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GABRIELA MARTIN BONILHA

PERFIS MICROBIOLÓGICOS E IMUNOLÓGICOS DISTINTOS DISCRIMINAM DOENÇAS PERI-IMPLANTARES E PERIODONTAIS.

DISTINCT MICROBIOLOGICAL AND IMMUNOLOGICAL PROFILES DIFFERENTIATE PERI-IMPLANT AND PERIODONTAL DISEASES.

Piracicaba

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Dissertação apresentada à Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas como parte dos requisitos exigidos para obtenção do título de Mestra em Clínica Odontológica, na Área de Periodontia.

Dissertation presented to the Piracicaba Dental School of the University of Campinas in partial fulfillment of requirements for the degree of Master in Clinical Dentistry, in Periodontology area.

Orientador: Prof. Dr. Renato Corrêa Viana Casarin

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PROF. DR. DANILO LAZZARI CIOTTI

PROFª. DRª. MABELLE DE FREITAS MONTEIRO

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DEDICATÓRIA

Dedico este trabalho aos meus pais, que me apoiaram incondicionalmente e me incentivaram a realizá-lo.

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RESUMO

A periodontite e a peri-implantite são doenças inflamatórias induzidas por biofilme que afetam os tecidos moles e ósseos que sustentam os dentes/implantes. Embora semelhantes em sintomas e tratamento, seu nível de semelhança permanece questionável. **Objetivo:** O objetivo deste estudo de caso controle transversal foi avaliar e comparar o perfil microbiano (taxonomicamente) e citocinas inflamatórias de sítios de peri-implantite e periodontite. **Materiais e métodos:** Quarenta participantes foram selecionados para participar do estudo, sendo 20 com diagnóstico de Estágio 3-4, Grau B/C de periodontite e 20 com peri-implantite. Eles foram alocados em dois grupos, de acordo com o diagnóstico de sua doença (grupo periodontite e grupo peri-implantite). Os parâmetros clínicos iniciais foram avaliados através de uma sonda milimetrada Carolina do Norte: índice de placa (IP), sangramento à sondagem (SS), nível de inserção clínica (NIC), profundidade de sondagem (PS) de pacientes periodontais e com peri-implantite. Além destes, também foram utilizados os parâmetros de índice gengival (IG) e posição da margem gengival (PMG) para pacientes periodontais. A coleta de biofilme foi realizada utilizando pontas de papel endodôntico estéril de um dente/implante de cada paciente de ambos os grupos para posterior extração de DNA (Qiagen MiniAmp Kit), sequenciamento (Illumina MiSeq) e avaliação taxonômica dos dados. Realizou-se a coleta do fluido gengival através de pontas de papel endodôntico estéril para análise dos marcadores inflamatórios de cada grupo (equipamento Luminex/MAGpix). **Resultados**: Na análise microbiológica, a periodontite apresentou uma diversidade alfa maior do que a peri-implantite e a diferença na diversidade beta foi observada entre os grupos. Embora algumas espécies tenham sido compartilhadas em ambos os nichos, espécies como *Streptococcus parasanguinis, Streptococcus mutans, Cutibacterium acnes, Stomatobaculum sp.* e *Aerococcus viridans* foram significativamente mais abundantes no grupo peri-implantite. Além disso, a peri-implantite tem sido associada a uma redução na resposta imune Th2 com aumento na expressão de Th17 quando comparada à doença periodontal. **Conclusão:** A Periodontite e a Peri-implantite apresentam comunidades microbianas e padrões inflamatórios distintos, representando um ambiente distinto para destruição dos tecidos, o que deve ser considerado no tratamento e nos aspectos preventivos.

Palavras-chave: Peri-implantite; Periodontite; Microbiota; Citocinas

ABSTRACT:

Periodontitis and peri-implantitis are biofilm-induced inflammatory diseases that affect the soft and bony tissues that support the teeth/implants. Although similar in symptoms and treatment, their level of similarity remains questionable. **Aim:** The objective of this cross-sectional, case-control study was to evaluate and compare the microbial profile (taxonomically) and inflammatory cytokines of peri-implantitis and periodontitis sites. **Material and methods:** Forty participants were selected to participate in the study, 20 with a diagnosis of Stage 3-4, Grade B/C periodontitis and 20 with peri-implantitis. They were allocated into two groups, according to the diagnosis of their disease (periodontitis group and peri-implantitis group). Initial clinical parameters were evaluated through a North Carolina millimeter-gauged probe: plaque index (PI), bleeding on probing (BP), level of clinical attachment loss (CAL), probing depth (PD) of periodontal patients and with peri-implantitis. In addition to these, the parameters of gingival index (GI) and gingival margin position (GMP) were also used for periodontal patients. Biofilm collection was carried out using sterile endodontic paper points from a tooth / implant from each patient of both groups for subsequent DNA extraction (Qiagen MiniAmp Kit), sequencing (Illumina MiSeq) and taxonomic evaluation of the data. Gingival crevicular fluid was also collected with sterile endodontic paper points to analyze the inflammatory markers of each group (Luminex / MAGpix equipment). **Results:** In microbiological analysis, periodontitis presented a higher alpha-diversity than peri-implantitis and the difference in beta-diversity was observed between groups. Although some species were shared in both niches, species such as *Streptococcus parasanguinis*, *Streptococcus mutans*, *Cutibacterium acnes*, *Stomatobaculum sp*. and *Aerococcus viridans* were significantly more abundant in the peri-implantitis group. Furthermore, peri-implantitis has been linked to a reduction in the Th2 immune response with an increase in Th17 expression when compared to periodontal disease. **Conclusion:** Periodontitis and Peri-implantitis present dissimilar microbial communities and inflammatory patterns, representing a distinct environment for tissues destruction, what should be considered in treatment and preventive aspects.

Key-words: Peri-implantitis; Periodontitis; Microbiota; Cytokines

SUMÁRIO

1 INTRODUÇÃO

Nas últimas décadas, os implantes dentários representaram a terapia mais aceita para a substituição de elementos dentários perdidos (Stanford, 2007). Contudo, assim como ocorre nos dentes, o acúmulo de biofilme estimula um processo inflamatório, resultando inicialmente em doenças que afetam os tecidos moles, como a mucosite e, em seguida, na peri-implantite (Lang et al. 2011, Jepsen et al. 2015). A prevalência da mucosite peri-implantar e da peri-implantite varia de 19% a 65% e de 1% a 47%, respectivamente (Ferreira et al. 2009, Koldsland et al 2010, Casado et al. 2013). Clinicamente, a peri-implantite pode ser descrita como uma destruição óssea em torno dos implantes dentários osseointegrados devido ao acúmulo de biofilme e uma resposta inflamatória desequilibrada do hospedeiro (Caton et al. 2018, Papapanou et al. 2018). Esta definição é bastante semelhante à descrição da doença periodontite. Assim, historicamente, os padrões etiológicos da peri-implantite foram considerados os mesmos da periodontite (Becker et al. 2014). No entanto, alguns estudos recentes apontam certas divergências quanto às características microbianas, epigenéticas e também anatômicas- características estas, que podem impactar na patogênese da peri-implantite (Becker et al. 2014, Yu et al. 2018).

