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## ORIGINAL ARTICLE OPEN ACCESS

# Soft-Tissue Phenotype as a Risk Indicator of Peri-Implantitis and Peri-Implant Soft-Tissue Dehiscence—A Cross-Sectional Study

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**Keywords:** cytokines | dental implants | keratinized mucosa | multiplex immunoassay | peri-implant diseases

## ABSTRACT

**Aim:** To investigate the association, as well as to characterize the associated panel of pro- and anti-inflammatory markers, between the different components of the peri-implant phenotype and the presence of peri-implantitis/peri-implant soft-tissue dehiscence (PISTD).

**Materials and Methods:** A total of 324 implants in 112 patients were included. The following components of the peri-implant phenotype were clinically measured through the use of a manual periodontal probe or a digital calliper: keratinized mucosa width (PIKM-W), mucosal thickness (MT), attached mucosa (AM) and vestibulum depth (VD). The presence of peri-implantitis and PISTD was assessed through clinical and radiographic examination. Mixed-models logistic regression analyses were performed to analyse the association between peri-implant phenotype and the presence of peri-implantitis or PISTD, adjusting for relevant confounders. Multiplex immunoassays were employed to evaluate the peri-implant crevicular fluid levels of a panel of pro- and anti-inflammatory markers.

**Results:** Peri-implant health, peri-implant mucositis and peri-implantitis were diagnosed in 36.6%, 21.4% and 42% of the patients (classified according to their worst implant) and 35.2%, 34.3%, and 30.5% of the implants, respectively. In the multi-level multiple regression model, the absence of PIKM-W (odds ratio [OR]=9.24; 95% CI: 2.73–31.28), the absence of attached mucosa (OR=19.58; 95% CI: 6.12–62.56) and a reduced (<4mm) vestibulum depth (OR=2.61; 95% CI: 1.05–6.48) were associated with peri-implantitis. Similarly, the absence of PIKM-W (OR=6.32; 95% CI: 1.67–23.83), a thin (<2mm) mucosa (OR=157.75; 95% CI: 14.06–1769.9) and a reduced vestibulum depth (OR=3.32; 95% CI: 1.02–10.84) were associated with the presence of PISTD. Implants with PIKM-W=0 mm showed statistically significantly higher levels of interferon- $\gamma$  in both regular ( $\geq 2$  maintenance/year) and irregular (<2 maintenance/year) compliers ( $p=0.046$  and  $p=0.012$ ). In irregular compliers, the absence of PIKM-W was also associated with statistically significantly higher levels of interleukin (IL)-1 $\beta$  and IL-21 ( $p=0.016$ ,  $p=0.046$ ). These associations were independent of the effect of relevant confounders (e.g., plaque, compliance with maintenance, etc.).

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**Conclusions:** Within their limits, the present findings indicate that (a) peri-implant soft-tissue phenotype appears to be associated with the presence of peri-implantitis and PISTD, and (b) in the absence of PIKM-W, the inflammatory response seems to be dys-regulated and the soft-tissue remodelling up-regulated.

## 1 | Introduction

Given its high prevalence (Derks and Tomasi 2015; Derks et al. 2016; Romandini et al. 2019, 2021a) and limited efficacy of treatment procedures (Rocuzzo et al. 2020; Baima et al. 2022; Romandini et al. 2022, 2024; Derks et al. 2022; Regidor et al. 2023), early diagnosis and primary prevention are critical in the management of peri-implantitis. Primary prevention of peri-implantitis focuses on treating peri-implant mucositis as its precursor (Costa et al. 2012; Verket et al. 2023) and tackling modifiable risk factors (Darby 2022; Carra et al. 2023; Berglundh et al. 2024; Bencze et al. 2024). Among the possible risk factors, the peri-implant phenotype has recently received much attention, although the scientific evidence is still controversial (Rocuzzo, Grasso, and Dalmaso 2016; Thoma et al. 2018; Monje and Blasi 2019; Lim et al. 2019; Tavelli et al. 2021; Romandini et al. 2021a; Gharpure et al. 2021; Ramanauskaite, Schwarz, and Sader 2022; Ravidà et al. 2022).

A possible source of this controversy is that most of the available studies focused on the individual components of the peri-implant phenotype separately: the peri-implant keratinized mucosa (PIKM), the mucosa thickness and the attached mucosa. Moreover, relevant associated anatomical conditions (i.e., vestibulum depth) have been frequently disregarded (Rocuzzo, Grasso, and Dalmaso 2016; Monje and Blasi 2019). Additionally, most of the available studies are at risk of confounding bias, because the analyses were not adjusted for relevant confounders (e.g., plaque, maintenance, implant location, periodontal status) (Romanos, Grizas, and Nentwig 2015; Rocuzzo, Grasso, and Dalmaso 2016; Monje and Blasi 2019; Romandini et al. 2021a; Carvalho et al. 2023).

One of the possible mechanisms explaining this association is the existence of a pro-inflammatory environment consequent to a lack of soft-tissue seal that provides mechanical stability and protection of the underlying tissue in the absence of an adequate soft-tissue phenotype (Zigdon and Machtei 2008; Boynuegri, Nemli, and Kasko 2013). Furthermore, the disturbance of the cell layer of the peri-implant epithelium attributable to absence/inadequate PIKM may facilitate the infiltration of pathogenic bacteria into the connective tissue, possibly resulting in the initiation of peri-implant inflammatory responses (Mori et al. 2016). Specifically, the available data have pointed out that peri-implantitis lesions are characterized predominantly by neutrophils, macrophages and RANKL expressing CD4+ T and B cells together with high pro-inflammatory cytokines expression levels (Carcuac and Berglundh 2014; Heyman et al. 2022). Th1/Th2 cell balance, together with Th17 cells and the T-regulatory cells (Treg), was shown to have a pivotal role in immune response regulation for infected peri-implant tissues (Giro et al. 2021; Teixeira et al. 2017). Nevertheless, there is currently a lack of a thorough assessment of the pro- and anti-inflammatory markers expressed within different peri-implant phenotypes (Inizio modulo and Fine modulo).

Therefore, the primary aim of this study was to investigate the association between the different components of the peri-implant phenotype (PIKM-W, mucosal thickness, attached mucosa and vestibulum depth) with the presence of peri-implantitis and peri-implant soft-tissue dehiscence (PISTD), controlling for relevant confounding variables. Secondly, this study aimed at identifying the differential expression of a panel of pro- and anti-inflammatory markers in the peri-implant crevicular fluid (PICF) around implants with different soft-tissue phenotypic characteristics. The leading hypothesis of the present study was that peri-implant soft-tissue phenotype is a risk indicator for both peri-implantitis and PISTD.

## 2 | Materials and Methods

The present investigation was structured as a cross-sectional study and implemented in accordance with the Helsinki Declaration, as revised in 2013. The study protocol received approval from the Clinical Research Ethics Committee of Gazi University (Ankara, Turkey) (Protocol ID: E-21071282-050.99-129310). Every participant was provided with information regarding the objectives of the study and received a comprehensive explanation of the procedures involved. Prior to their participation, written informed consent was obtained. The reporting of this cross-sectional study follows the STROBE guidelines (von Elm et al. 2007).

### 2.1 | Participants

Participants were selected from patients participating in the supportive peri-implant care (SPIC) program of the Department of Periodontology at Gazi University (Ankara, Turkey) from July 2021 to April 2022. Patient-level exclusion criteria were as follows: smokers (current smokers or former smokers who quit less than 2 years before enrollment), uncontrolled medical conditions (e.g., diabetes mellitus with HbA1c  $\geq$  7.0%), pregnant or lactating females, history of periodontal or peri-implant therapy during the previous 6 months or systemic antibiotic use during the previous 3 months. Implant-level exclusion criteria were the following: less than 12 months prosthetic loading, removable implant-supported restoration (i.e., overdentures), implants positioned too buccally (subjective evaluation), history of soft-tissue augmentation, presence of an overhanging restoration preventing accurate probing or collection of PICF samples.

