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Tratamiento no quirúrgico de la periimplantitis

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Dña. Carlota Blanco Reboredo,

Declara no tener ningún conflicto de interés con esta tesis doctoral.

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A mis padres,

porque todas las metas que consigo
es gracias a vosotros.

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CONTENIDOS

AGRADECIMIENTOS **15**

RESUMEN **17**

RESUMO **19**

ABSTRACT **21**

ABREVIATURAS **23**

1. INTRODUCCIÓN **27**

1.1. ENFERMEDADES PERIIMPLANTARIAS 27

1.1.1. Definición 27

1.1.2. Epidemiología 28

1.1.3. Patogénesis 29

1.1.3.1. Progresión de mucositis a periimplantitis 29

1.1.3.2. Inicio y progresión de la enfermedad 30

1.1.4. Características microbiológicas 32

1.1.5. Factores / indicadores de riesgo 34

1.1.5.1. Relacionados con el paciente 34

- Historia de periodontitis: 34
- Ausencia de mantenimiento periodontal: 35
- Control de placa: 36
- Tabaco: 36
- Diabetes: 37

1.1.5.2. Relacionados con el implante 38

- Mucosa queratinizada: 38
- Profundidad de vestíbulo: 39
- Infección residual: 39

1.1.5.3. Relacionados con la prótesis 39

- Exceso de cemento: 39

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

- Restauraciones sobrecontorneadas: 40

1.1.5.4. Relacionados con el operador 40

- Factores iatrogénicos: 40

1.1.6. Relación entre la periimplantitis y la inflamación sistémica 41

1.1.6.1. Concepto de inflamación sistémica de grado bajo 41

1.1.6.2. Relación entre la periodontitis y la inflamación sistémica de grado bajo 41

1.1.6.3. Evidencia de la relación de la periimplantitis con la inflamación sistémica 43

1.1.7. Tratamiento de la periimplantitis 44

1.1.7.1. Tratamiento no quirúrgico de la periimplantitis 45

- Curetas y ultrasonidos 46
- Aeropulidores 46
- Láser 47
- Terapia fotodinámica 48
- Antisépticos 49
- Antimicrobianos locales 50
- Probióticos 52
- Antibióticos sistémicos 52

1.1.7.2. Tratamiento quirúrgico de la periimplantitis 54

- Eficacia del tratamiento quirúrgico con cirugía de acceso o cirugía resectiva: 54
- Eficacia del tratamiento quirúrgico con cirugía reconstructiva: 55

2. JUSTIFICACIÓN E HIPÓTESIS 59

2.1. JUSTIFICACIÓN 59

2.2. HIPÓTESIS 60

2.2.1. Hipótesis Nula 60

2.2.2. Hipótesis Alternativa 60

3. OBJETIVOS 63

3.1. OBJETIVOS GENERALES 63

3.2. OBJETIVOS ESPECÍFICOS 63

4. MATERIAL Y MÉTODOS. RESULTADOS 67

4.1. ESTUDIO #1 68

USC DE SANTIAGO DE COMPOSTELA

4.1.1. Objetivo 68
4.1.2. Material y métodos 68
4.1.3. Resultados 68
4.1.4. Conclusiones 68
4.2. ESTUDIO #2 79
4.2.1. Objetivo 79
4.2.2. Material y métodos 79
4.2.3. Resultados 79
4.2.4. Conclusiones 79
4.3. ESTUDIO #3 95
4.3.1. Objetivo 95
4.3.2. Material y métodos 95
4.3.3. Resultados 95
4.3.4. Conclusiones 95
4.4. ESTUDIO #4 107
4.4.1. Objetivo 107
4.4.2. Material y métodos 107
4.4.3. Resultados 107
4.4.4. Conclusiones 107

5. DISCUSIÓN 123

6. CONCLUSIONES 139

7. REFERENCIAS BIBLIOGRÁFICAS 143

8. ANEXOS 171

8.1. ÍNDICES DE CALIDAD DE LAS PUBLICACIONES. 171
8.1.1. Adjunctive systemic metronidazole to nonsurgical therapy of peri-implantitis with intrabony defects: a retrospective case series study. 171
8.1.2. Adjunctive benefits of systemic metronidazole on non-surgical treatment of peri-implantitis. A randomized placebo-controlled clinical trial. 172
8.1.3. Peri-implantitis, systemic inflammation, and dyslipidemia: a cross-sectional biochemical study. 173
8.1.4. The systemic impact of non-surgical treatment of peri-implantitis with or without adjunctive systemic metronidazole: Secondary analysis of a randomized clinical trial. 174

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

8.2. ÍNDICES DE TABLAS Y FIGURAS 177
8.2.1. Tablas…… 177
8.2.2. Figuras……..... 177
8.3. DICTAMEN COMITÉ ÉTICO DE GALICIA..... 179

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UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