Torna-se importante destacar que estruturas periféricas de suporte dos dentes e implantes são bastante distintas e essas diferenças podem ter importantes efeitos na susceptibilidade e progressão da doença (Berglundh et al. 2011; Robitaille et al. 2016). Implantes osseointegrados apresentam contato direto entre osso- titânio e ausência de ligamento periodontal (Gulati et al. 2014). Deste modo, o impacto é determinado pelo suprimento vascular reduzido, menor quantidade e orientação paralela das fibras supracrestais e proporção alterada de células (Ivanovski et al. 2018). Na peri-implantite, o tecido conjuntivo inflamatório infiltra-se ao redor dos implantes prolongando-se para a crista óssea alveolar e está relacionado à densidade elevada de células osteoclastogênicas quando comparadas aos dentes (Berglundh et al. 2011). Além disso, os tecidos moles peri-implantares mostram uma resposta inflamatória mais acentuada ao acúmulo de placa do que os que circundam um dente (Salvi et al. 2012).

Em um estudo recente, Schincaglia et al. 2017 mostraram em um modelo de mucosite e gengivite induzida, um comportamento diferente durante a interrupção dos meios de controle mecânicos/químicos do biofilme. Embora os implantes, apresentaram um acúmulo menor de placa, mudanças mais heterogêneas na estrutura do microbioma puderam ser constatadas. Além disso, apesar da inflamação ao redor dos dentes e implantes ter se correlacionado positivamente com IL-1 α e IL-1 β e suas proporções de *Selenomonas* e *Prevotella*, apenas os sítios de gengivite apresentaram uma correlação positiva mais forte com lactoferrina r IL-1ra e uma correlação negativa mais forte com *Rothia sp*. Por outro lado, a mucosite peri-implantar, correlacionou-se positivamente com certos táxons microbianos não associados à gengivite. Esse modelo experimental controlado reforça algumas diferenças imunológicas entre as doenças observadas em vários estudos. Dentro de vários biomarcadores, a IL-1β está consistentemente associada à peri-implantite. Estudos transversais mostraram maior concentração ou superexpressão do gene IL-1β nos tecidos com peri-implantite, como também um potencial discriminatório para implantes saudáveis (Faot et al. 2015, Hall et al. 2015, Wang et al. 2015). Juntamente com a IL-1 β, outros estudos mostraram níveis mais altos de IL-8, TNF-α e redução da molécula anti-inflamatória PPARγ em implantes doentes (Faot et al. 2015, Hall et al. 2015, Casado et al. 2013).

Outro estudo interessante avaliou a cascata TH17 / Treg e mostrou uma resposta Th17 predominante e uma diminuição da resposta Treg na presença de peri-implantite quando comparada à condição saudável periimplantar, causada principalmente pela regulação positiva de IL-23 e baixa regulação do TGF-β (Ouyang et al. 2008, Fietta et al. 2009, Mardegan et al. 2017). No entanto, quase todas as comparações realizadas utilizaram uma comparação entre peri-implantite e implantes saudáveis, não permitindo comparar e determinar se e como as doenças periodontais e peri-implantares são semelhantes (Duarte et al. 2016). Considerando o perfil microbiano, conclusões semelhantes podem ser alcançadas. Em 2016, Robitaille et al. denominaram periodontite e peri-implantite como doenças fraternas em vez de idênticas. Segundo os autores, embora patógenos periodontais possam ser identificados em sítios com peri-implantite, as técnicas abertas de identificação microbiana usadas em poucos estudos observaram uma comunidade diferenciada em torno dos implantes. Foi constatado que 60% dos indivíduos compartilharam

menos de 50% de todas as espécies entre os biofilmes periodontal e peri-implantar e 85% dos indivíduos compartilharam menos de 8% das espécies abundantes entre dente e implante (Dabdoub et al. 2013). Os principais microbiomas associados à peri-implantite e periodontite também são significativamente diferentes (Maruyama et al. 2014), com pouquíssimos patógenos periodontais detectados em peri-implantite (Koyanagi et al. 2013). Altos níveis de anaeróbios assacarolíticos (por exemplo, *Eubacterium nodatum, Eubacterium braquy, Eubacterium saphenum, Filifator alocis* e *Slackia exigua*) são encontrados nas bolsas de implantes afetados pela peri-implantite, sugerindo que os periodontopatógenos podem não ser a única causa da doença (Tamura et al. 2013).

Uma revisão recente da literatura indicou que a peri-implantite representa uma infecção mista heterogênea que inclui microrganismos periodontopatogênicos, bastonetes gram-positivos anaeróbicos assacarolíticos não-cultiváveis e outros bastonetes gram-negativos não cultiváveis e, raramente, microrganismos oportunistas, como bastonetes entéricos e *Staphylococcus aureus* (Lafaurie et al. 2017). No entanto, há necessidade de mais estudos avaliando a comunidade e comparando diferentes condições (Retamal-Valdes et al. 2019), em especial, concentrando-se em entender se a peri-implantite é uma condição diferente da periodontite, um estudo de caso-controle, controlando alguns vieses como os parâmetros clínicos periodontais e peri-implantares, o tipo de implante e o tipo de reabilitação, ainda é necessário.

No entanto, considerando esses aspectos, podem ser observados vários pontos a serem determinados. De fato, não há resposta para: O perfil do biofilme da peri-implantite é diferente das bolsas periodontais nas mesmas condições clínicas e de sondagem? O perfil de citocinas é semelhante? Essas questões somente poderiam ser resolvidas considerando todos os aspectos no mesmo local, usando abordagens abertas e análises adequadas.

Assim, o objetivo do presente estudo foi avaliar e comparar o perfil microbiano (taxonomicamente) e inflamatório dos sítios de peri-implantite e periodontite pois, o conhecimento destas diferenças irá ajudar à estabelecer novos protocolos de tratamento que sejam mais eficientes para cada condição.

2 ARTIGO

Distinct microbiological and immunological profiles differentiate peri-implant and periodontal diseases.

Bonilha G.M.[1], Monteiro M.F.[1], Sallum E.A.[1], Pimentel S.P.[2], Ruiz K.G.S.[1], Casati M.Z.[1], Casarin R.C.V.[1]

[1] Department of Prosthodontics and Periodontics, Periodontics Division, Piracicaba Dental School, University of Campinas, Piracicaba, SP, Brazil.

[2] Dental Research Division, School of Dentistry, Paulista University- UNIP, São Paulo, SP, Brazil.

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Corresponding author:
Renato Corrêa Viana Casarin
Department of Prosthodontics and Periodontics, Periodontics Division
Piracicaba Dental School, P.O. BOX 52
University of Campinas – UNICAMP
Avenida Limeira 901, Piracicaba, SP, Brazil. ZIP CODE: 13414-903,
Phone/FAX: 55 19 21065301
e-mail: rcasarin@unicamp.br

Abstract:

Periodontitis and peri-implantitis are biofilm-induced inflammatory diseases that affect the soft and bony tissues that support the teeth/implants. Although similar in symptoms and treatment, their level of similarity remains questionable. **Aim:** The objective of this cross-sectional, case-control study was to evaluate and compare the microbial profile (taxonomically) and inflammatory cytokines of peri-implantitis and periodontitis sites. **Material and methods:** Forty participants were selected to participate in the study, 20 with a diagnosis of Stage 3-4, Grade B/C periodontitis and 20 with peri-implantitis. They were allocated into two groups, according to the diagnosis of their disease (periodontitis group and peri-implantitis group). Initial clinical parameters were evaluated through a North Carolina millimeter-gauged probe: plaque index (PI), bleeding on probing (BP), level of clinical attachment loss (CAL), probing depth (PD) of periodontal patients and with peri-implantitis. In addition to these, the parameters of gingival index (GI) and gingival margin position (GMP) were also used for periodontal patients. Biofilm collection was carried out using sterile endodontic paper points from a tooth / implant from each patient of both groups for subsequent DNA extraction (Qiagen MiniAmp Kit), sequencing (Illumina MiSeq) and taxonomic evaluation of the data. Gingival crevicular fluid was also collected with sterile endodontic paper points to analyze the inflammatory markers of each group (Luminex / MAGpix equipment). **Results:** In microbiological analysis, periodontitis presented a higher alpha-diversity than peri-implantitis and the difference in beta-diversity was observed between groups. Although some species were shared in both niches, species such as *Streptococcus parasanguinis*, *Streptococcus mutans*, *Cutibacterium acnes*, *Stomatobaculum sp*. and *Aerococcus viridans* were significantly more abundant in the peri-implantitis group. Furthermore, peri-implantitis has been linked to a reduction in the Th2 immune response with an increase in Th17 expression when compared to periodontal disease. **Conclusion:** Periodontitis and Peri-implantitis present dissimilar microbial communities and inflammatory patterns, representing a distinct environment for tissues destruction, what should be considered in treatment and preventive aspects.