### 2.2 | Peri-Implant Soft-Tissue Phenotype (Exposure)

The following soft-tissue phenotype characteristics were recorded at the mid-buccal site of each study implant by an experienced and previously calibrated investigator (S.C.I.):

- PIKM-W, measured in mm with a manual UNC-15 probe as the apico-coronal distance from the mucosal margin to the muco-gingival junction after staining the alveolar mucosa with Lugol's iodine (2%) solution. PIKM-W was also categorized as adequate ( $\geq 2$  mm), inadequate ( $< 2$  and  $> 0$  mm) or absent (0 mm).
- Attached mucosa, determined by subtracting the probing pocket depth (PPD) from PIKM-W.
- Mucosal thickness, measured 1 mm below the mucosal margin (Schwarz, Claus, and Becker 2017), by inserting an endodontic reamer to the soft tissue, and measuring the distance between the tip of the reamer and the stopper through a digital calliper. Mucosal thickness was also categorized as thick ( $\geq 2$  mm) and thin ( $< 2$  mm) (Avila-Ortiz et al. 2020).
- Vestibulum depth, collected dichotomously as shallow ( $< 4$  mm) or deep ( $\geq 4$  mm) as the distance between the mucosal margin and the most pronounced site of concavity of the muco-buccal fold after retracting with a bilateral retractor (Monje and Blasi 2019).

### 2.3 | Peri-Implant Parameters, Diseases and Soft-Tissue Dehiscence (Outcomes)

The same calibrated examiner measured the following peri-implant parameters at six aspects of each implant, using a manual UNC-15 periodontal probe (PCP15; Hu-Friedy, Chicago, IL, USA):

- Modified plaque index (mPI) (Mombelli et al. 1987);
- Modified sulcular bleeding index (mBI) (Mombelli et al. 1987);
- Bleeding and suppuration on probing (BoP/SoP), based on the presence/absence of bleeding or pus around implants 30 s after gentle probing. BoP extent was also expressed at the implant level as the percentage of sites with BoP (Verket et al. 2023);
- PPD.

Moreover, the presence of PISTD was measured (in mm) with a manual UNC-15 probe as the exposure either of the prosthetic abutment or the implant neck or the implant surface (Sanz-Martín et al. 2020; Romandini, Pedrinaci et al. 2021). PISTD status was further categorized as present (PISTD  $> 0$  mm) or absent (PISTD = 0 mm).

Peri-apical digital radiographs of the included implants were obtained. Two calibrated investigators (S.C.I. and B.U.) measured the marginal bone level from the implant shoulder to the first bone-implant contact using a software program (ImageJ, National Institutes of Health, Bethesda, MD, USA). The mean value between the mesial and the distal measurement was considered as the implant bone level. The inter-examiner agreement calculation was performed by measuring twice 20 randomly selected radiographic images (ICC = 0.91; 95% CI: 0.89–0.95;  $p < 0.001$ ).

Given the absence in most cases of baseline documentation, peri-implantitis was defined at the implant level as the presence BoP and/or SoP, and radiographic bone loss  $\geq 3$  mm (Berglundh et al. 2018). If a baseline radiograph (at time of prosthetic loading) was available for an implant fulfilling the criteria to be regarded as peri-implantitis, the presence of true bone loss was confirmed through direct evidence. Peri-implant health was defined as the absence of SoP and, at most, one site with BoP. All the remaining cases were considered as peri-implant mucositis.

### 2.4 | Descriptive and/or Confounding Variables

Demographic, medical/dental and clinical history were considered for descriptive purposes and/or as possible confounders. History data collection was based on patient files assessment and, thereafter, verified by interviewing the participants. The considered patient-level variables included age (years), gender (male, or female), presence of systemic diseases, number of implants and frequency of SPIC recalls. Specifically, patients were categorized as regular ( $\geq 2$  SPIC/year) and irregular ( $< 2$  SPIC/year) compliers (Romanos, Grizas, and Nentwig 2015). At the implant level, function time (years), implant position (anterior-canine to canine, or posterior), jaw (maxilla, mandible), type of prosthesis (single crown, partial or full-arch fixed dental prostheses) and implant-abutment connection (platform switching, internal, external connection) were considered.

Clinical examination performed by the same experienced investigator (S.C.I.) included the assessment of periodontal status according to both the CDC/AAP (i.e., no periodontitis/mild periodontitis, moderate/severe periodontitis, edentulous) (Eke et al. 2012) and the 2017 World Workshop classification criteria (i.e., periodontal health, gingivitis, stage I–II periodontitis, stage III–IV periodontitis, edentulous) (Caton et al. 2018), and the assessment of the full-mouth plaque and bleeding scores (FMPS/FMBS).

### 2.5 | PICF Sampling

PICF sampling was performed on two sites from each implant, using the filter paper technique. In patients with multiple implants, the implant with the deepest PPD was targeted and the sampling was performed on a different day to avoid any influence from previous probing. However, when patients could not come on a separate day for sampling, the implant with the highest bone level was sampled before any probing. Before sampling, the supra-marginal plaque was removed, and the implant was isolated with cotton rolls and gently air-dried. Afterwards, a paper strip of standard length and height (Periopaper, Pro Flow, Amityville, NY, USA) was inserted into the peri-implant sulcus/pocket until feeling mild resistance and left in place for 30 s (Wassall and Preshaw 2016). In case of visible blood/saliva/suppuration contamination, the sample was discharged, and another sample was taken from a different site. Sampled fluid volume was measured with a calibrated Periotron 8000 instrument (Oraflow Inc.). Samples were placed in Eppendorf tubes® (Eppendorf AG) containing 250 mL phosphate-buffered saline and stored in the laboratory at  $-80^{\circ}\text{C}$  until analysis.

## 2.6 | Laboratory Procedures (Measurement of Biomarkers)

Immediately before analysis, the samples were allowed to equilibrate at ambient temperature for 30 min. The following elution protocol was applied to remove bacterial biofilms and cellular elements: vortexing for 30 min, centrifugation at 300 rpm (8.7g) for 60 min at 4°C and followed by an additional 2 min of centrifugation at 12,000 rpm (13,800g) at 4°C. The supernatant of the samples was screened for the assessment of Th1 (interleukin [IL]-1 $\beta$ , IL-2, IL-12, interferon [IFN]- $\gamma$ , tumour necrosis factor- $\alpha$  [TNF- $\alpha$ ], macrophage inflammatory protein-1 $\alpha$  [MIP-1 $\alpha$ ]), Th2 (IL-4, IL-5, IL-6, IL-10, IL-13, granulocyte-macrophage colony-stimulating factor [GM-CSF]), Th17 (IL-17A, IL-21, IL-23) and Treg (IL-10, transforming growth factor- $\beta$  [TGF- $\beta$ ]) cytokines using the T-cell Magnetic Bead Panel by employing a customized Quantibody Array kit (Milliplex Human High Sensitivity T-cell Magnetic Bead Panel, 96-well plate assay, HSTCMAG28SPMX and Milliplex MAP TGF- $\beta$ 1 Single Plex Magnetic Bead Kit, Millipore, Merck, Germany). The immunoassay was conducted in accordance with the manufacturer's instructions. The Luminex MAGPIX instrument with xPONENT software (MAGPX17241722), a CCD-based instrument that combines essential components of xMAP capture and detection with the use of magnetic beads, was used. The MAGPIX Calibration kit (cat No. MPX-CAL-K25) was used to calibrate the instrument and assay. This approach demonstrated a lack of significant cross-reactivity between the antibodies targeting a specific analyte and any of the other analytes included in the panel. The assay sensitivity minimum detectable concentration (MinDC) was calculated using MILLIPLEX Analyst 5.1. to determine the detection limits for the assay mathematically. The levels of biomarkers were quantified in picograms per millilitre (pg/mL) using Belysa Analysis 1.1.0 Immunoassay Curve Fitting software (version: 4.2.1705.0, Merck KGaA, Darmstadt, Germany) on both Windows 10 and macOS (beta). The software used a standard curve specific to each biomarker for the calculations.

## 2.7 | Data Analysis

A priori sample size calculation was conducted considering a mean mBI of  $0.12 \pm 0.37$  in the adequate PIKM-W group and  $0.39 \pm 0.60$  in the inadequate/absent PIKM-W group, using as reference a previous study (Romanos, Grizas, and Nentwig 2015). A minimum of 106 implants was calculated to be necessary to achieve an 80% statistical power with  $\alpha = 0.05$ . Assuming a conservative value of one implant per patient, a minimum of 106 patients was targeted for inclusion. Missing data were handled through complete case analysis with covariate adjustment (Groenwold et al. 2012).

