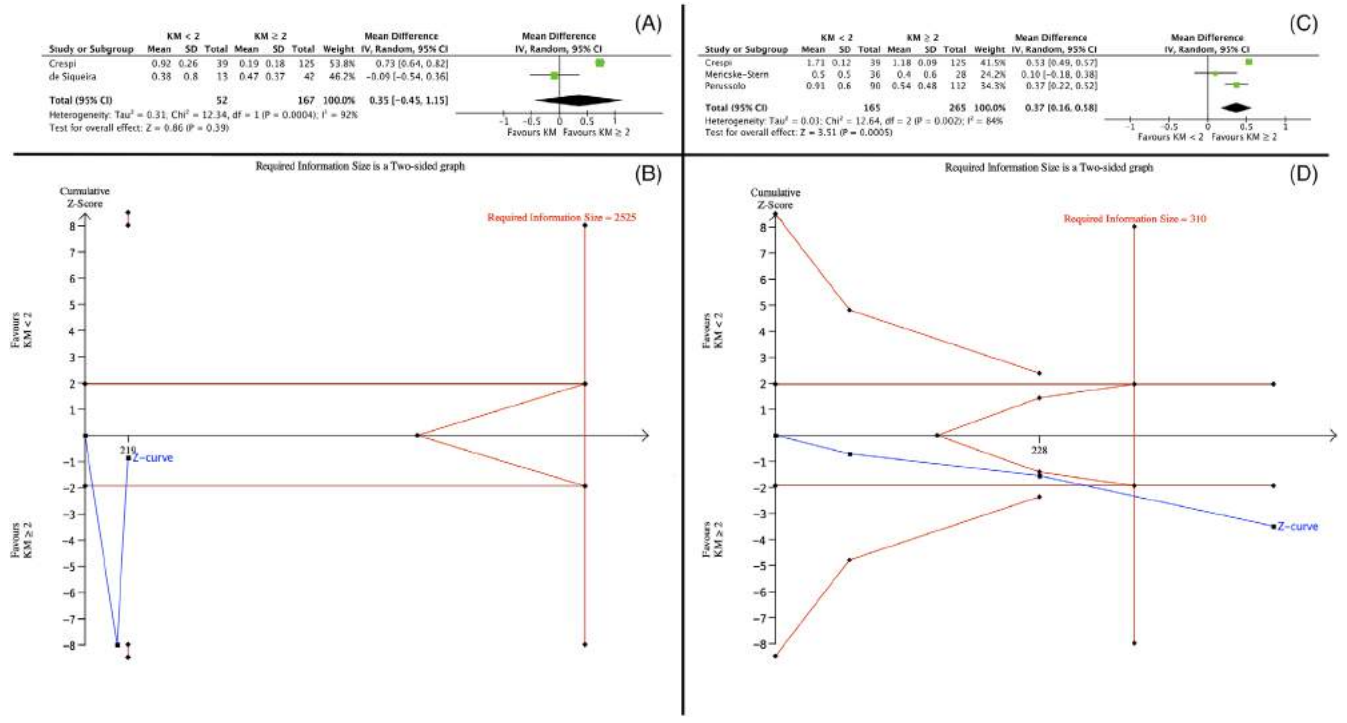

FIGURE 3 Meta-analysis (A) and trial sequential analysis (B) of soft-tissue recession; meta-analysis (C) and trial sequential analysis (D) of mean plaque index

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) overcomes 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 was not performed.

3.4.6 | Brushing discomfort assessment

One study assessed the brushing discomfort in both clinical scenarios.[30] Visual analogue scale (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, 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 shown to be related to increased mPI and more discomfort after brushing.