Key-words: Peri-implantitis; Periodontitis; Mibrobian Profile; Inflammatory Cytokines

Introduction:

In recent decades, dental implants have represented the most accepted therapy for the replacement of missing teeth due to their high long-term success rate (French et al. 2021). However, the accumulation of plaque stimulates an inflammatory response, as in teeth, initially resulting in diseases such as peri-implant mucositis and then peri-implantitis (Berglundh et al. 2018). The prevalence of implants presenting peri-implant mucositis and peri-implantitis ranges from 85.3% and 9.2%, respectively (Pimentel et al. 2018). Due to their similarities in clinical expression, the etiologic patterns of peri-implantitis have been considered the same as those of periodontitis (Becker et al. 2014). However, recent studies point out certain divergences regarding microbial, epigenetic, and anatomical characteristics, which can directly impact the pathogenesis of peri-implantitis (Yu et al. 2018, Kotsakis & Olmedo, 2021).

It is important to note that peripheral structures supporting teeth and implants are quite different and these differences can have important effects on disease susceptibility and progression (Berglundh et al. 2011; Robitaille et al. 2016). Osseointegrated implants present direct bone-titanium contact and the absence of periodontal ligament (Gulati et al. 2014). Thus, the impact is determined by the reduced vascular supply and the altered proportion of cells (Ivanovski et al. 2017). In peri-implantitis, the inflammatory connective tissue infiltrates around the implants extending to the alveolar bone crest and is related to the high density of osteoclastogenic cells when compared to teeth, resulting in faster-progressive destruction compared to periodontal sites (Berglundh et al. 2011; Monje et al. 2019).

Several studies had been done targeting the identification of microbial, immunological, or another etiological factor exclusively, or at least majorly associated, with Peri-implantitis. However, the multiplicity of methodologies limits a wider comprehension of this disease. Initially, the submucosal biofilm in peri-implantitis condition was characterized as presenting predominantly gram-negative species and which, when compared to subgingival biofilm in periodontitis, showed lower species diversity and also species that had not been isolated subgingivally, and which are unique to that niche. (Shibli et al. 2008). More recent findings showed up

that the peri-implantitis niche is enriched by other species than those usually associated with periodontal disease (Belibasakis & Manoil, 2021). On the other hand, it is well accepted that an imbalance between the bacterial load and the patient's immune response (Zitzmann & Berglundh, 2008), is the key to the establishment of peri-implant diseases, resulting in increased tissue volume and marginal bleeding, and greater production of peri-implant crevicular fluid, thus generating a greater inflammatory exudate (Corrêa et al. 2019). Studies also evaluated the cytokine, proteolytic enzymes, and other host-related factors in peri-implant crevicular fluid (Zheng et al. 2015, Che et al. 2017), agreeing that PI sites could present distinct profiles (Belibasakis & Manoil, 2021). However, there is a need to widely understand the cytokine-microbial interactions occurring around implants, and compare them to periodontal sites, targeting a clearer view of disease pathogenesis.

Recently, Wang et al. 2021, using a machine learning-assisting technology, identify an association between *F. nucleatum* and *P. intermedia* with increased risk, while low-risk immune profile was characterized by enhanced complement signaling and higher levels of Th1 and Th17 cytokines. However, the study only included peri-implantitis sites undergoing to surgical therapy. Also, Ganesan et al. 2021, assessing 5 pairs of health and diseased implants, concluded that microbial dysbiosis in the peri-implant sulcus might promote abandonment of host-bacterial transactions that dictate the health and instead drive a move towards chronic programming of a non-healing wound. Both studies, although enrolls deep-sequencing analysis, do not compare peri-implant and periodontal sites. Inducing peri-implant mucositis and gingivitis in a split-mouth design, Schincaglia et al. 2017 were the only to compare both sites using open-ended approaches. The study shows that while gingivitis showed a stronger positive correlation with lactoferrin and IL-1ra and a stronger negative correlation with *Rothia*, peri-implant mucositis correlated positively with certain microbial taxa not previously associated with gingivitis (increased *S. artemidis, E. corrodens, Ottowia sp.* HOT894, and *N. meningitidis*), which indicates the differential environment between dental implants and natural dentition. However, there are no shreds of evidence in literature when both teeth or implants have already presented severe disease.

Although peri-implantitis is often seen as similar to periodontitis, in terms of pathogenicity and treatment, there is evidence of particular characteristics of peri-implantitis that can explain their discrepant progressive rate and also the challenging treatment. Each environment has its differences, and both the microbial profile and cytokines potentially behave differently. Thus, this present study aimed in elucidating particular differences of the disease in peri-implant sites in the immunological and microbiological scope. Thus, the objective of this work is to highlight factors that can serve for greater prevention and more effective treatment of peri-implantitis.

Materials and methods:

This study was a case–control trial, conformed to the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines, comparing Periodontitis and Peri-implantitis subjects and was approved by the Institutional Review Board (IRB) of Piracicaba Dental School (CAAE 51169721.8.0000.5418). Recruitment ocurred from June 2020 to November 2021, and consent was obtained before the collection of data and samples.

Study population:

Participants were sequentially recruited from patients referred for periodontal/ peri-implant disease treatment. Inclusion criteria were as follows: **Perio Group:** 20 subjects with Periodontitis Stage 3 / 4, Grade B / C (Caton et al. 2018, Papapanou et al. 2018), with at least 15 teeth and at least 6 teeth presenting 6 sites with probing depth ≥7 mm and **Peri Group:** 20 subjects with Peri-implantitis (Berglundh et al. 2018); presence of bleeding and / or suppuration on probing, bone loss and increased probing depth in relation to previous exams.

Exclusion criteria were as follows: **General Exclusion Criteria**: systemic change or use of medication (antibiotics) - 6 months; pregnant and lactating women; periodontal / peri-implant treatment in the 6 months prior to the study. **Specific exclusion criteria: Perio Group:** Teeth with furcation or endodontic involvement, teeth endodontically treated, with occlusal trauma, extensive restorations and / or fractures; and **Peri Group:** Implants rehabilitated with cemented prostheses with excess cement; Screw-retained prostheses with failure of adaptation or loss of

torque; Implants with mobility or occlusal trauma; Implants which adequate clinical examination was not possible (inadequate emergency profile, poor positioning, etc.).

- Clinical periodontal measurements:

Initial clinical parameters were evaluated using a millimeter-gauged probe: plaque index (PI), gingival index (GI), bleeding on probing (BOP), position of the gingival margin (PGM), level of clinical attachment loss (CAL), probing depth (PD) of periodontal patients. Patients with peri-implantitis were assessed for BOP, PI, PD and CAL. All clinical parameters were obtained using a North Carolina periodontal probe, by a calibrated examiner (MFM).