Mean  $\pm$  standard deviation (SD) and/or median (interquartile ranges, IQRs) were used as descriptors for quantitative variables, while number (percentage) was used for qualitative variables. When the assumptions of normal distribution were not met, the Mann-Whitney *U* test was employed to ascertain the presence of a disparity between two groups of the qualitative variable, whereas the Kruskal-Wallis *H* test, followed by post hoc group comparisons with a Bonferroni-adjusted Mann-Whitney *U* test, was performed in case of more than two categories. Multi-level

(mixed-models) simple and multiple logistic regression analyses were then performed to analyse the association between peri-implant phenotype characteristics and the presence of peri-implantitis or PISTD, taking into account the clustering of multiple implants within the same participants. Multiple logistic regression analyses for both outcomes were adjusted for the following variables: SPIC compliance, periodontal status (CDC/AAP), implant brand, mPI, type of prosthesis, location and jaw. The multiple logistic regression model targeting PISTD as the dependent variable was additionally adjusted for peri-implant health status (peri-implantitis vs. no peri-implantitis).

For the PICF biomarkers, median and IQRs expressed concentrations (pg/mL) per 30s. The total quantity levels of PICF were determined by calculating the estimated volume of one sample obtained from each subject and compared between the groups using the Kruskal-Wallis *H* test, as the data were commonly non-normally distributed. Determining the protein-protein interaction datasets interacting with each biomarker's degree of confidence, regression analyses were performed to predict the contribution of biomarkers to PIKM-W status. First, normalization was applied to the markers' concentration levels to the range [0; 1] for standardization. By defining PIKM-W status as the dependent variable, all biomarkers were included in the multiple logistic regression analysis. The biomarker with the highest  $\beta$  value was recognized as the most influential independent factor for PIKM-W categorization. Cytokine networks were built based on the most influential biomarker and associated with their interactions (Inizio modulo and Fine modulo).

## 3 | Results

After screening 161 patients with 456 implants, a total of 112 patients with 324 dental implants were included (Figure S1). Table 1 provides descriptive statistics of the study population and implants. Most of the included patients were women (73.2%), with no/mild periodontitis (58.9%) and with a mean age at examination of 54.7 years. Most of the implants were located in the mandible (53.1%), rehabilitated through bridges (69.8%), and had a mean loading time of 6.2 years. Regarding the peri-implant phenotype characterization, the majority of implants had an adequate PIKM-W (56.8%), an absence of attached mucosa (59.6%), a thin mucosal thickness (57.7%) and a deep vestibulum depth (55.2%). Ninety-nine implants had peri-implantitis (30.5%), while 111 implants had peri-implant mucositis (34.3%).

### 3.1 | Association Between Soft-Tissue Phenotype and Peri-Implant Parameters

Table 2 reports clinical and radiographic parameters at the implant level according to PIKM-W and mucosal thickness in regular and irregular compliers.

In regular compliers, there were no statistically significant differences among PIKM-W groups in mPI, mBI, BoP, PPD, PISTD and bone level values. Lower PPD values were observed within the adequate and inadequate PIKM-W groups when comparing thick and thin mucosal thicknesses ( $p = 0.031$  and  $p = 0.016$ , respectively). Only within the inadequate PIKM-W group, a lower

**TABLE 1** | General characteristics of the study population and implants.

Patient-level characteristics	N = 112
Age (years), mean (SD)	54.7 (11.3)
Gender, N (%)	
Male	30 (26.8)
Female	82 (73.2)
Diabetes status, N (%)	
No diabetes	101 (90.2)
Diabetes (HbA1c < 7.0%)	11 (9.8)
Periodontal status (WWP), N (%)	
Periodontal health	15 (13.4)
Gingivitis	34 (30.4)
Stage I–II periodontitis	32 (28.6)
Stage III–IV Periodontitis	18 (16.1)
Edentulous	13 (11.6)
Periodontal status (CDC/AAP), N (%)	
No/mild periodontitis	66 (58.9)
Moderate/severe periodontitis	33 (29.5)
Edentulous	13 (11.6)
Full-mouth plaque score (FMPS), mean (SD)	29.5 (17.3)
Full-mouth bleeding score (FMBS), mean (SD)	28.7 (17.2)
Peri-implant health status, N (%)	
Peri-implant health	41 (36.6)
Peri-implant mucositis	24 (21.4)
Peri-implantitis	47 (42.0)
Implant-level characteristics	N = 324
Jaw, N (%)	
Maxilla	152 (46.9)
Mandible	172 (53.1)
Position, N (%)	
Anterior (canine–canine)	76 (23.5)
Posterior	248 (76.5)
Type of prosthesis, N (%)	
Single crown	57 (17.5)
Bridge	226 (69.8)
Full-arch fixed restoration	41 (12.7)
Implant brand, N (%)	
S	47 (14.5)
N	75 (23.2)

(Continues)

**TABLE 1** | (Continued)

Implant-level characteristics	N = 324
A	80 (24.6)
Other	122 (37.7)
Implant–abutment connection, N (%)	
Internal	105 (32.4)
External	48 (14.8)
Platform switching	171 (52.8)
Loading time (years), mean (SD)	6.16 (3.5)
PIKM-W (mm), mean (SD)	2.23 (1.9)
Platform switching	171 (52.8)
PIKM-W, N (%)	
Absence (0 mm)	67 (20.7)
Inadequate (>0 mm; <2 mm)	73 (22.5)
Adequate (≥2 mm)	184 (56.8)
Attached mucosa (mm), mean (SD)	0.75 (1.3)
Attached mucosa, N (%)	
Absence (0 mm)	193 (59.6)
Presence (>0 mm)	131 (40.4)
Mucosal thickness (mm), mean (SD)	1.46 (0.7)
Mucosal thickness, N (%)	
Thin (<2 mm)	187 (57.7)
Thick (≥2 mm)	137 (42.3)
Vestibulum depth, N (%)	
Reduced (≤4 mm)	145 (44.8)
Deep (>4 mm)	179 (55.2)
Peri-implant health status, N (%)	
Peri-implant health	114 (35.2)
Peri-implant mucositis	111 (34.3)
Peri-implantitis	99 (30.5)

Note: Total number varies according to missing data for each variable. Implant brands: S, Straumann; N, Nobel Biocare; A, AstraTech.

Abbreviations: N, number; PIKM-W, peri-implant keratinized mucosa width; SD, standard deviation.

BoP extent was found in thick compared to thin mucosal thickness ( $p = 0.009$ ). Regardless the amount of PIKM-W, implants with thick mucosal thickness did not present any buccal PISTD. However, statistically significant higher PISTD values for thin mucosal thickness were observed only within implants with adequate PIKM-W ( $p = 0.005$ ).

In irregular compliers, all the clinical and radiographic parameters exhibited significant differences among the groups in favour of adequate PIKM-W ( $p < 0.05$ ). When comparing thick with thin mucosal thickness, statistically significant differences were observed only in PISTD values within implants with adequate PIKM-W ( $p = 0.001$ ) and with absence of

**TABLE 2** | Clinical and radiographic parameters according to keratinized mucosa width and mucosal thickness in regular and irregular compliers.