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RESUMEN

Hasta el momento el tratamiento no quirúrgico de la periimplantitis había demostrado ser ineficaz para el control de la enfermedad. Pero, una serie de publicaciones de casos han mostrado el posible beneficio adicional del tratamiento no quirúrgico en combinación con antibiótico sistémico. Teniendo en cuenta estos resultados clínicos prometedores, llevamos a cabo esta investigación en la cual el objetivo fue evaluar la eficacia del tratamiento no quirúrgico de la periimplantitis junto con metronidazol y su posible asociación con la inflamación sistémica. Para ello se llevaron a cabo cuatro investigaciones, en los cuales incluimos una serie de casos donde mostramos el efecto de esta terapia de tratamiento sobre las lesiones de periimplantitis, un estudio transversal para estudiar la implicación de la periimplantitis en los biomarcadores sistémicos, y un ensayo clínico aleatorizado a triple ciego que dividimos en dos partes para evaluar la eficacia de este tratamiento a nivel clínico, radiográfico y microbiológico y por otro lado su implicación en los biomarcadores sistémicos. Tras llevar a cabo estas investigaciones observamos que el tratamiento no quirúrgico junto con el uso coadyuvante de metronidazol es efectivo en la reducción de la inflamación, ganancia ósea radiográfica y reducción de la carga bacteriana en las lesiones de periimplantitis, y se consigue la resolución de la periimplantitis es más de la mitad de los casos tratados y por otro lado abrimos una vía de investigación donde se observa una posible relación entre la periimplantitis y la inflamación sistémica de bajo grado, ya que observamos un aumento de biomarcadores inflamatorios en pacientes con periimplantitis y mostramos cómo su tratamiento puede repercutir a nivel sistémico en la reducción de la inflamación.

Palabras clave: periimplantitis, tratamiento no quirúrgico, antibiótico, inflamación, biomarcadores sistémicos.

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RESUMO

Ata agora, o tratamento non cirúrxico da periimplantite demostrou ser ineficaz para controlar esta enfermidade. Pero, unha serie de publicacións de casos mostraron o posible beneficio adicional do tratamento non cirúrxico en combinación con antibióticos sistémicos. Tendo en conta estes prometedores resultados clínicos, realizamos esta investigación na que o obxectivo era avaliar a eficacia do tratamento non cirúrxico da periimplantite xunto co metronidazol e a súa posible asociación coa inflamación sistémica. Para iso realizáronse catro investigacións, nas que incluímos unha serie de casos nos que se mostra o efecto deste tratamento terapéutico nas lesións de periimplantite, un estudo transversal para estudar a implicación da periimplantite nos biomarcadores sistémicos e un ensaio clínico aleatorizado triple cego que dividimos en dúas partes para avaliar a eficacia deste tratamento a nivel clínico, radiográfico e microbiolóxico e, por outra banda, a súa implicación nos biomarcadores sistémicos. Despois de realizar estas investigacións, observamos que o tratamento non cirúrxico xunto co uso adyuvante de metronidazol é efectivo para reducir a inflamación, a ganancia ósea radiográfica e a redución da carga bacteriana nas lesións de periimplantite, e conséguese a resolución da enfermidade en máis da metade dos casos tratados, e por outra banda abrimos unha vía de investigación onde se observa unha posible relación entre a periimplantite e a inflamación sistémica de baixo grao, posto que observamos un aumento dos biomarcadores inflamatorios en pacientes con periimplantite, e mostramos como o seu tratamento pode ter un impacto sistémico na redución da inflamación.

Palabras chave: periimplantite, tratamento non cirúrxico, antibiótico, inflamación, biomarcadores sistémicos

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ABSTRACT

Until now, non-surgical treatment of peri-implantitis has not proven to be effective in controlling this disease. However, case series reports have shown the possible additional benefit of non-surgical treatment in combination with systemic antibiotics. Taking into account these promising clinical results, we conducted this research in which the aim was to evaluate the efficacy of non-surgical treatment of peri-implantitis with adjuntive metronidazole and its possible association with systemic inflammation. To this end, four investigations were carried out, in which we included a case series where we showed the effect of this treatment therapy on peri-implantitis lesions, a cross-sectional study to evaluate the involvement of peri-implantitis in systemic biomarkers, and a triple-blind randomized clinical trial that we divided into two parts to evaluate the efficacy of this treatment at the clinical, radiographic and microbiological level and, on the other hand, its involvement in systemic biomarkers. After carrying out these investigations, we observed that non-surgical treatment with the adjuvant use of metronidazole is effective in reducing inflammation parameters, a radiographic bone gain and reducing the bacterial load in peri-implantitis lesions, and resolution of peri-implantitis is achieved in more than half of the cases treated. On the other hand, we opened a line of research where a possible relationship between peri-implantitis and low-grade systemic inflammation is observed, since we observed an increase in inflammatory biomarkers in patients with peri-implantitis and we show how its treatment can have a systemic impact on reducing inflammation.

Keywords: peri-implantitis, non-surgical treatment, antibiotic, inflammation, systemic biomarkers.