- Plaque sample

For taxonomic analysis of periodontal and peri-implant biofilms, biofilm samples were collected. All samples were obtained before periodontal examination. Before subgingival/submucosal plaque sampling, supragingival/supramucosal plaque was removed carefully by sterile curets. The site was isolated using cotton rolls and gently dried with an air syringe to avoid contamination with saliva. Biofilm samples were obtained by the standard filter paper points from the buccal aspects of teeth/implants. Filter paper points were placed in the gingival/peri-implant sulcus and left in place for 30 seconds. The paper points were inserted in the microcentrifuge tube containing Tris-EDTA solution. All samples were immediately frozen and stored at -20° C until laboratory analyses. Biofilm samples were removed from paper strips by adding 200ul of phosphate-buffered saline (PBS) and vortexing for 1 minute. The paper point was removed and the DNA isolated using the Qiagen MiniAmp kit (Valencia, CA), following the manufacturer's recommendations. Oral prophylaxis or non-surgical periodontal treatment was not initiated before sample collection, and individuals were enrolled in a periodontal treatment program as required.

DNA sequencing and data analysis

The hypervariable V3-V4 region of the 16S rRNA gene was amplified using the primers and the PCR conditions previously described by Klindworth et al. (2013). According to the manufacturer's recommendation, the PCR purification was performed using magnetic beads (AMPUre XP Bead, Beckman Agencourt) in the proportion of 0.8 beads/PCR volume. After the adapters' ligation, a new PCR purification was performed using magnetic beads (AMPUre XP Bead, Beckman

Agencourt) in the proportion of 1,12 beads/PCR volume. The library normalization was carried out using the SequalPrep™ Normalization Plate (96) Kit (Applied Biosystems™), and the pooled library was quantified. Equimolar DNA concentrations were pooled and sequenced on the Illumina Miseq platform to produce 300bp paired-end sequences.

Bioinformatic analysis was performed using the QIIME 2 2020.6 (Bolyen et al., 2019). Demultiplexed FASTQ files were obtained from the sequencing facility, and the q2-cutadapt (Martin, 2011) was used to remove the primers before the denoising process was performed with q2-DADA2 (Callahan et al. 2016). The pipeline align-to-tree-mafft-fasttree (q2-phylogeny) was used to align all amplicon sequence variants (ASVs) with mafft (Katoh et al. 2002) and to construct a phylogeny with fasttree2 (Price et al. 2010). Taxonomy was assigned to ASVs using the q2-feature-classifier (Bokulich et al. 2018a) classify-sklearn naïve Bayes taxonomy classifier trained against the expanded Human Oral Microbiome (eHOMD, V15.2) Database (Escapa et al., 2018). The Alpha-diversity metrics (Shannon (Spellerberg, 2003)), beta diversity metrics (weighted UniFrac (Lozupone et al. 2007), unweighted UniFrac (Lozupone et al. 2005), and Principle Coordinate Analysis (PCoA) were estimated using q2-diversity core-metrics-phylogenetic pipeline after samples were rarefied to 10591 sequences per sample. Differences in alpha diversity (within samples differences) were measured using the pairwise differences (Bokulich et al. 2018b). For beta diversity (between-sample differences), the differences between groups were measured with the permanova and permdisp tests (q2-diversity). The core microbiome (considered the core microbiome as species presented in at least 50% of the samples from a group) was calculated using the q2-feature-table core features in a collapsed species level table. The visualization was performed using q2-feature-table heatmap (to visualize the relative abundance of species) and PhyloToAST (Dabdoub et al., 2016). The differential abundance between species was calculated using ANCOM-BC (Lin & Peddada, 2020).

Analysis of inflammatory markers

Gingival and peri-implant crevicular fluid was collected from all individuals involved in the study, at sites with probing depth greater than 7 mm and bleeding. During the collection of the material, the site involved was properly isolated and dried

with sterilized cotton rolls. The supragingival biofilm was removed and samples of gingival fluid were obtained by placing paper points between the tooth / periodontal tissue interface, for 30 seconds (Casarin et al. 2010). Two paper points were used per site to obtain an adequate volume of crevicular fluid. The volume of fluid collected was measured with Periotron® (Periotron 8000, Proflow Inc., Amityville, NY, USA) and the paper points were then placed in microcentrifuge tubes (eppendorf), coded for each individual and experimental periods with 150μl of phosphate buffer solution (PBS) and 0.05% Tween-20. The samples were stored for further analysis.

Before the analysis, the samples were diluted in 60μl of buffer from the Millipore kit, vortexed for 30 minutes and then centrifuged for 10 minutes at 10,000 rpm. Aliquots of each gingival fluid sample were analyzed for IL-1β, IL-4, IL-6, IL-8, IL-10, IL-17, TNF-α and IFN-ɣ by Luminex / MAGpix technology , which not only determines the presence but also quantifies in an absolute way, the concentration of different markers in the same sample, using commercially available kits following manufacturer's instructions. Briefly, samples were diluted in PBS + Tween5% buffer, and vortexed for 30 seconds, prior to analysis. After gentle centrifugation, 25 μL of supernatants was placed in 96-well plates along with immunomarked beads specific for each cytokine/protease. After beads incubation, secondary antibodies and substrate were provided and plates read using the MAGpix platform. The concentration of each analytical was expressed in pg / μl. Samples with quantification below the detection limit of the analysis were recorded as "zero" and samples above the quantification limit of the standard curve were recorded with a value equal to the highest value of the curve.

Data analysis

The inflammatory data were submitted to the multivariate analysis after log transformation of the cytokine concentration. The hierarquical cluster was computed for samples and cytokines and a heatmap was plotted based on the standardized cytokine concentration. The Principal Component Analysis was computed for all cytokines and a factorial analysis analyzed the importance of each cytokine to differentiate the identified components. All analysis were performed considering the significance level of 5%.

RESULTS

Table 1 describes the demographic and clinical characteristics of the patients included in the study. Peri-implantitis patients presented lower plaque index than periodontitis ($p<0.05$). All other variables were not different between groups ($p>0.05$).

Table 1. Clinical and demographic data from both groups.

	Periodontitis	**Peri-implantitis**
Age (years)	42.2±3.8	45.9±7.7
Female (%)	80	73
FmCAL	2.3±0.3	2.7±0.9
FmPI	38.5±16.9	26.7±12.7*
FmBoP	25.5±12.3	28.3±9.4

*(Student's t test, $p<0.05$) (FmBoP – Full Mouth Bleeding on Probing; FmPI – Full Mouth Plaque Index; FmCAL – Full Mouth Clinical Attachment Level;

Regarding the microbiological aspects, periodontitis and peri-implantitis presented distinct microbiome. Periodontitis presented a higher alpha-diversity (figure 1A) than peri-implantitis (Mann-Whitney test, $p=0.003$). Furthermore, different beta-diversities were observed between groups in the PCoA for both phylogenetic metrics (figure 1B and 1C), where distinct clusters were formed for the periodontitis and peri-implantitis samples. A significant difference was described for the Weighted Unifrac distances (PERMANOVA test, $p=0.001$; permdisp, $p= 0.494$) and for the Unweighted Unifrac distances (PERMANOVA test, $p=0.001$; permdisp, $p= 0.074$).