		mPI			mBI			BoP extent			PPD			PISTD (buccal)			Radiographic bone level		
		Mean (SD)	Med (min-max)	Thick vs. thin MT (p)	Mean (SD)	Med (min-max)	Thick vs. thin MT (p)	Mean (SD)	Med (min-max)	Thick vs. thin MT (p)	Mean (SD)	Med (min-max)	Thick vs. thin MT (p)	Mean (SD)	Med (min-max)	Thick vs. thin MT (p)	Mean (SD)	Med (min-max)	Thick vs. thin MT (p)
Adequate PIKM-W (>=2 mm)	Thick	0.07 (0.16)	0.0 (0.0-0.5)	0.411	0.03 (0.13)	0.0 (0.0-0.16)	0.689	23.80 (33.14)	0.0 (0.0-100.0)	0.094	2.78 (1.23)	2.16 (1.83-4.33)	0.005 <sup>a</sup>	0.0 (0.0)	0.0 (0.0-0.0)	0.005 <sup>a</sup>	0.57 (1.15)	0.0 (0.0-5.12)	0.884
	MT	0.16 (0.35)	0.0 (0.0-1.0)		0.10 (0.29)	0.0 (0.0-0.66)		37.02 (32.04)	16.6 (0.0-100.0)		3.12 (1.82)	2.66 (1.0-7.66)		0.40 (0.73)	0.0 (0.0-2.0)		0.81 (1.67)	0.0 (0.0-7.92)	
	Total	0.14 (0.27)	0.0 (0.0-1.0)		0.07 (0.24)	0.0 (0.0-0.66)		29.76 (30.83)	16.6 (0.0-100.0)		2.83 (1.24)	2.50 (1.0-7.66)		0.30 (0.65)	0.0 (0.0-2.0)		0.63 (1.55)	0.0 (0.0-7.92)	
Inadequate PIKM-W (>0 mm; <2 mm)	Thick	0.20 (0.44)	0.0 (0.0-1.0)	0.942	0.0 (0.0)	0.0 (0.0-0.0)	0.173	23.77 (28.47)	0.0 (16.6-83.33)	0.009 <sup>a</sup>	2.72 (0.88)	2.66 (3.0-4.5)	0.016 <sup>a</sup>	0.0 (0.0)	0.0 (0.0-0.0)	0.542	0.62 (1.47)	0.0 (0.0-3.46)	0.104
	MT	0.14 (0.24)	0.0 (0.0-0.66)		0.80 (1.30)	0.0 (0.0-3.0)		53.32 (21.72)	33.3 (50.0-100.0)		3.46 (0.77)	2.33 (1.66-6.33)		0.39 (0.99)	0.0 (0.0-4.0)		1.76 (1.67)	0.0 (0.0-7.03)	
	Total	0.18 (0.33)	0.0 (0.0-1.0)		0.12 (0.54)	0.0 (0.0-3.0)		31.32 (34.46)	16.6 (0.0-100.0)		2.84 (0.89)	2.16 (1.66-6.33)		0.33 (0.92)	0.0 (0.0-4.0)		0.97 (1.85)	0.0 (0.0-7.03)	
Absence of PIKM-W (0 mm)	Thick	0.29 (0.39)	0.0 (0.0-1.0)	0.781	0.31 (0.61)	0.0 (0.0-2.0)	0.305	50.38 (38.19)	50.0 (0.0-100.0)	0.439	3.43 (1.79)	2.66 (1.83-7.83)	0.277	0.0 (0.0)	0.0 (0.0-0.0)	0.277	1.03 (1.78)	0.0 (0.0-4.51)	0.877
	MT	0.37 (0.55)	0.0 (0.0-1.0)		0.16 (0.40)	0.0 (0.0-1.0)		38.17 (34.95)	16.6 (0.0-100.0)		3.04 (1.65)	2.33 (1.66-8.33)		0.53 (0.92)	0.0 (0.0-5.0)		1.03 (1.50)	0.0 (0.0-7.78)	
	Total	0.30 (0.47)	0.0 (0.0-1.0)		0.18 (0.48)	0.0 (0.0-2.0)		40.32 (38.35)	16.6 (0.0-100.0)		3.08 (1.79)	2.33 (1.66-8.33)		0.48 (1.22)	0.0 (0.0-5.0)		1.04 (1.95)	0.0 (0.0-7.78)	
Adequate vs. inadequate vs. absence of PIKM-W (p)		0.972		0.448		0.959	0.818						0.660				0.521		
Irregular compliers (<2/year)	Thick	0.32 (0.41)	0.33 (0.0-2.0)	0.377	0.43 (0.69)	0.5 (0.0-3.0)	0.204	54.95 (39.97)	33.3 (0.0-100.0)	0.778	3.60 (2.04)	2.33 (1.0-10.0)	0.778	0.01 (0.13)	0.0 (0.0-4.0)	0.001 <sup>a</sup>	1.22 (2.12)	0.0 (0.0-8.98)	0.161
	MT	0.54 (0.64)	0.5 (0.0-2.0)		0.22 (0.46)	0.33 (0.0-2.0)		45.81 (40.36)	33.3 (0.0-100.0)		3.38 (1.83)	2.33 (1.0-10.0)		0.39 (0.84)	0.0 (0.0-2.5)		1.17 (2.36)	0.0 (0.0-9.0)	
	Total	0.44 (0.79)	0.5 (0.0-2.0)		0.33 (0.60)	0.33 (0.0-3.0)		50.28 (40.20)	33.3 (0.0-100.0)		3.46 (1.94)	2.33 (1.0-10.0)		0.18 (0.60)	0.0 (0.0-4.0)		1.11 (2.17)	0.0 (0.0-9.0)	

(Continues)

TABLE 2 | (Continued)

		mPI			BoP extent			PPD			PISTD (buccal)			Radiographic bone level					
		Mean (SD)	Med (min-max)	Thick vs. thin MT (p)	Mean (SD)	Med (min-max)	Thick vs. thin MT (p)	Mean (SD)	Med (min-max)	Thick vs. thin MT (p)	Mean (SD)	Med (min-max)	Thick vs. thin MT (p)	Mean (SD)	Med (min-max)	Thick vs. thin MT (p)			
Inadequate PIKM-W (>0mm; <2mm)	Thick	1.03 (1.38)	1.0 (0.0-3.0)	0.812	1.00 (0.93)	0.5 (0.0-2.0)	0.228	70.0 (44.72)	50.0 (0.0-100.0)	0.691	4.81 (1.95)	3.66 (2.16-8.0)	0.261	0.40 (0.89)	0.0 (0.0-2.0)	0.937	2.24 (2.28)	0.82 (0.0-9.52)	0.751
	MT	0.75 (0.88)	0.5 (0.0-3.0)		0.46 (0.46)	0.33 (0.0-2.0)		67.88 (32.49)	50.0 (0.0-100.0)		3.82 (1.57)	3.16 (1.88-7.16)		0.30 (0.66)	0.0 (0.0-1.5)		2.05 (2.87)	0.0 (0.0-7.80)	
Absence of PIKM-W (0mm)	Total	0.79 (0.94)	0.5 (0.0-3.0)	0.118	0.53 (0.55)	0.5 (0.0-2.0)	<b>0.035<sup>a</sup></b>	68.15 (33.55)	50.0 (0.0-100.0)	0.198	3.95 (1.62)	3.33 (1.88-8.0)	0.313	0.31 (0.64)	0.0 (0.0-2.0)	<b>0.001<sup>a</sup></b>	2.08 (2.78)	0.0 (0.0-9.52)	0.402
	Thick	0.81 (0.82)	0.5 (0.0-3.0)		0.60 (0.67)	0.5 (0.0-2.0)		78.95 (30.62)	83.3 (16.6-100.0)		4.53 (1.78)	3.83 (1.88-8.33)		0.0 (0.0)	0.0 (0.0-0.0)		2.40 (2.75)	1.21 (0.0-7.56)	
Adequate vs. inadequate vs. absence of PIKM-W (p)	Thin	0.52 (0.68)	0.5 (0.0-2.0)		0.21 (0.39)	0.33 (0.0-1.0)		78.57 (39.33)	83.3 (0.0-100.0)		4.33 (1.95)	3.50 (2.0-7.0)		1.33 (1.35)	0.0 (0.0-4.0)		2.92 (2.23)	2.30 (0.0-7.91)	
	MT	0.75 (0.79)	0.5 (0.0-3.0)		0.56 (0.65)	0.5 (0.0-2.0)		78.87 (30.71)	83.3 (0.0-100.0)		4.48 (1.67)	3.83 (1.88-8.33)		1.01 (1.21)	0.0 (0.0-4.0)		2.75 (2.23)	2.24 (0.0-7.91)	
			<b>0.032<sup>a</sup></b>			<b>0.011<sup>a</sup></b>			<b>&lt;0.001<sup>a</sup></b>		<b>&lt;0.001<sup>a</sup></b>			<b>&lt;0.001<sup>a</sup></b>		<b>&lt;0.001<sup>a</sup></b>			

Note: All the p-values in bold are statistically significant,  $p < 0.05$ .

Abbreviations: BoP, bleeding on probing; mBI, modified bleeding index; mPI, modified plaque index; MT, mucosal thickness; PIKM-W, keratinized mucosa width; PISTD, peri-implant soft tissue dehiscence; PPD, probing pocket depth.

<sup>a</sup>Significantly different between groups,  $p < 0.05$ .

PIKM-W groups ( $p=0.001$ ), as well as in terms of mBI within implants with absence of PIKM-W ( $p=0.035$ ).

### 3.2 | Association Between Soft-Tissue Phenotype and Peri-Implantitis

The prevalence of peri-implant health, peri-implant mucositis and peri-implantitis according to different PIKM-W groups is shown in Figure 1, while a principal component analysis in regular and irregular compliers is reported in Figures S2 and S3, respectively.

Results from multilevel logistic regression analyses on the association between soft-tissue characteristics and peri-implantitis are shown in Table 3. Analyses adjusted for confounders indicated how the absence of PIKM-W (OR=9.24), the absence of attached mucosa (OR=19.58) and a reduced vestibulum depth (OR=2.61) were associated with peri-implantitis. Mucosal thickness did not show statistically significant associations.