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ABREVIATURAS

AMX:	amoxicilina
APR:	reactante de fase aguda
aPDT:	terapia fotodinámica
BoP:	sangrado al sondaje
CAL:	nivel de inserción clínica
CHX:	clorhexidina
EC:	células endoteliales
EP:	enfermedad periodontal
Hs- PCR:	proteína C reactiva de alta sensibilidad
ICT:	infiltrado de células inflamatorias
IL:	interleucina
KM:	mucosa queratinizada
LDL:	lipoproteína de baja densidad
LGI:	inflamación de grado bajo
LPS:	lipopolisacáridos
MTZ:	metronidazol
NSPIT:	tratamiento no quirúrgico periimplantitis
OR:	odd ratio

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PCR:	proteína C reactiva
PGE:	prostaglandina
PMN:	polimorfonucleares
PS:	profundidad de sondaje
PTFE:	politetrafluoroetileno
RCT:	ensayo clínico aleatorizado
TNF:	factor de necrosis tumoral
US:	ultrasonido
WBC:	glóbulos blancos
VD:	profundidad de vestíbulo

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1

Introducción

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1. INTRODUCCIÓN

1.1. ENFERMEDADES PERIIMPLANTARIAS

1.1.1. Definición

Las enfermedades periimplantarias fueron descritas por primera vez en el Primer *Workshop* de Periodoncia de 1993. Desde esta fecha, se han dado diferentes definiciones de estas entidades patológicas. De acuerdo con el último *Workshop* de 2017, las enfermedades periimplantarias son condiciones inflamatorias inducidas por la acumulación de bacterias patógenas que se adhieren a la superficie del implante formando biopelículas (Berglundh et al., 2018). Se pueden distinguir dos condiciones patológicas: la mucositis periimplantaria y la periimplantitis.

- Mucositis periimplantaria: condición patológica inducida por placa que afecta a los tejidos blandos que rodean al implante dental, caracterizada por ser una lesión inflamatoria de la mucosa que rodea al implante, sin pérdida del hueso de soporte periimplantario más allá de los cambios como resultado de la remodelación ósea inicial (Heitz-Mayfield & Salvi, 2018).

- Periimplantitis: condición patológica inducida por placa que afecta a los tejidos que rodean al implante dental, caracterizada por la inflamación de la mucosa periimplantaria y pérdida progresiva de hueso de soporte del implante (Schwarz et al., 2018).

La presencia de una lesión inflamatoria es común en ambas condiciones patológicas, la diferencia entre ambas es la presencia o ausencia de la pérdida progresiva del hueso de soporte (Lindhe & Meyle, 2008).

Desde el punto de vista clínico podemos distinguir tres entidades bien definidas en los tejidos que rodean al implante (tabla 1) (Berglundh et al., 2018; Tonetti et al., 2023).

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Tabla 1. Diagnóstico condiciones periimplantarias	
Condición periimplantaria	**Principales características clínicas**
Salud periimplantaria	*Ausencia de*: • Eritema • Sangrado al sondaje o una localización con sangrado al sondaje • Aumento de la profundidad de sondaje • Supuración
Mucositis periimplantaria	*Presencia de:* • Eritema • + 2 localización con sangrado al sondaje • Aumento de la profundidad de sondaje • Supuración *Ausencia de:* • Pérdida ósea
Periimplantitis	*Presencia de:* • Eritema • Sangrado al sondaje • Aumento de la profundidad de sondaje y/o recesión del margen de la mucosa • Supuración • Pérdida ósea *En ausencia de registros previos:* • Presencia de sangrado y/o supuración al sondaje • Profundidad de sondaje ≥ 6mm • Pérdida de hueso ≥ 3mm apical al hombro intraóseo del implante

1.1.2. Epidemiología

La prevalencia de la periimplantitis ha sido muy variable a lo largo de los años, debido sobre todo a la falta de un consenso en la definición de esta enfermedad. La variabilidad en la prevalencia se muestra de manera clara en el estudio llevado a cabo por Derks y cols. (Derks, Schaller, et al., 2016a), en el cual analizaron los resultados según la cantidad de pérdida de hueso del implante, de esta manera las prevalencias oscilaron desde un 45% (pérdida de hueso >0,5mm), 26,9% (pérdida de hueso >1mm), 14,5% (pérdida de hueso >2mm), 10,1% (pérdida de hueso >3mm) y 5,9% (pérdida de hueso >4mm). Además, se llevaron a cabo dos metaanálisis donde analizaron los resultados de estudios epidemiológicos y se muestran prevalencias que oscilan desde el 1% al 47% (Monje et al., 2016) y del 12,5% al 36,5% (Derks & Tomasi, 2015).

Una característica importante en relación con la prevalencia de la periimplantitis es que no tiene el mismo patrón de progresión en todos los implantes. A diferencia de la mayoría de las formas de periodontitis, la periimplantitis no progresa de manera uniforme

alrededor de todos los implantes. Esto significa que la prevalencia evaluada a nivel de paciente puede sobreestimar la frecuencia de implantes afectados. Por lo que las prevalencias de esta enfermedad se deben analizar no solo a nivel de paciente sino también a nivel de implante.