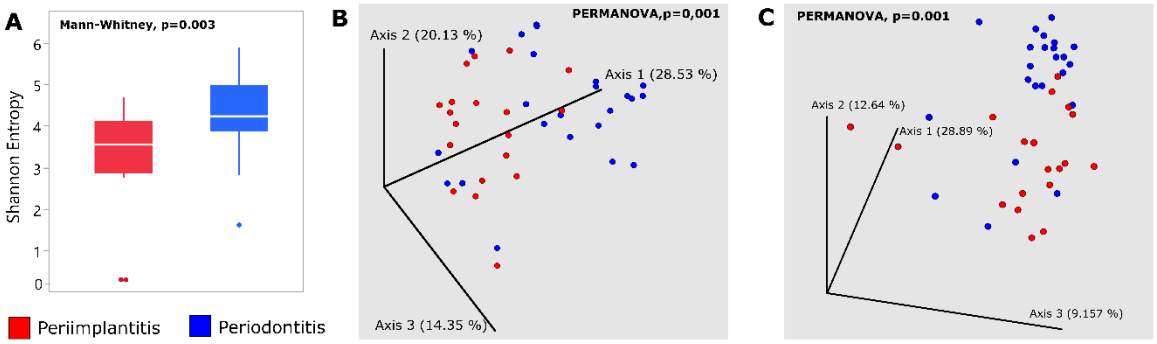

Figure 1. Diversity metrics. A) Alpha diversity demonstrated by the Shannon metric. B) Principal coordinate analysis of the Weighted Unifrac distance. C) Principal coordinate analysis of the Unweighted Unifrac distance.

At species level, differences were described for prevalence and abundance metrics. Periodontitis presented a higher core microbiome than the Periimplantitis group (figure 2), which can be related to the greater alpha diversity in periodontitis and the higher heterogeneity and the presence of great number of low prevalent taxa in periimplantitis community. Species well described in periodontal disease, such as *P. gingivalis, T. denticola, T forsythia, F. alocis* and *P. micra*, were observed within the 39 most prevalent species in the Periodontitis group. For Periimplantitis group, 17 species composed the core microbiome.

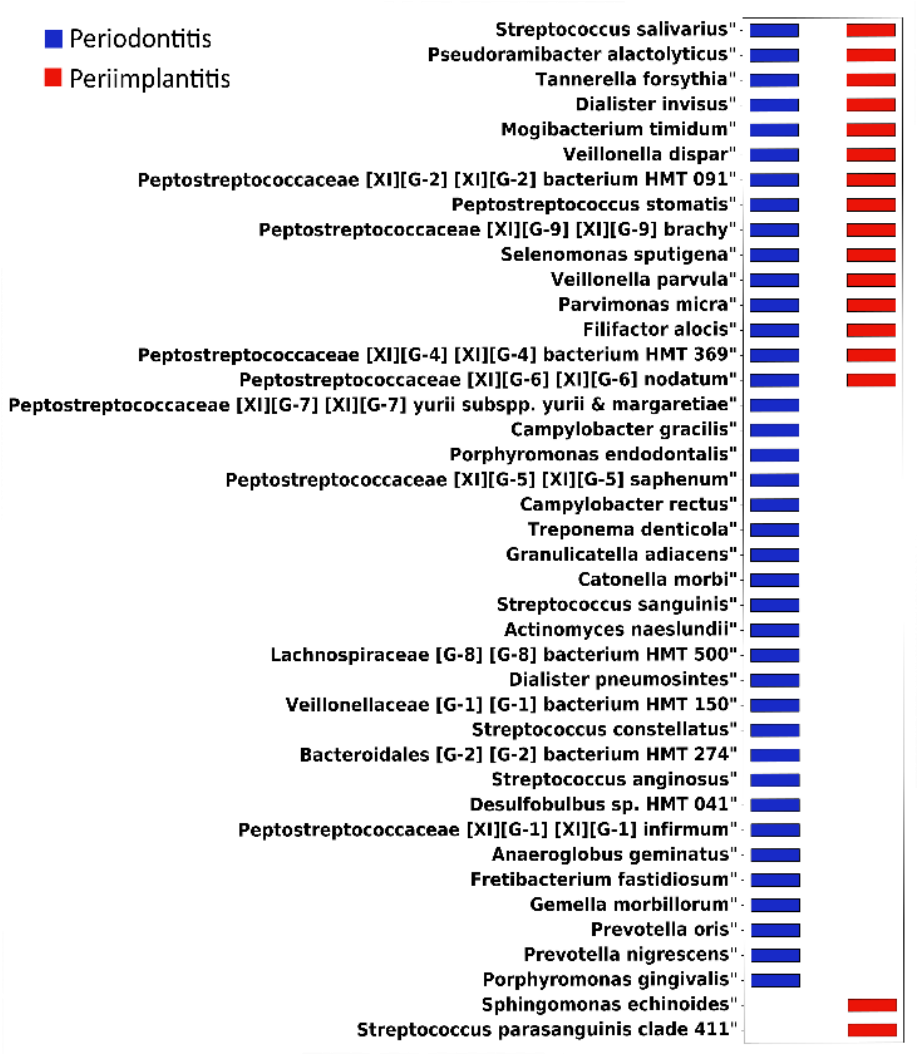

Figure 2. Core microbiome of the periodontitis and peri-implantitis groups. Core microbiome of each group was described as species presented in at least of 50% of the samples from a group.

Additionally, 90 species were described as differentially abundant between groups (figure 3) and they described great differences between periodontitis and periimplantitis communities.

Although most species present in peri-implant disease are also shared in periodontal disease, we can note that species such as *Clostridiales, Streptococcus parasanguinis,* and *Streptococcus mutans, Cutibacterium acnes, Atopobium sp., Stomatobaculum sp*. and *Aerococcus viridans* were differentially more abundant in the peri-implantitis group and with low presence in the periodontitis group. In the periodontitis group, we can observe that species such as *Selenomonas sp., Capnocytophaga granulosa, Campylobacter rectus, Treponema denticola, Capnocytophaga gingivalis, Eikenella corrodens* and several species of *Prevotella*

such as *Prevotella baroniae, Prevotella maculosa, Prevotella nigrescens* were differentially more prevalent.