4.2 | Level of evidence for KMW as a risk factor

This study conducted the analysis using the GRADE assessment to observe the strength of recommendation for the results of this 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, and so o, 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 gray literature to be performed to avoid an under or an overestimation of the beneficial or harmful effect due to the selective publication of studies.[31] Since that was performed in this 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 <2 mm 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 <2 mm, the 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.[32] 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.[9] However, the reported difference cannot be considered clinically significant (a 0.11–0.18 mm difference between test and control) and based on the pooled data of two to four studies. The one soft-tissue parameter that seems to play a more significant role in minimizing MBL is the peri-implant STH.[1] This was first demonstrated in an experimental canine model.[33] Later on, studies have demonstrated that this tissue dimension plays an important role in reducing MBL.[34,35]

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

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.[36] Clinically, the progression of the peri-implant condition from peri-implant mucositis to peri-implantitis was most associated with increased PD and BOP

values.[37] One study has shown that 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.[38] 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),[39] such findings are to be interpreted with caution. This is due to the authors reporting a 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 nonsignificant PD reduction (0.56 mm) is reported when both APF alone and APF plus a graft are grouped into the analysis. 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.[9]

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

This review included two 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. comparing implants with keratinized mucosa versus those with alveolar mucosa reported that REC was significantly more likely at implants with a lack of KMW.[40] Also, the third 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 6–12 months of the 2–5 years follow-up, supporting the tissue remodeling concept. This may refute the perception that KMW influences REC of peri-implant tissues.

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

The longitudinal studies included in this review showed a 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.[41] This study also observed that implant sites with KMW < 2 mm had significantly higher mPI scores than sites with KMW ≥ 2 mm.[41] 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.

4.3.5 | 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. 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 multifaceted 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 this 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 four 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 to (2) determine a less arbitrary and more precise, well-evidenced KMW cut-off value.

Another weakness of this 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. This 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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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Andrea Ravidà and Hom-Lay Wang conceived the concept/design. Andrea Ravidà and Claudia Arena participated in the data collection. Andrea Ravidà and Vito Carlo Alberto Caponio involved in the data analysis/interpretation. Giuseppe Troiano conducted the statistics. Mustafa Tattan and Andrea Ravidà drafting the article. Muhammad H. A. Saleh and Hom-Lay Wang critical revision of article. All authors approved of article.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Database	Search strategy	Number of records
PubMed/Medline	("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")	661
Scopus	("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")	2922
Web of Science	("dental implant" OR "dental implantation" OR "oral implant" OR "implant" OR "dental implants") (All Fields) AND ("gingival height" OR "tissue thickness" OR "tissue biotype" OR "tissue phenotype" OR "tissue width" OR "keratinized mucosa") (All Fields)	782

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.

(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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Supplementary Table 3 : Newcastle-Ottawa scale to evaluate risk of bias of prospective cohort study

Author/year	Country	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability cases/controls	Ascertainment of exposure	Same method of ascertainment
Mericske-stern/1994	Switzerland	A	A	A	A	A	A	A
Bengazi/1996	Sweden	I	A	I	I	I	A	A
Schrott/2009	USA	A	A	A	A	A	A	A
Fernandes-Costa/2019	Brazil	I	A	I	I	I	A	A

A: adequate
I: inadequate

Table S4: Risk of bias of included non RCTs.

	Confounding	Selection of participants	Classification of interventions	Deviation from intended interventions	Missing Data	Measurement of outcomes	Selection of the reported result	Overall risk of bias
Crespi et al. 2010	Low	Low	Low	Low	Low	Low	Low	Low
Boynueğri et al. 2013	Low	Low	Low	Low	Low	Low	Low	Low
Perussolo et al. 2018	Low	Low	Moderate	Low	Moderate	High	Low	High
de Siqueira et al. 2016	Low	Low	Low	Low	Low	Low	Low	Low
Lim et al. 2018	Low	Low	Low	Low	Moderate	Low	Low	Moderate

Appendix: Information related to methodology - Risk of bias assessment ad Data synthesis and summary of findings

Risk of bias assessment

The included RCT was assessed using the revised Cochrane Collaboration's tool for assessing risk of bias in randomized trials (RoB 2) (Sterne et al., 2019). The following domains were assessed:

- Risk of bias arising from the randomization process.
- Risk of bias due to deviations from the intended interventions (effect of assignment to intervention).
- Risk of bias due to deviations from the intended interventions (effect of adhering to intervention).
- Missing outcome data.
- Risk of bias in measurement of the outcome.