Teniendo en cuenta la definición del *Workshop* de periodoncia del 2017 la prevalencia de esta enfermedad en España es del 20% a nivel de implante, y del 24% a nivel de paciente (Rodrigo et al., 2018).

1.1.3. Patogénesis

El factor etiológico primario para el inicio y progresión de la enfermedad es la presencia de bacterias patógenas que se adhieren a la superficie del implante formando comunidades complejas, denominadas biopelículas (Berglundh et al., 1992) (Zitzmann et al., 2002), pero la respuesta inflamatoria local resultante y el desequilibrio entre la interacción huésped – parásito son la clave en la patogénesis de la destrucción del tejido.

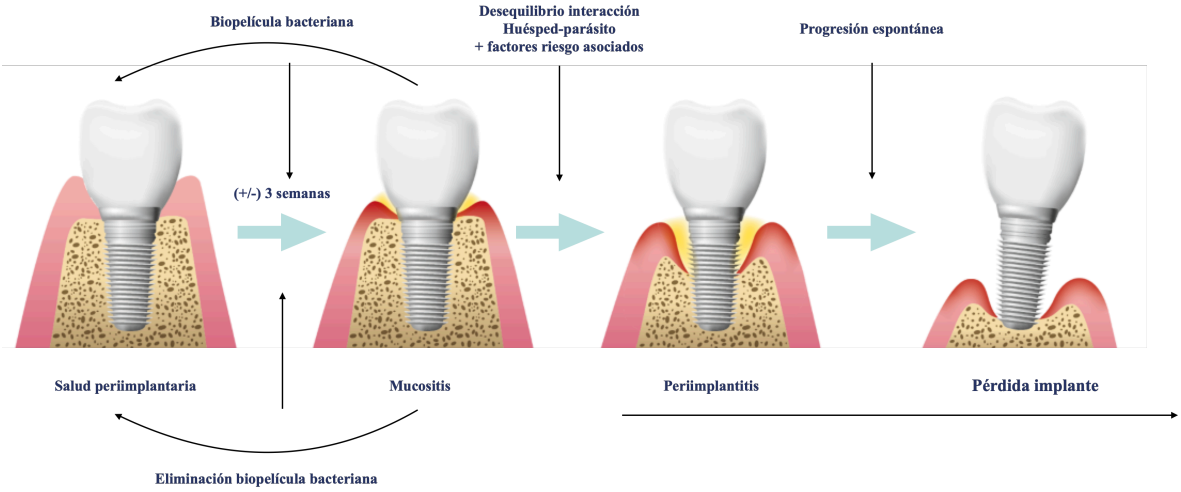


Figura 1.Esquema patogénesis periimplantitis.

1.1.3.1. Progresión de mucositis a periimplantitis

Al igual que en las enfermedades periodontales la gingivitis es precursora a la periodontitis, en las enfermedades periimplantarias siguen ese mismo patrón, en el cual la mucositis es precursora a la periimplantitis (Zitzmann et al., 2001).

La mucositis periimplantaria se desarrolla a partir de una mucosa periimplantaria sana después de la acumulación de biopelículas bacterianas alrededor de los implantes

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dentales osteointegrados en contacto con la mucosa periimplantaria durante al menos 3 semanas (Pontoriero et al., 1994). Existe una relación causa - efecto entre la acumulación de biopelículas bacterianas alrededor de los implantes y el desarrollo de la respuesta inflamatoria. Además, se ha demostrado que la mucositis es clínicamente reversible después la restitución del control de la biopelícula, aunque puede llevar más de 3 semanas para la reversibilidad clínica (Salvi et al., 2012).

Desde el punto de vista clínico, la conversión de mucositis a periimplantitis se evaluó en un estudio observacional retrospectivo que incluyó a 80 pacientes que inicialmente padecían mucositis periimplantaria (Costa et al., 2012). Durante 5 años, la incidencia de periimplantitis fue menor en aquellos pacientes que seguían un programa de mantenimiento periodontal (18%) que en aquellos que no se llevó a cabo el programa de mantenimiento periodontal (43%). Por lo que la conversión de mucositis a periimplantitis se correlacionó positivamente con el tiempo de función, particularmente en ausencia de mantenimiento periodontal.

Desde el punto de vista histológico, la reacción inflamatoria de los tejidos frente a la formación de placa se ha estudiado tanto en estudios en animales como en humanos (Abrahamsson et al., 1998; Ericsson et al., 1995; Schwarz et al., 2014). En el análisis histológico se observa un infiltrado de células inflamatorias (ICT) con distintos grados en su extensión apical, lateral al epitelio y separada de la cresta ósea por una zona de tejido conectivo sano de alrededor de 1.0 y 1.9mm. El mecanismo exacto de cómo este ICT se extiende apical a la cresta provocando la pérdida de hueso todavía está sin determinar.