### 3.3 | Association Between Soft-Tissue Phenotype and PISTD

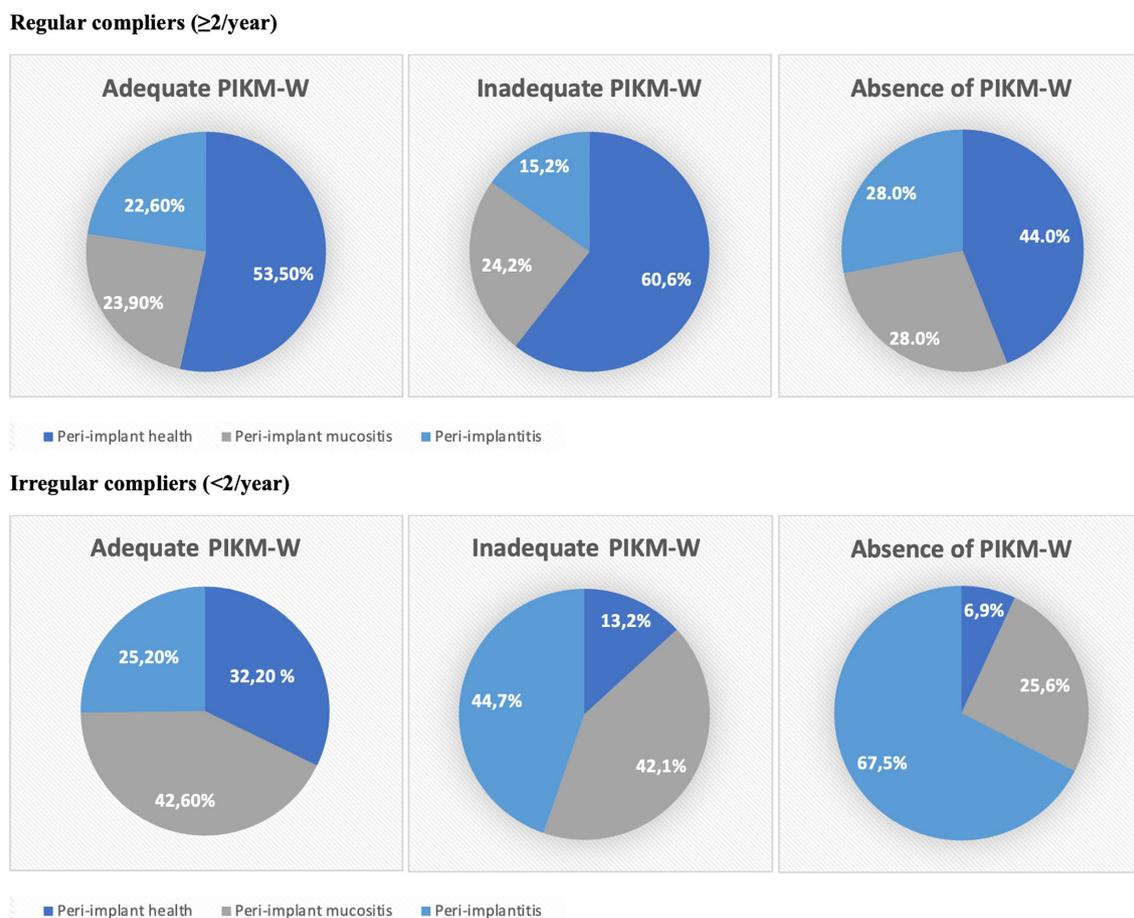
Results from multilevel logistic regression analyses on the association between soft-tissue characteristics and PISTD are shown

in Table 4. Analyses adjusted for confounders (including peri-implant health status) indicated how the absence of PIKM-W (OR=6.32), a thin mucosa (OR=157.75) and a reduced vestibulum depth (OR=3.32) were associated with the presence of PISTD. The attached mucosa did not show, however, any statistically significant association with PISTD.

### 3.4 | Pro- and Anti-Inflammatory Markers According to PIKM-W

Implants with absence of PIKM-W showed more PICF volume than implants with adequate/inadequate PIKM-W in both regular (mean: 0.78 vs. 0.66 and 0.62  $\mu\text{L}$ ) and irregular compliers (mean: 1.03 vs. 0.75 and 0.77  $\mu\text{L}$ ), but the difference was statistically significant only in irregular compliances ( $p=0.024$ ). Implants with the absence of PIKM-W also showed statistically significantly higher levels of IFN- $\gamma$  compared to other groups in both regular and irregular compliers ( $p=0.046$  and  $p=0.012$ ) (Table 5). In irregular compliers, absence of PIKM-W was also associated with statistically significantly higher levels of IL-1 $\beta$  and IL-21 ( $p=0.016$ ,  $p=0.046$ ). The expression level of IL-5 was under the limit of detection (0.49 pg/mL).

The cytokine networks of pro- and anti-inflammatory markers and PIKM-W groups for regular and irregular compliers are illustrated in Figure 2. Within regular compliers, TGF- $\beta$  clustered with absence of PIKM-W, whereas only IL-17A was found



**FIGURE 1** | Frequency distribution (%) of peri-implant health, peri-implant mucositis and peri-implantitis cases according to keratinized mucosa width in regular and irregular compliers. PIKM-W was categorized as adequate ( $\geq 2$  mm), inadequate ( $< 2$  and  $> 0$  mm), and absent (0 mm).

**TABLE 3** | Association between individual soft-tissue characteristics and peri-implantitis: Multi-level logistic regression analyses.

Variable	Unadjusted			Adjusted <sup>a</sup>		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
PIKM-W (each mm increase)	0.79	0.64–0.96	<b>0.018</b>	0.71	0.54–0.92	<b>0.009</b>
PIKM-W						
Adequate ( $\geq 2$ mm)	Ref	Ref	Ref	Ref	Ref	Ref
Inadequate ( $> 0$ mm; $< 2$ mm)	1.88	0.75–4.67	0.175	1.92	0.68–5.37	0.215
Absence (0 mm)	7.13	2.64–19.25	<b>&lt;0.000</b>	9.24	2.73–31.28	<b>&lt;0.001</b>
Attached mucosa (each mm increase)	0.54	0.36–0.79	<b>0.002</b>	0.40	0.25–0.64	<b>&lt;0.001</b>
Attached mucosa						
Presence ( $> 0$ mm)	Ref	Ref	Ref	Ref	Ref	Ref
Absence (0 mm)	10.29	4.32–24.5	<b>&lt;0.001</b>	19.58	6.12–62.56	<b>&lt;0.001</b>
Mucosal thickness (each mm increase)	0.75	0.45–1.25	0.271	0.75	0.42–1.32	0.315
Mucosal thickness						
Thick ( $\geq 2$ mm)	Ref	Ref	Ref	Ref	Ref	Ref
Thin ( $< 2$ mm)	1.23	0.60–2.49	0.570	1.14	0.52–2.49	0.750
Vestibulum depth						
Deep ( $> 4$ mm)	Ref	Ref	Ref	Ref	Ref	Ref
Reduced ( $\leq 4$ mm)	2.33	1.04–5.18	<b>0.038</b>	2.61	1.05–6.48	<b>0.039</b>

Note: All the *p*-values in bold are statistically significant,  $p < 0.05$ .

Abbreviations: CI, confidence interval; OR, odds ratio; PIKM-W, peri-implant keratinized mucosa width; Ref, reference category.

<sup>a</sup>Model adjusted for SPIC compliance, periodontal status (CDC/AAP), implant brand, modified plaque index, type of prosthesis, location and jaw.

**TABLE 4** | Association between individual soft-tissue characteristics and the presence of a peri-implant soft-tissue dehiscence: Multi-level logistic regression analyses.