Based on the overall risk of bias, the included RCT was categorized into low risk of bias, high risk of bias, or expressing some concerns, according to the following tailored criteria:

- *High risk of bias* if high risk of bias was ide ntified in at least one domain.
- *Some concerns* if the study presents some concerns in at least one domain, but not to be at high risk of bias for any domain.
- *Low risk of bias* if low risk of bias was identified for all domains.

The non-randomized controlled trials (non-RCT) were assessed using the ROBINS-I tool (Sterne et al., 2016). The following domains were assessed:

1. Pre-intervention
    a. Bias due to confounding.
    b. Bias in selection of participants into the study.
2. At intervention
    a. Bias in classification of interventions.
3. Post-intervention
    a. Bias due to deviations from intended interventions.
    b. Bias due to missing data.
    c. Bias in measurement of outcomes.

d. Bias in selection of the reported result.

Based on the overall risk of bias, each non-RCT was categorized as being low, moderate, serious or critical risk, or no information according to the following criteria:

- *Low risk of bias* if low risk of bias was identified for all domains.
- *Moderate risk of bias* if low and moderate risk of bias was identified for all domains.
- *Serious risk of bias* if serious risk of bias was identified in ≥1 domain, but no critical risk of bias was identified in any domain.
- *Critical risk of bias* if critical risk of bias was identified in ≥1 domain.
- *No information* if no clear indication that the study is at serious or critical risk of bias, and there is a lack of information in one or more key domains of bias.

The prospective cohort study were assessed using Newcastle-Ottawa scale (Wells, 2014). The following domains were assessed:

- Adequacy of case definition.
- Representativeness of the cases.
- Selection of controls.
- Definition of controls.
- Comparability cases/controls.
- Ascertainment of exposure.
- Same method of ascertainment.

Based on the overall risk of bias, each study was categorized as being low, moderate or serious risk of bias, according to the following criteria:

- *Low risk of bias* if all the domains were considered adequate.
- *Moderate risk of bias* if one of the domains was considered inadequate.
- *Serious risk of bias* if two or more domains were considered inadequate.

Data synthesis and summary of findings

Following article selection, the level of agreement between the reviewers regarding study selection was calculated using Cohen's kappa coefficient (κ). For 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. Trial sequential analysis (TSA) was performed with the goal of identifying the power of the meta-analytic findings and to adjust results for the presence of type I and II errors. The required information size (RIS), alpha-spending function, trial sequential monitoring boundaries for benefits and harms and futility boundaries were calculated. Meta-analytic data from Reviewer Manager were directly converted and entered into the trial sequential analysis software (version 0.9 beta, www.ctu.dk/tsa). The type I risk error was set at 0.05 with a power of 80% (type II error 20%). Heterogeneity correction was applied according to the results of the previously performed meta-analysis. The crosses between the cumulative *Z*-curve, the trial sequential monitoring boundary, the futility boundary and the RIS threshold were graphically evaluated and assessed.

The certainty in the evidence (the quality of the evidence) was evaluated via the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for each comparison between the study groups at the outcome level (Guyatt et al., 2008). The evaluation was performed utilizing the GRADEpro platform (McMaster University, Hamilton, Canada) for diagnostic studies. Generally, the certainty in the evidence can be ranked as: high, moderate, low, or very low. When the certainty in the evidence is assessed from direct comparisons; and randomized controlled trials start as high-certainty evidence. Observational studies start as low-certainty evidence. A single-arm study is an observational study since lack of randomization compromises all comparative statistical inference. Serious or very serious issues of risk of bias, inconsistency, indirectness, imprecision, and publication bias reduce the certainty (Guyatt et al. 2008). Some factors (mostly relevant to observational studies) may increase the level of certainty, including the magnitude of treatment effect and the presence of a dose-response effect.
The topics evaluated were risk of bias, indirectness, inconsistency, imprecision, and publication bias, following the statements of the instructions for completing the GRADE pro system (Gopalakrishna et al., 2014; Zhang, Akl, & Schunemann, 2018). Risk of bias was assessed by making an overall judgment based on the risk of bias (elaborated earlier in this manuscript) for each study providing direct evidence for the comparison of interest. The indirectness of evidence was assessed through the search for four different sources of indirectness: differences regarding the population of interest and those who have participated

in the studies, differences in intervention assessed and the intervention of interest, differences in desired outcomes and outcomes measured, and presence of indirect comparison (Guyatt et al., 2011).The inconsistency was assessed by calculating the Higgins Index (I^2) statistic and by visual assessment of forest plots when available. The imprecision was assessed using sample size and the confidence interval of the direct estimates.