1.1.3.2. Inicio y progresión de la enfermedad

Desde el punto de vista clínico, no hay estudios prospectivos que evalúen el inicio y progresión de la periimplantitis de manera natural. Sin embargo, se llevaron a cabo estudios observacionales retrospectivos (Derks, Schaller, et al., 2016b; Fransson et al., 2010; Lee et al., 2017; Papantonopoulos et al., 2015) que proporcionan estimaciones sobre el inicio y patrón de pérdida ósea asociada a la periimplantitis. Los datos que se proporcionan en estos estudios indican que:

- La prevalencia de estas lesiones está relacionada con el tiempo de función. Los implantes con más tiempo en función tienen mayor riesgo de desarrollar periimplantitis.
- El inicio se desarrolla desde los 3 años en función.
- El inicio se relaciona con factores predisponentes locales.

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- La periimplantitis progresa con un patrón no lineal y acelerado.

Desde el punto de vista histológico, se han llevado a cabo numerosos estudios en animales para evaluar la periimplantitis experimental con el denominado "modelo de ligadura"(Lindhe et al., 1992). El protocolo comprende una fase de destrucción activa del tejido alrededor de los implantes osteointegrados, en el cual se coloca una ligadura en una posición submucosa, esta rompe el sellado mucoso del implante y además promueve la formación de biopelículas bacterianas. La lesión inflamatoria resultante inicia la destrucción del tejido, incluida la pérdida ósea. Además, una vez eliminadas las ligaduras y bajo la formación continua de placa, puede ocurrir la progresión de la enfermedad. Este modelo de estudio busca imitar la periimplantitis que se produce de manera natural y se basa en el modelo llevado a cabo anteriormente de la periodontitis experimental. En los estudios (Albouy et al., 2009; Carcuac et al., 2013; Carcuac & Berglundh, 2014; Lindhe et al., 1992; Schwarz, Sculean, et al., 2015) se observa que, a diferencia de la periodontitis:

- El ICT se extiende apical al epitelio de unión con invasión del tejido conectivo.
- Tamaño de la lesión más del doble que en periodontitis (3.5 mm2 vs. 1.5 mm2).
- Gran cantidad de infiltrado inflamatorio (↑↑↑células plasmáticas,↑↑↑ polimorfonucleares y ↑↑↑macrófagos) con mayor cantidad de vasos sanguíneos y desaparición casi total del colágeno y fibroblastos.
- Algunas localizaciones muestran el epitelio de la bolsa ulcerado.
- Ausencia de barrera epitelial entre la lesión y la biopelícula, por lo tanto, hay una potencial invasión del tejido conectivo subepitelial.
- Las zonas laterales y apicales al ICT se extienden a la cresta ósea, cuya superficie está cubierta de osteoclastos (lesión no encapsulada).
- Capacidad de progresión espontánea.
- Las características de la superficie del implante influyen en su progresión, siendo mayor en los implantes con superficie modificada.

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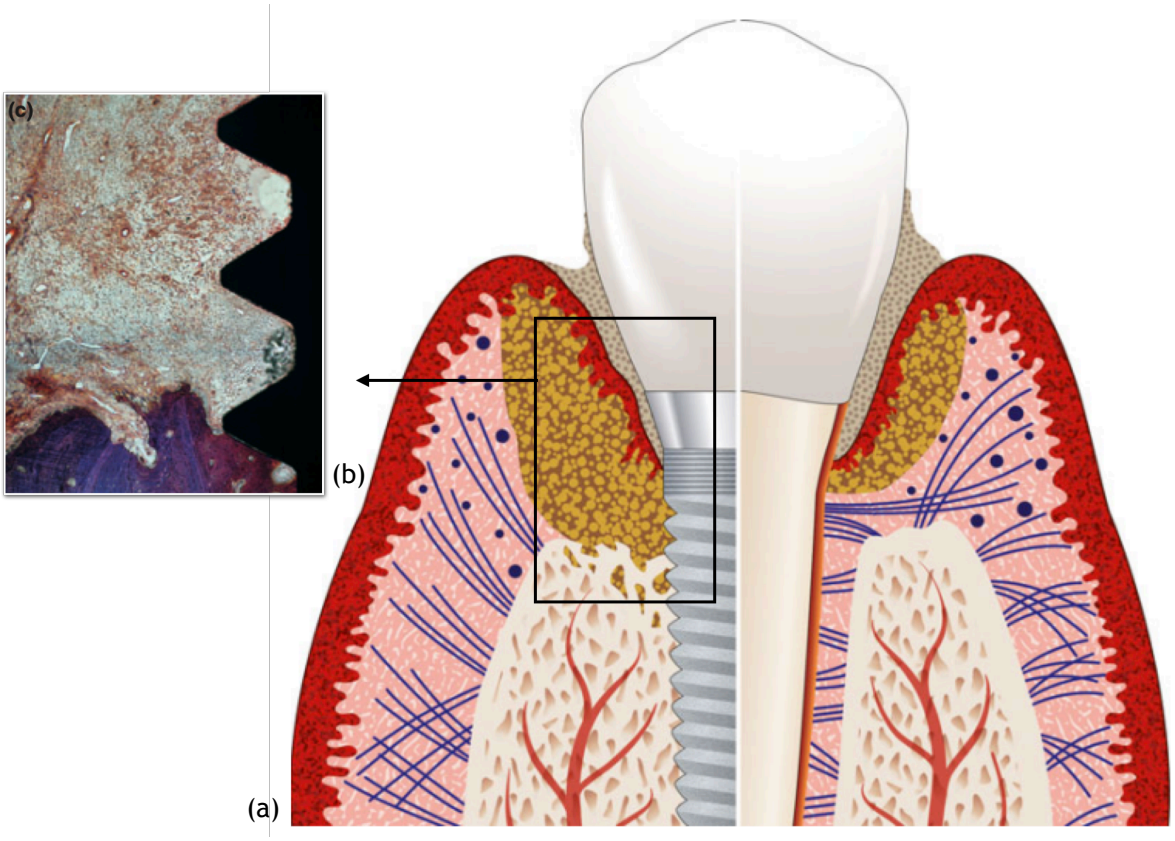