Variable	Unadjusted			Adjusted <sup>a</sup>		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
PIKM-W (each mm increase)	0.72	0.56–0.92	<b>0.010</b>	0.63	0.44–0.88	<b>0.008</b>
PIKM-W						
Adequate ( $\geq 2$ mm)	Ref	Ref	Ref	Ref	Ref	Ref
Inadequate ( $> 0$ mm; $< 2$ mm)	0.94	0.33–2.66	0.911	1.38	0.38–4.99	0.620
Absence (0 mm)	4.80	1.73–13.29	<b>0.002</b>	6.32	1.67–23.83	<b>0.007</b>
Attached mucosa (each mm increase)	0.95	0.67–1.32	0.743	1.04	0.67–1.60	0.862
Attached mucosa						
Presence ( $> 0$ mm)	Ref	Ref	Ref	Ref	Ref	Ref
Absence (0 mm)	1.11	0.47–2.62	0.810	0.58	0.19–1.75	0.332
Mucosal thickness (each mm increase)	0.02	0.003–0.07	<b>&lt;0.001</b>	0.02	0.003–0.08	<b>&lt;0.001</b>
Mucosal thickness						
Thick ( $\geq 2$ mm)	Ref	Ref	Ref	Ref	Ref	Ref
Thin ( $< 2$ mm)	126.73	14.44–1111.83	<b>&lt;0.001</b>	157.75	14.06–1769.90	<b>&lt;0.001</b>
Vestibulum depth						
Deep ( $> 4$ mm)	Ref	Ref	Ref	Ref	Ref	Ref
Reduced ( $\leq 4$ mm)	2.54	1.02–6.37	<b>0.046</b>	3.32	1.02–10.84	<b>0.047</b>

Note: All the *p*-values in bold are statistically significant,  $p < 0.05$ .

Abbreviations: CI, confidence interval; OR, odds ratio; PIKM-W, peri-implant keratinized mucosa width; Ref, reference category.

<sup>a</sup>Model adjusted for SPIC compliance, periodontal status (CDC/AAP), implant brand, modified plaque index, type of prosthesis, location, jaw and peri-implantitis status.

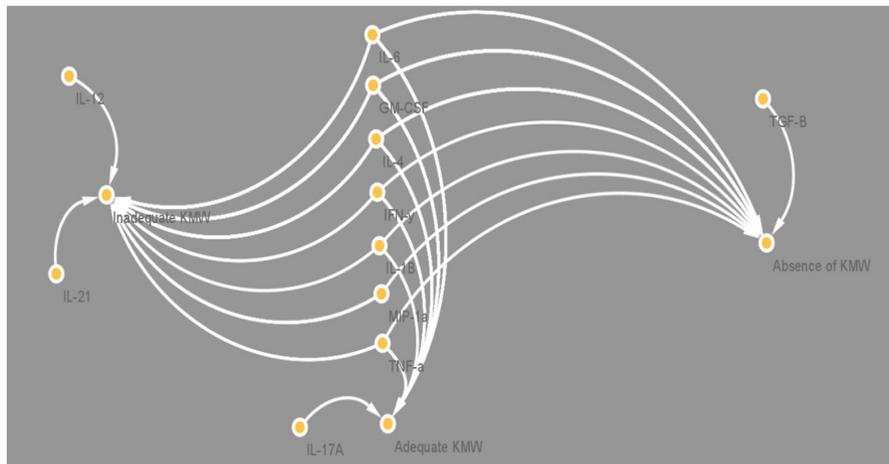
TABLE 5 | T-cell-related cytokines according to keratinized mucosa width in regular and irregular compliers.

Biomarker (median [IQR])	Regular compliers				Irregular compliers				p
	Luminex-30 s (pg/mL)				Luminex-30 s (pg/mL)				
	Adequate PIKM-W (≥2 mm) (n = 21)	Inadequate PIKM-W (<2 and >0 mm) (n = 15)	Absence of PIKM-W (=0 mm) (n = 14)	p	Adequate PIKM-W (≥2 mm) (n = 29)	Inadequate PIKM-W (<2 and >0 mm) (n = 19)	Absence of PIKM-W (=0 mm) (n = 21)	p	
IL-1β	6.88 (2.28; 36.37)	14.66 (6.04; 28.42)	18.71 (6.13; 51.50)	0.772	12.02 (6.46; 53.08)	16.45 (5.67; 49.48)	27.64 (14.24; 90.52)	<b>0.016<sup>a</sup></b>	
IL-2	0.50 (0.00; 1.23)	0.49 (0.00; 1.64)	0.98 (0.00; 1.20)	0.403	0.66 (0.00; 0.94)	0.84 (0.00; 1.15)	0.67 (0.00; 1.61)	0.689	
IL-6	0.70 (0.18; 1.02)	0.88 (0.45; 2.21)	1.14 (0.49; 2.60)	0.113	0.58 (0.18; 2.72)	0.98 (0.18; 3.09)	1.78 (0.87; 4.76)	0.207	
IL-7	14.52 (6.02; 20.03)	19.84 (6.08; 23.66)	18.75 (1.02; 32.14)	0.697	19.12 (5.34; 39.90)	18.28 (6.72; 35.57)	19.76 (6.11; 41.25)	0.650	
IL-8	184.42 (64.32; 336.17)	234.45 (163.16; 491.64)	284.49 (240.01; 607.45)	0.056	228.76 (147.64; 428.08)	243.20 (207.23; 447.01)	333.39 (113.39; 638.08)	0.250	
IL-12	11.34 (5.01; 21.12)	9.45 (6.88; 18.51)	5.54 (2.34; 9.92)	0.103	41.46 (11.46; 69.90)	31.34 (4.21; 51.12)	10.89 (2.11; 41.43)	0.297	
IL-17A	1.79 (0.93; 3.15)	2.01 (0.90; 2.98)	3.26 (1.20; 4.83)	0.245	2.74 (0.84; 4.46)	2.73 (1.73; 5.52)	5.02 (1.76; 5.82)	0.184	
IL-21	22.25 (2.74; 31.50)	22.79 (2.69; 38.64)	31.28 (3.78; 48.27)	0.639	27.25 (7.37; 51.82)	34.83 (24.45; 64.25)	45.76 (31.30; 67.43)	<b>0.046<sup>a</sup></b>	
IL-23	20.42 (5.03; 112.56)	31.90 (8.78; 192.23)	35.42 (7.08; 230.61)	0.194	31.24 (5.87; 123.14)	39.07 (5.95; 141.38)	42.31 (6.22; 155.17)	0.212	
IFN-γ	1.47 (1.35; 1.73)	1.73 (1.47; 1.88)	1.85 (1.41; 5.57)	<b>0.046<sup>a</sup></b>	1.47 (1.35; 1.73)	1.73 (1.60; 1.98)	1.40 (0.61; 1.73)	<b>0.012<sup>a</sup></b>	
TNF-α	0.83 (0.51; 1.91)	1.61 (1.11; 2.49)	2.84 (0.83; 3.45)	0.140	1.74 (0.69; 3.63)	2.16 (0.93; 4.32)	4.48 (1.19; 7.89)	0.080	
MIP-1α	1.13 (0.00; 5.62)	0.83 (0.00; 4.30)	1.44 (0.00; 5.71)	0.222	1.24 (0.00; 5.87)	1.10 (0.00; 5.42)	1.53 (0.00; 8.76)	0.412	
GM-CSF	2.26 (0.84; 7.68)	3.08 (1.16; 6.08)	2.12 (0.96; 7.68)	0.387	5.00 (1.43; 13.22)	5.22 (1.67; 9.87)	5.72 (2.80; 9.56)	0.065	
IL-4	0.13 (0.00; 17.78)	0.17 (0.00; 21.38)	0.15 (0.00; 18.15)	0.304	1.01 (0.00; 15.56)	1.48 (0.00; 24.31)	0.97 (0.00; 20.14)	0.187	
IL-5	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	NE	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	NE	
IL-10	6.08 (0.98; 11.00)	3.71 (0.30; 8.12)	6.23 (0.69; 7.93)	0.405	5.06 (1.87; 9.59)	5.23 (3.12; 11.92)	4.18 (0.68; 6.91)	0.459	
IL-13	6.78 (3.31; 10.43)	8.16 (5.17; 12.15)	5.21 (1.19; 6.78)	0.089	4.07 (0.45; 13.41)	4.73 (0.87; 12.75)	5.06 (0.81; 14.23)	0.571	
TGF-β	21.23 (3.29; 76.32)	35.71 (5.98; 63.82)	67.82 (6.91; 90.26)	0.571	45.16 (16.53; 85.05)	53.13 (9.98; 99.81)	69.22 (14.56; 105.49)	0.209	

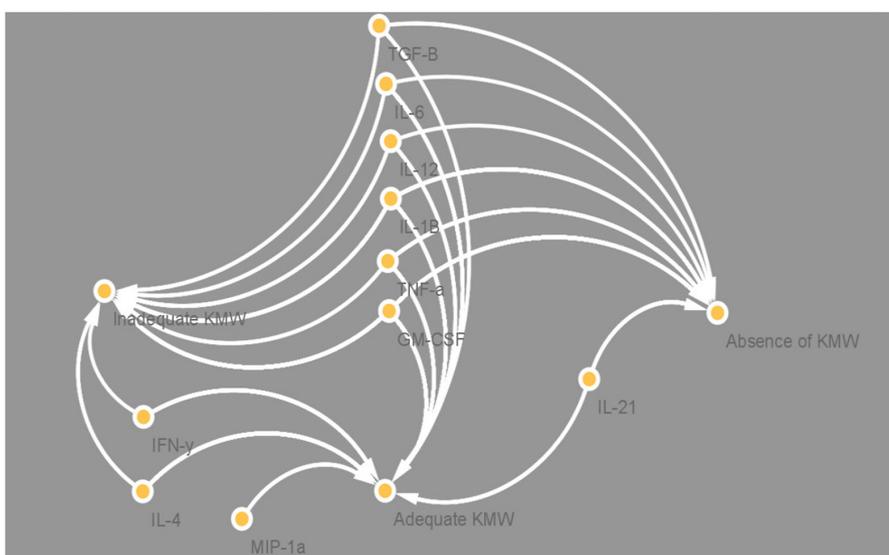
Note: All the p-values in bold are statistically significant,  $p < 0.05$ .