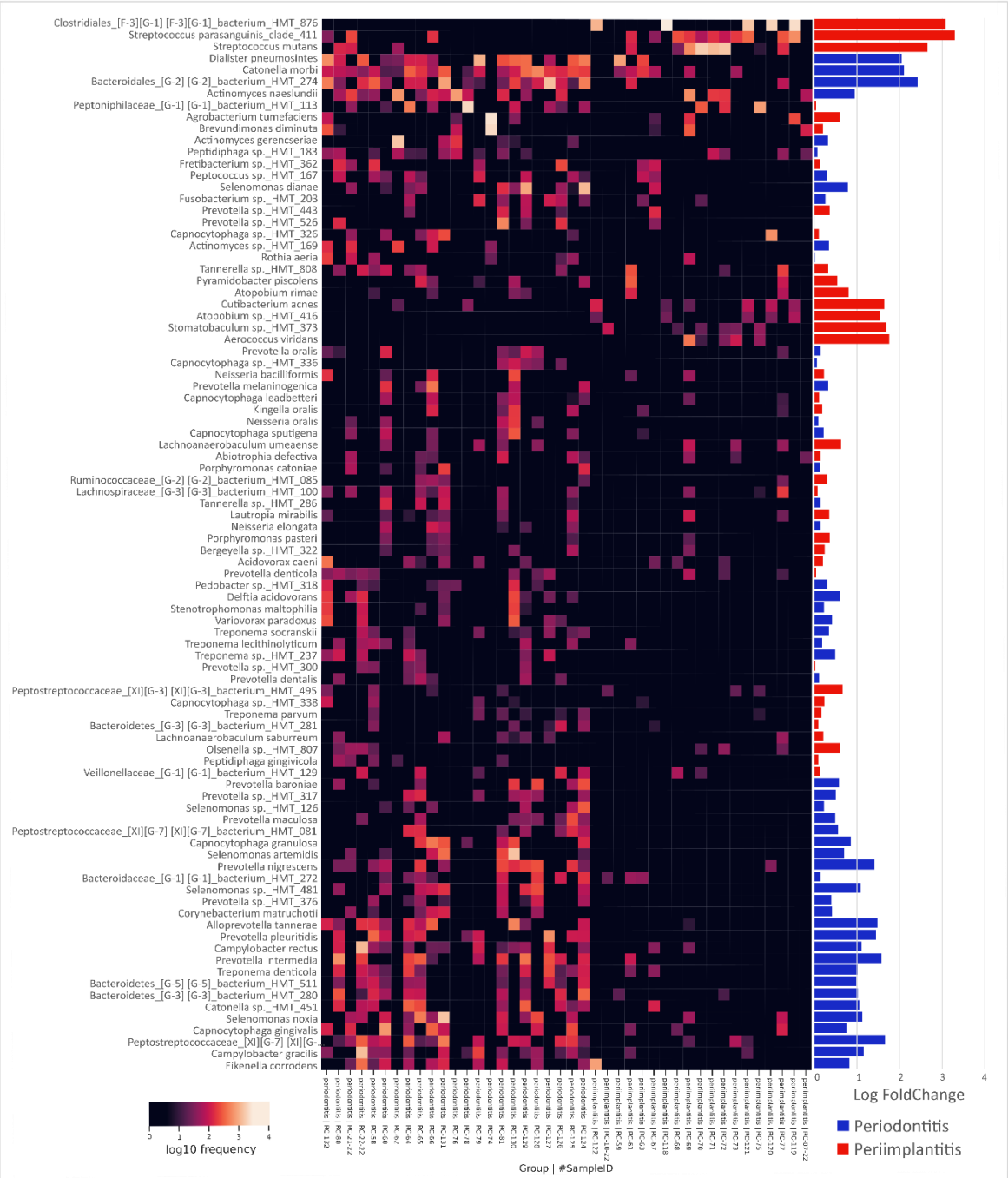

Figure 3. Heatmap of the relative abundance of the differentially abundant species. Species identified as differentially abundant between groups by the ANCOM-BC analysis were included in the heatmap. The relative abundance is described as normalized relative frequencies and the differences between groups was described as log of the fold change. The blue bar represents the species more abundant in Periodontitis and the red bar the more abundant in peri-implantitis.

Table 2. Periodontal/Peri-implant crevicular fluid cytokine profile in periodontitis and peri-implantitis sites.

	Periodontitis		**Peri-implantitis**		
	Mean	SD	**Mean**	SD	*p-value*[#]
IFNy	**2.9**	1.2	**1.6**	1.5	*<0.0001*
IL-10	**3.8**	2.1	**2.3**	1.7	*0.002*
IL-17	**2.1**	0.8	**1.5**	0.7	*0.006*
IL-1β	**74.6**	99.1	**45.1**	121.7	*0.008*
IL-4	**10.6**	16.5	**2.5**	3.5	*<0.001*
TNFa	**4.0**	4.5	**1.7**	1.0	*0.001*
Treg (IL-10) / TH17 (IL-17)	**1.9**	0.9	**1.5**	0.7	*<0.0001*
TH1 (IFN-y) / TH2 (IL-4)	**0.6**	0.4	**3.2**	4.8	*<0.0001*

[#]Student's t test; $p<0.05$.

Regarding the cytokine data, multivariate analysis demonstrated the pattern in the cytokine released for each sample. Six clusters were identified in the data, and they partially differentiate the periodontitis and peri-implantitis samples. Interestingly, most of the peri-implantitis samples were characterized by lower concentration of IL-1β, and lower or medium values of IL-4. Additionally, peri-implantitis presented medium values of IL-17 while most of the periodontitis samples were clustered based on extreme lower or higher values of IL-17.

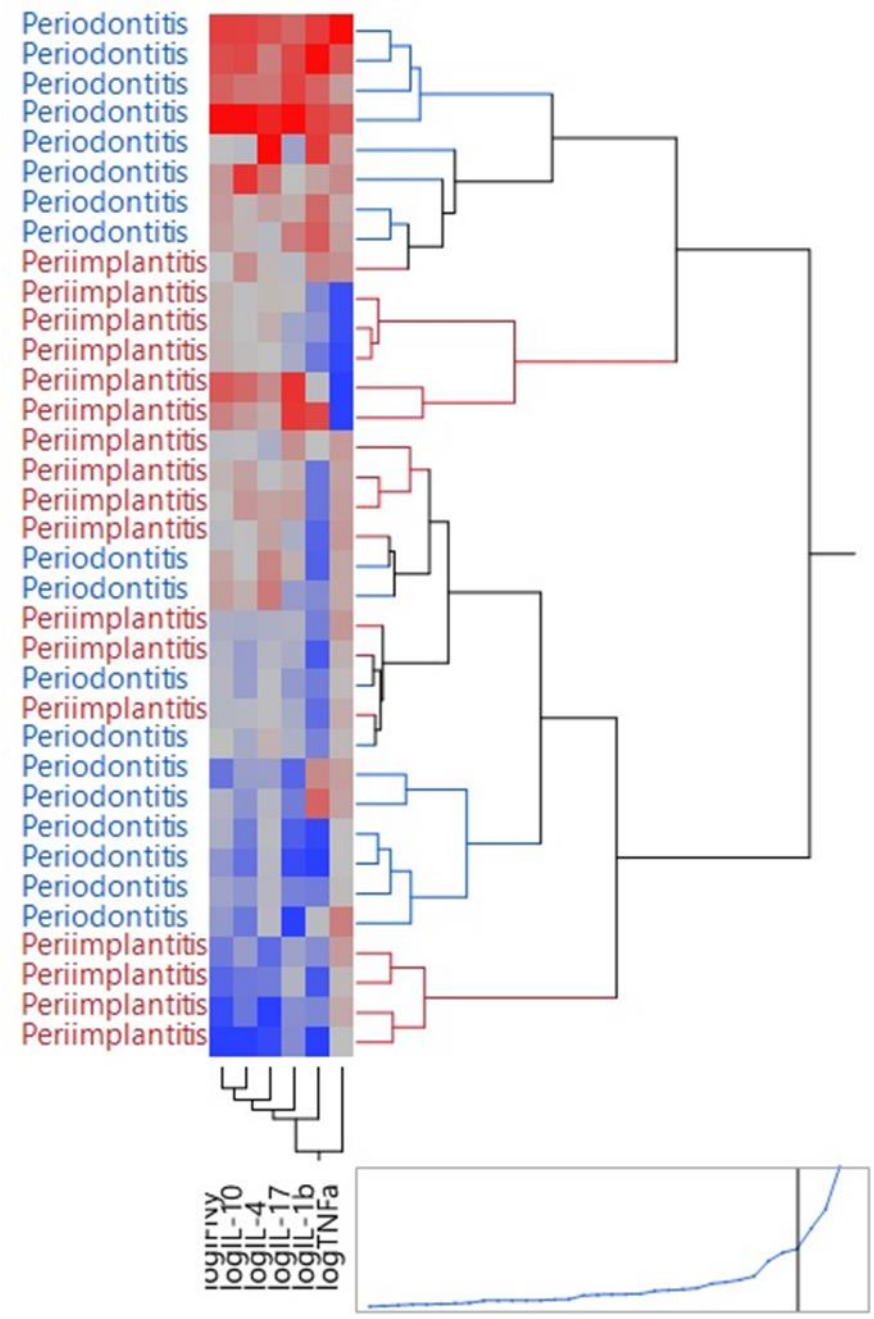

Figure 4. Hierarchical cluster and heatmap of the log transformed cytokines' concentration. The samples and the cytokines were clustered based on similarities in the cytokine released pattern and the cytokine concentrations were represented by the heatmap, where blue colors characterized the lower concentrations and the red tons the higher concentrations.