APPENDIX #5: ADDITIONAL SUPPORT FOR CANDIDATE ANDREA RAVIDÀ'S ELIGIBILITY FOR EARNING THE PHD DESIGNATION

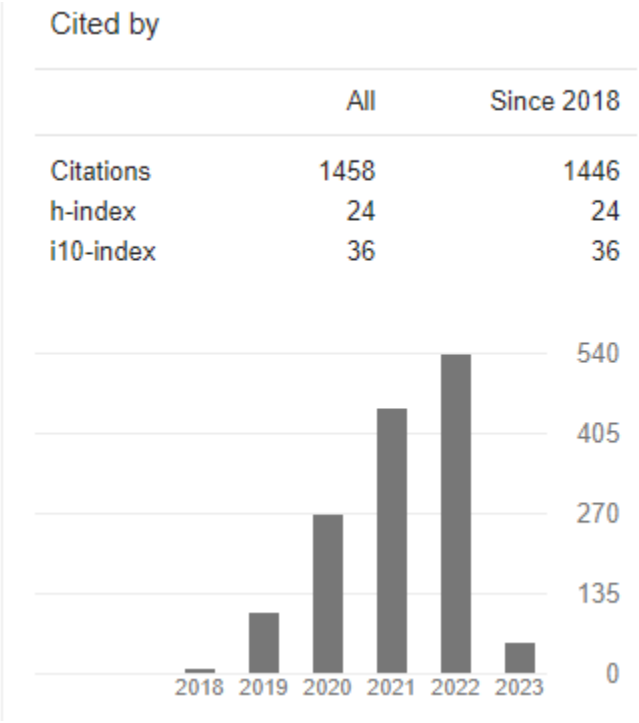
PubMed:

As of February 1, 2023, Andrea Ravidà has co-authored a total of **70** citations indexed in MEDLINE/PubMed, including **22** as first author

Google Scholar:

Andrea Ravidà has been cited **1,458** times as of February 1, 2023.

https://scholar.google.com/citations?view_op=search_authors&mauthors=Andrea+Ravid%C3%A0&hl=en&inst=9017564595980421810&oi=ao



https://scholar.google.com/citations?hl=en&user=ehX6ddcAAAAJ

Times cited as per Google Scholar, PubMed, and the publishing journal: the 4 papers as of January 10, 2023.

SEARCH DATE 2023.01.05	STUDY #1 THREAD	STUDY #2 HX	STUDY #3 MBL	STUDY #4 KERATIN	TOTAL
	Published online 2022.12.28	NOV 2021	DEC 2022	JUN 2022	
Google Scholar	0	9	0	1	10
PubMed	0	4	0	0	4
Publishing journal	0	2	0	0	2

Journal articles co-authored by PhD Candidate Andrea Ravidà that are published and indexed in MEDLINE/PubMed as of February 2, 2023. The citations are listed in reverse chronologic order.

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4. Siu TL, Dukka H, Saleh MHA, Tattan M, Dib Z, **Ravidà A**, Greenwell H, Wang HL, Araujo MG. Flap versus flapless alveolar ridge preservation: a clinical and histological single-blinded, randomized controlled trial. J Periodontol 2022. doi: 10.1002/jper.22-0213. PMID: 35924603.
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Additionally, the following paper that was co-authored by PhD Candidate Andrea Ravidà as the corresponding author was accepted for publication:

a. Saleh MHA, Urban IA, Alrmali A, **Ravidà A**. Papilla reconstruction using a vertical interproximal tunnel approach (VITA). Int J Oral Implantol 2023. doi: n/a. PMID: n/a.