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-γ; IL, interleukin; IQR, interquartile range; MIP-1α, macrophage inflammatory protein-1α; n, number of implants; NE, not estimable; pg/mL, picogram per millilitre; PIKM-W, keratinized mucosa width; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α.

<sup>a</sup>Significantly different between groups,  $p < 0.05$ .

(a) Regular compliers ( $\geq 2$ /year)

(b) Irregular compliers (&lt;2/year)

**FIGURE 2** | Module network categorized according to PIKM-W in (a) regular and (b) irregular compliers.

to cluster with adequate PIKM-W. Within irregular compliers, although no specific cytokine was identified for absence of PIKM-W and inadequate PIKM-W, MIP-1 $\alpha$  was found to cluster with adequate PIKM-W. IL-21 clustered with both the absence of PIKM-W and adequate PIKM-W.

#### 4 | Discussion

The results from the present study revealed that several components of the peri-implant soft-tissue phenotype are associated with the presence of peri-implantitis and PISTD. Specifically, the absence of PIKM-W and reduced vestibulum depth were associated with both, while the absence of attached mucosa was only associated with peri-implantitis, and a thin mucosa was only associated with PISTD. These associations were independent from the effect of relevant confounders (e.g., plaque, compliance to maintenance, etc.). The analysis of pro- and anti-inflammatory markers suggests that these associations may involve a dysregulation of the Th1 and Th17 responses and an up-regulation of soft-tissue remodelling.

We did not observe differences in clinical and radiographic parameters between implants with adequate/inadequate/absence PIKM-W within patients attending SPIC regularly. Contrarily, implants with an adequate PIKM-W exhibited significantly lower mPI, mBI, BoP extent, PPD, PISTD and bone level values compared to implants with inadequate/absent PIKM-W in irregular compliers. These findings are consistent with previous studies (Frisch et al. 2015; Lim et al. 2019; Monje and Blasi 2019), underlining the major relevance of SPIC in the prevention of peri-implantitis in presence of risk indicators, including a frail soft-tissue phenotype.

In the present patient population, thick mucosa in implants with an inadequate PIKM-W showed lower BoP and PPD than thin mucosa in regular compliers, indicating the critical role of thickness phenotype for the sites with an adequate/inadequate PIKM-W on peri-implant health. However, thick mucosa did not show any positive effects at the sites with the absence of PIKM-W. Those findings support the idea that a thicker PIKM has a more protective influence than the mobile mucosa's thickness on peri-implant health situations, providing a soft-tissue seal that is less

susceptible to bacterial accumulation and tissue inflammation. In irregular compliers, thick mucosa was more associated with peri-implant tissue inflammation (i.e., mBI), revealing that inflammation around the peri-implant mucosa may also lead to an increase in peri-implant soft-tissue volume, which may obscure the effect of thickness phenotype on peri-implant health, especially in irregular compliance. Besides, although thicker/augmented mucosa has been reported to be associated with lower bone level (Thoma et al. 2018; Tavelli et al. 2021), we did not identify any significantly superior results of thick mucosa in terms of bone level for both regular and irregular compliers, in line with some previous reports (Garaicoa-Pazmino et al. 2021; Valles et al. 2022).

Results from multi-level multiple logistic regression analyses revealed that the absence of PIKM-W, a shallow vestibulum depth (<4 mm) and the absence of attached mucosa are associated with peri-implantitis. These findings are consistent with some previous studies (Monje and Blasi 2019; Kungsadalpipob et al. 2020; Gharpure et al. 2021), while others could not demonstrate any significant associations between peri-implant soft-tissue components and peri-implantitis (Lim et al. 2019; Romandini et al. 2021a). Regarding the presence of PISTD, the present study identified statistically significant associations with all the components of the peri-implant soft-tissue phenotype, except the presence of attached mucosa, corroborating the findings from previous studies (Evans and Chen 2008; Kan et al. 2011; Romandini, Pedrinaci et al. 2021). Considering that the apical displacement of the mucosal margin could be a consequence of peri-implantitis rather than its predisposing factor (Romandini et al. 2021b), the present analyses targeting PISTD were conducted accounting for peri-implantitis as a confounding factor.

There is evidence that plaque accumulation around implants results in a greater inflammatory infiltrate than periodontitis, characterized by abundant lymphocytes and plasma cells (Berglundh, Zitzmann, and Donati 2011; Isler et al. 2021; Zhang et al. 2022; Ozkocer et al. 2023). The considerably higher number of T cells (Gualini and Berglundh 2003; Carcuac and Berglundh 2014) and the wider range of cytokines produced by its subpopulations (Severino et al. 2016; Teixeira et al. 2017; Giro et al. 2021; Hentenaar et al. 2021) may reflect a well-regulated immune response. Since the presence of a keratinized epithelium and a dense connective tissue characteristic of the attached mucosa may act as a mechanical seal against bacteria, the presence of an adequate band of PIKM-W have been suggested to influence the inflammatory response within the peri-implant tissues (Romanos, Schröter-Kermani, and Strub 1996) and, in turn, to favour the resolution of peri-implant mucositis (Schwarz et al. 2018). The effect of PIKM on the levels of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-1 $\beta$  and prostaglandin E2 in PICF, has been demonstrated in previous studies (Boynueğri, Nemli, and Kasko 2013; Zigdon and Machtei 2008). Consistently, the present study indicated significantly elevated levels of IFN- $\gamma$ , IL-1 $\beta$  and IL-21 in implants lacking PIKM-W within irregular compliers, suggesting a dysregulation of the inflammatory response and an up-regulation of soft-tissue remodelling. Previous reports have pointed out that IFN- $\gamma$  and IL-1 $\beta$  may be relevant in peri-implant diseases (Teixeira et al. 2017; Ghassib et al. 2019). Moreover, Buyukozdemir Askin et al. (2015) have shown how the use of free gingival grafts to

modify the soft-tissue phenotype around dental implants may reduce the volume and amount of IL-1 $\beta$  in PICF. The expression of cytokines linked to the Th17 response has also been previously shown in peri-implant diseases (Giro et al. 2021; Severino et al. 2016; Teixeira et al. 2017). Although an increasing trend was seen in the sites with a lack of KM for all Th17-related cytokines, IL-21 was the only cytokine that revealed a statistical difference between PIKM groups in this study. Meanwhile, the present clustering results showed the relations between TGF- $\beta$ , which contributes to Treg response, and the lack of KM, and between IL-17A, which is the signature cytokine of Th17 cells, and adequate KMW in regular compliers, highlighting the broad role of Th17 and Treg response on the relation between PIKM and peri-implant health.

Although this study provides comprehensive data regarding the association between soft-tissue phenotype and the presence of peri-implantitis/PISTD, some limitations must be considered. They include (i) its cross-sectional design, which prevents verification of the temporality/causality of the associations; (ii) a limited generalizability, as the study involved a convenience sample of patients under maintenance in a specific university clinic, using strict inclusion criteria (i.e., exclusion of smokers, mispositioned implants, etc.); (iii) the use of only one implant per patient for the immunological analyses; and (iv) a risk of information bias related to (a) the use of indirect evidence to diagnose peri-implantitis in the majority of cases (Romandini, Berglundh et al. 2021; Berglundh et al. 2021) and (b) the definition of attached mucosa. Indeed, similar to previous studies, the method employed to measure this parameter could be inaccurate, because a large PPD can potentially exist within the peri-implant bony wall, with the possibility that some attached mucosa can be present on the outer side of the bone.