The PCA and factor analysis also described the importance of the IL-4, IL-1 and IL-17 in differentiating the periodontitis and peri-implantitis samples (Figure 5). The component 4 was the one that most distinguished the groups, and it was positively correlated to the IL-4 and IL-1β concentrations and negatively correlated to the IL-17 levels.

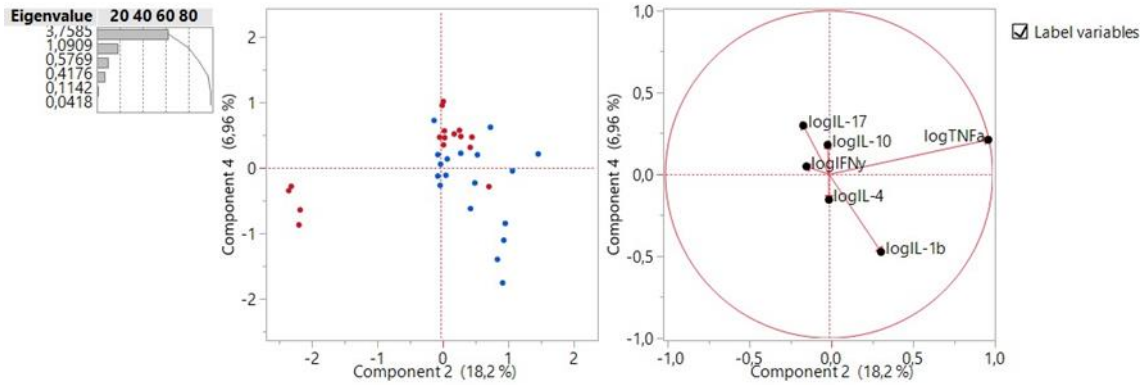

Figure 5. The principal component analysis of the cytokine concentration. The components 2 and 4 were represented in the plots. In the first graph, the red dots represent the peri-implantitis samples coordinates and the blue dots the periodontitis samples. In the second graph, a factor analysis of the cytokines and their correlation with each component were plotted.

DISCUSSION

With the rise of oral rehabilitation with dental implants, much evidence has shown that the most frequent complication of this therapy is inflammation of peri-implant tissues. Peri-implantitis is a clinical challenge for dental surgeons and prevention and treatment strategies for this disease must be integrated with modern concepts of oral rehabilitation (Smeets et al. 2014, Dell'Olmo et al. 2022). Meanwhile, all etiology concepts and also treatment strategies rely on previously acquired knowledge of the periodontal field. Although some studies attempted to understand which features could be characteristic for each disease, up to date, there is no study comparing periodontitis and peri-implantitis sites regarding their microbial community and cytokine profile. The present study shows a significant difference in these microbial-cytokine aspects, which demonstrates that these conditions are distinct entities and should be compared with caution.

Differences between the microbial profiles of the Peri and Perio groups were evaluated using 16S sequencing and both α-diversity and β-diversity. Statistically significant differences can be observed. The peri-implantitis group showed a lower

alpha diversity when compared to the periodontitis group, corroborating previous studies assessing microbial diversity in diseased peri-implant sites (Apatzidou et al. 2017, Daubert et al. 2018), indicating a lower bacterial diversity. Dabdoub et al. 2013 evaluating dental implants and adjacent teeth in a split-mouth design previously demonstrated a lower diversity in diseased implants than teeth at the same clinical condition (2.91 versus 3.03, respectively, p=0.023) at the Shannon index. This dissimilar community at diseased implants could also be noted at β-diversity analysis, when Weighted and mostly Unweighted Unifrac distances, clearly noticed a visible separation between the groups and a significant impact of most rare species for differentiating the two conditions.

Core microbiome analysis confirmed these findings. The periodontitis group had a higher microbial core when compared to the peri-implant disease. Interestingly, among the species exclusively related to Periodontitis, well-known pathobionts could be seen as *P. gingivalis, T. denticola, T. forsythia, F. alocis* and *P. micra* (Gita et al. 2016, Tiwari et al. 2020). Furthermore, only two species are exclusive to the microbial core of peri-implant environment - *Sphingomonas echinoides* and *Streptococcus parasanguinis clade 411. S. parasanguinis* has been previously associated to diseased implants, in a higher abundance, compared to diseased teeth (Dabdoub et al. 2013).

Additionally, heat map analysis (fig 3) reinforces a dissimilar microbiome between dental and implant sites. Of the species of the Socransky's red complex, we noticed that the presence of *Treponema denticola* is more related to the periodontitis group, as it was highly cited in other studies (Cortelli et al. 2013). As well as species: *Selenomonas sp., Capnocytophaga granulosa, Campylobacter rectus, Capnocytophaga gingivalis, Eikenella corrodens* and several species of *Prevotella* such as *Prevotella baroniae, Prevotella maculosa, Prevotella nigrescens* were differentially more expressed in periodontal diseases (Mombelli et al. 2001), being that *Prevotella* and *Selenomonas* were positively correlated with clinical inflammation in both teeth and implant sites (Schincaglia et al. 2017).

When evaluating the peri-implant disease group, species as *Clostridiales, Streptococcus parasanguinis*, *Streptococcus mutans, Cutibacterium acnes, Atopobium sp., Stomatobaculum sp., Treponema parvum*, *Olsenella_HMT_807* and

Aerococcus viridans were the most representative. These results corroborate studies such as the one by Kröger et al. 2018, who evaluated the microbiome at different levels of peri-implantitis severity and observed a greater abundance of the *Clostridiales bacterium* species, mainly in deeper peri-implant pockets. Dabdoub et al. 2013 also observed a higher abundance of *Atopobium rimae* at diseased implants, as occurred with *S. parasanguinis*. Moreover, the same occurred with *Streptococcus mutans*, which, despite being a bacterium highly related to the progression of caries disease (Banas & Drake, 2018), has been shown to be present at high levels in the diseased peri-implant environment (Kumar et al. 2012, Souza et al. 2013, Meza-Siccha et al. 2019).

Altogether, peri-implantitis sites are dominated by a less diverse and dissimilar community than teeth. However, microbial analysis at implant sites should consider specific features that could affect this community. Bacterial colonization, for example, is highly influenced by the topographical characteristics of the environment (Perera-Costa et al. 2014). Thus, evaluation of different implants, the non-standardization of the prosthetic components, and other characteristics linked to rehabilitation, such as surface roughness, type of metal used and surface energy, could affect this community (Teughels et al. 2006, Robitaille et al. 2016) . Indeed, these implant-related characteristics appear to drive the community highly than other oral niches. Dabdoub et al. 2013 assessing the congruence between adjacent peri-implant and periodontal microbiomes, observed that 60% of individuals share less than 50% of all species between their periodontal and peri-implant biofilms, and 85% of subjects share less than 8% of abundant species between tooth and implant (Dabdoub et al. 2013). Along with the topological pattern, dental and implant sites present significant histological differences, where an adaptation of the mucoperiosteal tissues to the transmucosal component of the implant (Thoma et al. 2014), along with different distribution of epithelium, fibers, cells, contribute to creating distinct ecosystems, affecting not only microbial but even the immunological aspects.

It is well established that, despite presenting similar symptoms to periodontitis, the peri-implant disease presents a faster progression of bone destruction. (Lindhe et al. 1992). In addition to the microbiological component, we must pay attention to the local immune response driven by the community harboring each environment. Cytokines are proteins synthesized during the patient's immune response and are capable of inducing osteoclastic activity and promoting peri-implant attachment loss

(Javed et al. 2011). Previous studies that evaluated pro- and anti-inflammatory mediators produced by the host demonstrated that peri-implant sites during mucositis development showed that, although tend to accumulate less biofilm, implants present a tendency to higher concentrations of inflammatory mediators (Schincaglia et al. 2017). This information contradicts the findings of this study, once there are significant changes in the microbiome of each condition. Furthermore, the local analysis of peri-implant crevicular fluid showed a differential host-related cytokine than dental sites.