Figura 2. Lesiones periodontitis versus periimplantitis. (a) Estructura de la lesión inflamatoria alrededor de un diente e implante (imagen copyright © Renvert - Giovannolli. Peri-implantitis, reproducida con permiso de Quintessence). (b) Imagen histológica de la extensión del ICT (adaptada de (Carcuac et al., 2013) y reproducida con permiso de John Wiley and Sons).

Las características histopatológicas de las lesiones de periimplantitis han mostrado ser más destructivas en comparación con la periodontitis experimental (Berglundh et al., 2011). Estas diferencias pueden explicar el patrón de progresión de estas lesiones en comparación con la periodontitis. Por tanto, estamos ante una infección profunda que llega al hueso marginal (herida abierta), no cicatrizante (epitelio ulcerado y desestructurado), y con una posible invasión tisular bacteriana.

1.1.4. Características microbiológicas

El microbioma oral ha ido cambiando nuestra comprensión sobre el papel de las bacterias en la patogénesis de las enfermedades periodontales y periimplantarias. Recientemente, se ha propuesto que la patogénesis de la enfermedad periodontal implica una sinergia polimicrobiana y disbiosis (es decir, una interacción compleja entre la microbiota comensal, la susceptibilidad del huésped y el medio ambiente) y no sólo el "impacto" de unos pocos microorganismos específicos (Hajishengallis, 2014).

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El microbioma de la periimplantitis se caracteriza por ser una infección anaeróbica mixta, con una composición similar a la microbiota subgingival de la periodontitis, pero de mayor complejidad, compuestas predominantemente por especies de bacterias gramnegativas no cultivables (Lafaurie et al., 2017). Se han llevado a cabo estudios para comparar el microbioma de la periimplantitis con implantes sanos (Casado et al., 2011), en los cuales se observa que en ambas localizaciones hay bacterias periodontopatógenas comunes, en lo que difieren es que se encuentra un mayor recuento de especies bacterianas del denominado complejo rojo asociado a periodontitis severas, con mayor proporción de *Porphyromonas gingivalis, Tannerella Forsythia*, y *Treponema denticola* (Persson & Renvert, 2014), y microorganismos del complejo naranja como *Prevotella intermedia/nigrescens* y *Fusobacterium nucleatum* (Mombelli & Décaillet, 2011). Además se ha visto que algunas bacterias que se encuentran con menos frecuencia en periodontitis crónica, como el *Aggregatibacter actinomycetemcomitans* (Mombelli et al., 2002), también es menos frecuente en las lesiones de periimplantitis (Mombelli & Décaillet, 2011). Los microorganismos no cultivables como las especies asociadas a los bacilos grampositivos anaerobios asacarolíticos y los bacilos gramnegativos no cultivables están más asociados con las lesiones de periimplantitis en comparación con los implantes sanos (Lafaurie et al., 2017). Además, los estudios observacionales han indicado que la periimplantitis está vinculada con mayor frecuencia a patógenos oportunistas como *Pseudomonas aeruginosa* y *Staphylococcus aureus* (Leonhardt et al., 1999), hongos (por ejemplo, *Candida albicans*, *Candida boidinii*, *Penicillum spp*., *Rhadotorula laryngis*, *Paelicomyces spp*.) (Albertini et al., 2015), y virus (*citomegalovirus humano*, *Epstein-Barr virus*) (Jankovic et al., 2011), apuntando así a una infección bastante compleja y heterogénea (Padial-Molina et al., 2016; Rakic et al., 2016). Además, en un metaanálisis reciente se ha observado una fuerte asociación entre la periimplantitis y la presencia de *Staphylococcus Epidermidis* (Carvalho É et al., 2023). Esta bacteria coloniza a nivel de los tejidos periimplantarios, pero no la superficie del implante, se ha relacionado con infecciones planctónicas supurativas en otros biomateriales, por lo que se sugiere que se asocia con una manifestación fenotípica diferente de periimplantitis, distinto al clásico "tipo de periodontitis". Pero la microbiota de las lesiones de periimplantitis no se ha estudiado exhaustivamente, por lo que se debe considerar como incompleto el microbioma de la periimplantitis. La diversidad del microbioma asociado a la periimplantitis debería dirigir la investigación hacia la comprensión de las interacciones entre el entorno inflamatorio y el desarrollo del microbioma en la periimplantitis.