## 5 | Conclusions

According to the present findings, peri-implant soft-tissue phenotype is associated with the presence of peri-implantitis and PISTD. Specifically, the absence of PIKM-W and reduced vestibulum depth were associated with both conditions, while the absence of attached mucosa was only associated with peri-implantitis, and a thin mucosa was only associated with PISTD. These associations were independent of the effect of relevant confounders. Based on the analysis of cytokines, it may be suggested that, in the absence of PIKM-W, the inflammatory response is dysregulated and the soft-tissue remodelling up-regulated. Future studies should assess the possible relevance of soft-tissue augmentation procedures in the prevention of peri-implantitis and PISTD.

### Author Contributions

S.C.I. contributed to study conception and design, data acquisition, analysis and interpretation, and manuscript drafting. G.A. contributed to study design and data acquisition, and critically revised the manuscript. M.R. contributed to data analysis and interpretation, and manuscript drafting. B.B. contributed to data analysis, and critically revised the manuscript. B.U. contributed to study design and data interpretation, and critically revised the manuscript. G.R. and A.S. contributed to study conception and design, and critically revised the manuscript.

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## Conflicts of Interest

The authors declare no conflicts 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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### Supporting Information

Additional supporting information can be found online in the Supporting Information section.

# QUESTIONNAIRE

## B3(25) Part 1 of 2

### Soft-Tissue Phenotype as a Risk Indicator of Peri-Implantitis and Peri-Implant Soft-Tissue Dehiscence—A Cross-Sectional Study

#### INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- **Some questions may have more than one correct answer;** in which case you must mark **all** the correct answers.

#### Introduction

**Question 1:** Which **TWO** factors are critical in the management of peri-implantitis?

- A:** Early diagnosis
- B:** Primary prevention
- C:** Treatment procedures
- D:** Secondary prevention

**Question 2:** Which **TWO** factors do primary prevention of peri-implantitis focus on?

- A:** Periodontal status
- B:** Treating peri-implant mucositis as its precursor
- C:** Tackling modifiable risk factors
- D:** Vestibulum depth

**Question 3: TRUE or FALSE?**

"Among the possible risk factors, the peri-implant phenotype has recently received much attention, although the scientific evidence is still controversial".

- A:** TRUE
- B:** FALSE

**Question 4:** Which of the following statements are **TRUE** with reference to the statement above?

- A:** Relevant associated anatomical conditions (i.e. vestibulum depth) have been frequently disregarded
- B:** A possible source of this controversy is that most of the available studies focused on the individual components of the peri-implant phenotype separately: the peri-implant keratinized mucosa (PIKM), the mucosa thickness and the attached mucosa
- C:** Nevertheless, there is currently a lack of a thorough assessment of the pro- and anti-inflammatory markers expressed within different peri-implant phenotypes

**Question 5:** Is it **TRUE** that the primary aim of this study was to investigate the association between the different components of the peri-implant phenotype (PIKM- W, mucosal thickness, attached mucosa and vestibulum depth) with the presence of peri-implantitis and peri-implant soft-tissue dehiscence (PISTD), controlling for relevant confounding variables?

- A:** YES
- B:** NO

#### Participants

**Question 6:** Which of the following were exclusion criteria for participants?

- A:** Smokers who quit less than a year before enrolment
- B:** Uncontrolled diabetes mellitus with HbA1c  $\geq 7.0\%$
- C:** History of periodontal or peri-implant therapy during the previous 3 months

#### Peri-Implant Parameters, Diseases and Soft-Tissue Dehiscence (Outcomes)

**Question 7:** Which clinical parameters were measured at six aspects of each implant?

- A:** Modified plaque index
- B:** Only the modified sulcular bleeding index and suppuration on probing (SoP)
- C:** Only probing pocket depth (PPD)
- D:** Modified plaque index, modified sulcular bleeding index, bleeding on probing (BoP) / SoP, and PPD

**Question 8:** Which of the following statements are **TRUE** regarding PICF sampling?

- A:** Was performed on one site from each implant
- B:** In patients with multiple implants, the implant with the deepest PPD was targeted and the sampling was performed on a different day to avoid any influence from previous probing
- C:** Before sampling, the supra-marginal plaque was removed, and the implant was isolated with cotton rolls and gently air-dried

**Question 9:** How was peri-implantitis defined in the study?

- A:** Presence of BoP and SoP
- B:** Radiographic bone loss  $\geq 5$  mm
- C:** Presence of BoP and/or SoP, bleeding and suppuration on probing) and radiographic bone loss  $\geq 3$  mm
- D:** Only presence of SoP

## Results

**Question 10:** Which of the following statements are **TRUE** regarding the included patients?

- A:** Most patients were men
- B:** Most patients had no / mild periodontitis
- C:** Most of the implants were located in the mandible (53.1%), rehabilitated through bridges (69.8%)
- D:** Mean loading time was 6.2 years

**THE END**

# QUESTIONNAIRE

## B3(25) Part 2 of 2

### Soft-Tissue Phenotype as a Risk Indicator of Peri-Implantitis and Peri-Implant Soft-Tissue Dehiscence—A Cross-Sectional Study

#### INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- **Some questions may have more than one correct answer;** in which case you must mark **all** the correct answers.

#### Discussion

**Question 1:** The present study revealed that which of the following components of the peri-implant soft-tissue phenotype are specifically associated with the presence of peri-implantitis and PISTD?

- A: Absence of PIKM-W
- B: Absence of attached mucosa
- C: Reduced vestibulum depth

**Question 2:** Is it **TRUE** or **FALSE** that the following statement underlines the major relevance of SPIC in the prevention peri-implantitis?

“Contrarily, implants with an adequate PIKM-W exhibited significantly lower mPI, mBI, BoP extent, PPD, PISTD and bone level values compared to implants with inadequate/absent PIKM- W in irregular compliers”.

- A: TRUE
- B: FALSE

**Question 3:** What was observed in patients attending supportive peri-implant care (SPIC) regularly?

- A: Significant differences in all parameters
- B: Only differences in bone levels
- C: Only differences in plaque index
- D: No differences in clinical parameters between keratinized mucosa width (PIKM-W) groups

**Question 4:** In irregular compliers, which PIKM-W group showed better clinical outcomes?

- A: Inadequate PIKM-W
- B: Absence of PIKM-W
- C: Adequate PIKM-W
- D: No difference between groups

**Question 5:** What role did thick mucosa play in implants with inadequate PIKM-W?

- A: Showed higher BoP and PPD
- B: Showed lower BoP and PPD
- C: Had no effect on clinical parameters
- D: Only affected bone levels

**Question 6:** Which cytokines showed significantly higher levels in the absence of PIKM-W?

- A: IFN- $\gamma$
- B: IL-1 $\beta$
- C: IL-21

**Question 7:** Which of the following were **NOT** a limitation of the study?

- A: Cross-sectional design
- B: Limited generalizability
- C: Use of more than one implant per patient
- D: A risk of information bias

#### Conclusions

**Question 8: TRUE or FALSE?**

"The study found that only the absence of PIKM-W was associated with both peri-implantitis and peri-implant soft tissue dehiscence (PISTD)".

- A: TRUE
- B: FALSE

**Question 9:** What did the cytokine analysis suggest in the absence of PIKM-W?

- A: Only inflammatory response is dysregulated
- B: Only soft-tissue remodeling is up-regulated
- C: The inflammatory response is dysregulated, and soft-tissue remodeling is up-regulated
- D: Neither inflammatory response nor soft-tissue remodeling was affected

**Question 10:** Future studies should access .....

- A: Soft-tissue augmentation procedures
- B: Prevention of peri-implantitis
- C: The relevance of soft-tissue augmentation procedures in preventing both peri-implantitis and PISTD
- D: The prevention of PISTD

**THE END**



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**I hereby declare that the completion of this document is my own effort without any assistance.**

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This activity is accredited for **FOUR (4) CLINICAL** CEU'S. You have to achieve 70% to pass this activity.

**ANSWER SHEET**

**B3(25)**

Soft-Tissue Phenotype as a Risk Indicator of Peri-Implantitis and Peri-Implant Soft-Tissue Dehiscence—A Cross-Sectional Study

*Time spent on activity						hour	min				
PART 1						PART 2					
	A	B	C	D	E		A	B	C	D	E
1						1					
2						2					
3						3					
4						4					
5						5					
6						6					
7						7					
8						8					
9						9					
10						10					

How relevant was the content of this activity to your scope of practice?			
			
Not at all	Somewhat	Mostly	Extremely
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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