Our adaptive immune response can be divided into humoral (B lymphocytes generating antibodies) and cellular mediated, the latter being represented by T lymphocytes that can be subdivided into helper or cytotoxic. Helper T lymphocytes can be classified into 4 distinct subgroups involved in antigen recognition and confrontation, these are divided into Th1, Th2, Th17 and Treg. The subpopulation of T cells called Th1, stimulates the production of cytokines IL-12, IFN-g, and TNF-a and are involved in inflammatory responses and in the activation of macrophages and cytotoxic T cells, while the Th2 subpopulation stimulates: IL -4, IL-5 and IL-13 and is involved in inducing B cell responses (antibody production) and anti-inflammatory responses (down-regulating pro-inflammatory macrophage activation) (Zhang et al. 2011). Th17 is related to the production of pro-inflammatory cytokines (IL-17, IL-21, IL-22) and activation of neutrophils (Jadidi & Mirshafiey, 2011) and finally, Treg has a regulatory function of inhibition of Th1, Th2 and Tc-mediated immune responses and is related to the production of TGFb, IL-10 and IL-35 (Braga et al. 2011). Any disruption in the balance between these host-response pathways could represent a tissue breakdown.

Assessing the different Th representants, we realized that in the peri-implantitis group there is response prone to a higher production of Th1- which is related to an acute-phase reaction to pathogens (Gigi et al. 2008) and lower production of Th2- which is related to the elimination of antigens and recovery of diseases (Gigi et al. 2008). Furthermore peri-implantitis environment was also related to an increase in Th17 production, which modifies the immune response, as it is related to inflammatory and autoimmune responses (Infante-Duarte et al. 2000) and can induce local inflammation in the target organs and also aid B cells in production of antibodies (Doreau et al. 2009).

Clustering the concentration of those cytokines (fig.4), there was a clear separation of seven clusters, which shows that most of the peri-implantitis samples were characterized by low concentration of IL-1β and medium-to-low values of IL-4. This data corroborates the results of other studies which also found an increased concentration of IL-1β in periodontal disease sites when compared to peri-implant sites (Schierano et al. 2008, Schincaglia et al. al. 2017). From our results, the marked immune response of periodontal disease was more associated with increased expression of IL-1β and IL-4. IL-1β is one of the main pro-inflammatory cytokines that is linked to bone resorption and induction of tissue-degrading proteinase production. This cytokine participates in inflammatory processes, immune regulation, and bone resorption, and the biological effects are directly linked to its concentration in tissues, which is high in periodontitis (Cheng et al. 2020).

However, IL-4 has been shown as a cytokine with a tissue-protective effect, as it has functions, for example, to decrease the function of macrophages, act as a mitogen of B cells and induce their differentiation after stimulation with LPS from bacteria, stimulate the change of the B cell isotype from IgM to IgE, among others (Anovazzi et al. 2013). Additionally, the cytokine IL-17 was also extensively evaluated in other studies, IL-17-secreting cells are being documented in inflammatory lesions of patients diagnosed with various inflammatory and autoimmune diseases, such as psoriasis, rheumatoid arthritis, type 1 diabetes and even periodontitis (Gaffen et al. 2014; Zenobia & Hajishengallis, 2015). Many studies have found that IL-17 expression was higher in patients with periodontitis compared to gingivitis and almost undetectable in healthy tissues (Honda et al. 2008; Okui et al. 2012; Moutsopoulos et al. 2012). Furthermore, they also demonstrated that patients with aggressive periodontitis had higher levels of IL-17 when compared to patients with chronic periodontitis (Shaker & Ghallab, 2012). Such results indicate a correlation of the expression of this mediator with disease severity and clinical parameters of periodontal destruction (Johnson et al. 2004; Lester et al. 2007; Dutzan et al. 2012). Severino et al. 2011 compared cytokine levels in healthy and diseased implants and found that in the peri-implantitis group, there was an increase in IL-17 inducing the production of other pro-inflammatory cytokines, contributing to the pathogenesis of bone loss in the peri-implant environment.

The principal component analysis (Fig. 5) was also important for the discrimination between the peri-implantitis and periodontitis groups, confirming the main role of IL-4 and IL-1β for periodontitis and a positive correlation with IL-17 levels with peri-implantitis. Although in this study both sites were affected by the disease, the different panels of predominant host response indicate a difference in cell functions and host response during the microbial challenge, which is essential to a better understanding of etiopathogenesis.

Meanwhile, is it remarkable that tissue destruction – periodontal or peri-implant – is the result of an intrinsic microbial-immune interaction. In this trial, both players of this cascade were different at each niche, but, in some kind, they should be considered together to explain disease. Within the the discriminative bacteria mentioned above, some studies have also linked their presence to specific host response activation. Socransky et al. 1998 demonstrated that IL-1 genotype positive subjects harbored higher levels of pathogens associated with periodontal dysbiosis, such as *T. denticola* and *C. rectus* and that both the relationship of periodontopathogens and the presence of IL-1β were associated with periodontitis in the same magnitude, indicating that these could be considered as markers for the disease (Gursoy et al. 2009). In addition to these associations, maternal infection of *C. rectus* has been shown to induce placental inflammation and decidual hyperplasia as well as a concomitant increase in fetal brain IFN-ɣ (Offenbacher et al. 2005). Thus, although this couldn't be determined in this transversal study, it is probably that peri-implantitis disease is the result of a non-classical periodontitis community and this specific microbiota activate different pathways in the host, resulting in a differential clinical phenotype.

The importance of knowing the microbiome profile and which biomarkers are most related to each disease becomes evident, so that the professional can plan the best approach for their treatment. Future studies may relate these microbiome profile and biomarkers to peri-implantitis and chronic periodontitis diseases in a greater number of participants, given the limited number of participants in this research. In addition, a comparison with a health control case could also be performed so that the microbiome profile driving a dysbiotic state and the relationship of these cytokines that drive the inflammatory profile of these diseases is even more evident. However, despite that, this study already evidences certain relationships of different

microbiome profiles and cytokines with both diseases that can serve as a basis for further studies of this relationship already established.

In conclusion, despite being similar, these diseases have different characteristics: although peri-implantitis is related to a lower microbiological diversity, it is associated with a reduction in Th2 in the immune response, with an increase in Th17 when compared to periodontitis. The knowledge of these differences will help to establish individual therapy protocols that will be more efficient for each one of them.

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3 CONCLUSÃO

Conclui-se que, apesar de semelhantes clinicamente, a Periodontite e a Peri-implantite apresentam comunidades microbianas e padrões inflamatórios distintos, representando um ambiente distinto de destruição tecidual, o que deve ser considerado no tratamento e nos aspectos preventivos destas condições.

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Assinado por:
jacks jorge junior
(Coordenador(a))

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Bairro: Areião **CEP:** 13.414-903
UF: SP **Município:** PIRACICABA
Telefone: (19)2106-5349 **Fax:** (19)2106-5349 **E-mail:** cep@fop.unicamp.br

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Authors
Bonilha, Gabriela
Casarin, Renato
Paz, Hélvis
Cerântola, Thayane
Stolf, Camila
Casati, Márcio
Monteiro, Mabelle
Pimentel, Suzana
Noronha, Melline
Carvalho, Lucas
Shaddox, Luciana
Santamaria, Mauro
Fernandes, Willian

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