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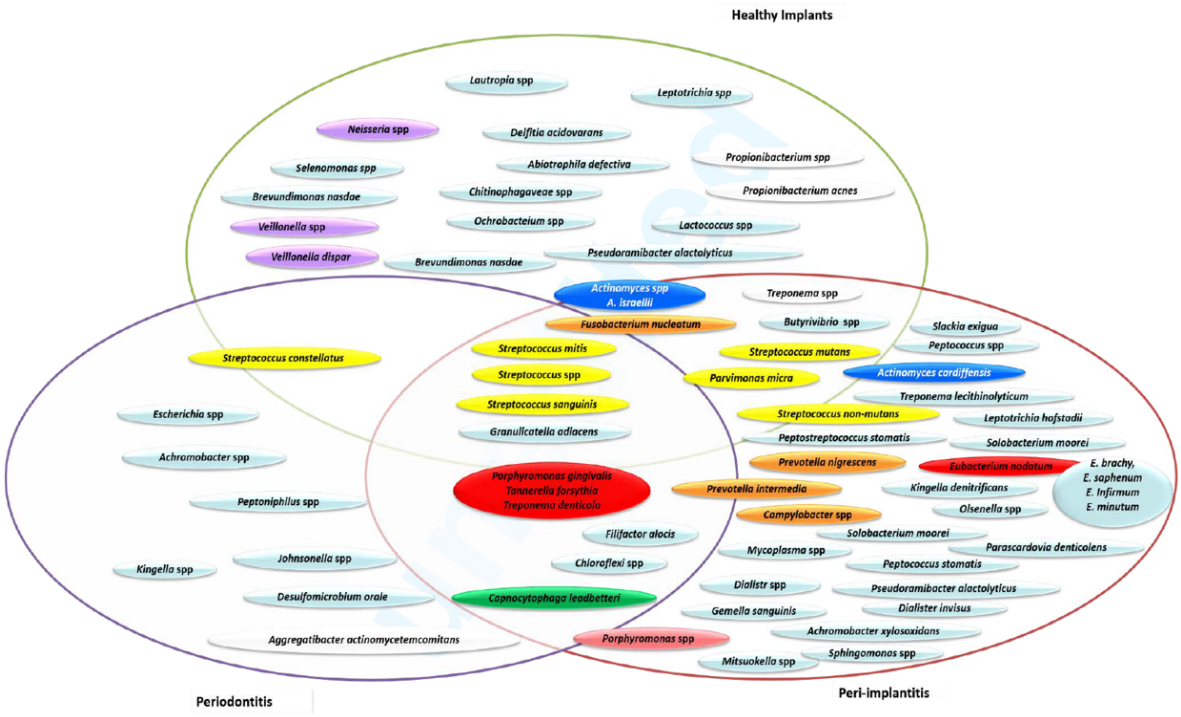


Figura 3. Microbioma y perfiles de las biopelículas de la periimplantitis. Imagen adaptada de (Lafaurie et al., 2017) y reproducida con permiso de John Wiley and Sons.

1.1.5. Factores / indicadores de riesgo

1.1.5.1. Relacionados con el paciente

- **Historia de periodontitis:** Se han realizado numerosos estudios transversales donde se ha asociado la prevalencia de la periimplantitis con la periodontitis (Roos-Jansåker, Lindahl, et al., 2006; Roos-Jansåker, Renvert, et al., 2006). En un estudio tras examinar a 109 pacientes con un seguimiento de 1 a 16 años, concluyeron que los pacientes con antecedentes de periodontitis tenían mayor riesgo de periimplantitis (odd ratio 6) (Koldsland et al., 2010, 2011). Varios estudios confirmaron esta asociación con diversos grados de fuerza (Casado et al., 2013; Máximo et al., 2008). Otros estudios correlacionaron la presencia de periodontitis con periimplantitis, reportando también asociaciones fuertes (Daubert et al., 2015; Derks, Schaller, Hakansson, et al., 2016; Ferreira et al., 2006). De hecho, Daubert y cols. encontraron que la periodontitis avanzada fue el indicador más fuerte para la presencia de periimplantitis de todas las variables examinadas, con un índice de riesgo no ajustado de 7 (Daubert et al., 2015). Derks y cols. en un estudio de 9 años de seguimiento que incluyó a 588 pacientes informó una odd ratio de 4 para

pacientes con periodontitis (Derks, Schaller, et al., 2016a). Las odd ratio variaron entre 2.2 y 19 (Schwarz et al., 2018), con un índice de riesgo de 9 después de un seguimiento de 10 años (Schou et al., 2006). Un metaanálisis reciente reveló que los pacientes susceptibles a la periodontitis tenían un riesgo 2.3 veces mayor de desarrollar periimplantitis en comparación con los pacientes periodontalmente sanos (Ferreira et al., 2018).

Por lo que existe una evidencia fuerte de estudios que asocian la historia de periodontitis como un indicador de riesgo de periimplantitis.

- **Ausencia de mantenimiento periodontal:** Se ha demostrado en estudios clásicos sobre las enfermedades periodontales que, la falta de una terapia de mantenimiento regular se asocia con pérdida de dientes y la pérdida de inserción clínica (Axelsson & Lindhe, 1978, 1981; Becker et al., 1984). De manera similar, recientemente se observó que la prevalencia de periimplantitis y la pérdida de implantes aumentaban en pacientes que no se adherían a un programa de mantenimiento (Monje et al., 2016; Ramanauskaite & Tervonen, 2016). Estos hallazgos han resaltado la importancia de las medidas de control por un profesional en la prevención de las enfermedades periimplantarias. Existen numerosos estudios donde se ha evaluado la posible asociación entre la falta de una terapia de mantenimiento regular y la periimplantitis. Costa y cols. informaron que la prevalencia de periimplantitis se duplicó en pacientes que no tuvieron visitas dentales durante los primeros cinco años tras la terapia de implantes, en comparación con aquellos que acudieron al menos una vez al año (Costa et al., 2012). Roccuzzo y cols. observaron que los pacientes que, durante un período de 10 años, no cumplieron con la terapia de mantenimiento recomendada requirieron significativamente más tratamiento para la periimplantitis (41%) que aquellos que asistieron a las visitas de seguimiento (27%) (Roccuzzo et al., 2010). Los resultados de un estudio transversal también concuerdan con estos, donde se observa que, los pacientes que cumplieron con el mantenimiento después de la terapia con implantes durante un tiempo de observación promedio de 3,8 años tuvieron menos probabilidades de ser diagnosticados con periimplantitis que los que no cumplieron (Monje et al., 2017). Además, en un estudio reciente evaluaron la importancia de la terapia de mantenimiento en la recurrencia de la periimplantitis tras su tratamiento, en este se observa que el riesgo de recurrencia de la enfermedad en pacientes con mantenimientos regulares es del 20% frente a un 70% en aquellos que no siguen una terapia de mantenimiento (Monje & Nart, 2024).

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Por tanto, existe una evidencia sólida de que la falta de un mantenimiento regular es un indicador de riesgo de periimplantitis.

- **Control de placa:** Los estudios que evaluaron el control de placa y su asociación con la periimplantitis demostraron una fuerte correlación. Un análisis reveló que los implantes de pacientes que no tenían una adecuada higiene oral tenían 3,8 veces más probabilidades de verse afectados por periimplantitis en comparación con aquellos con una buena higiene oral (Serino & Ström, 2009). Los modelos de regresión logística multinivel también demostraron que, a medida que se acumulaba la placa, aumentaban las probabilidades de desarrollar mucositis periimplantaria (Konstantinidis et al., 2015). En cuatro estudios, el control deficiente de la placa en el examen final fue el predictor estadístico más fuerte de la periimplantitis con odd ratio que oscilaron entre 5 y 14 (Aguirre-Zorzano et al., 2015; Ferreira et al., 2006; Rokn et al., 2017; Schwarz et al., 2017). Se observó una asociación más leve (OR de 3 a 4) en un estudio transversal (Canullo, Peñarrocha-Oltra, et al., 2016) y un estudio de casos y controles (de Araújo Nobre et al., 2015). Por lo tanto, no es sorprendente que el control de placa realizado por el propio paciente, reduzcan la inflamación clínica en el tejido blando periimplantario (Schwarz, Becker, et al., 2015). Aunque estas medidas no siempre logran una resolución clínica completa (solo el 38% de los implantes afectados experimentaron una resolución total) (Heitz-Mayfield et al., 2012), sí es posible reducir la carga microbiana en la bolsa periodontal si se mantiene un control meticuloso de la placa a largo plazo (Hellström et al., 1996). También se deben considerar otros factores que pueden estar relacionados con las medidas de higiene bucal en los implantes. Serino y Ström (Serino & Ström, 2009) evaluaron la accesibilidad para la higiene de las restauraciones soportadas por implantes en pacientes diagnosticados con periimplantitis, observaron que en aquellas localizaciones con buen acceso a la higiene presentaron periimplantitis sólo en el 18% de los casos, frente a un 65% de periimplantitis en aquellos que las restauraciones no permitían un buen acceso a la higiene.

  Por lo tanto, existe evidencia fuerte de que el control deficiente de la placa constituye un indicador de riesgo de periimplantitis.

- **Tabaco:** El tabaquismo tiene una asociación fuerte con la periodontitis, la pérdida de inserción y la pérdida de dientes (Axelsson et al., 1998; Tomar & Asma, 2000). La posible asociación entre el tabaquismo y la periimplantitis se ha evaluado en numerosos estudios. Lindquist y cols. observaron que los fumadores presentaban una pérdida ósea crestal sustancialmente mayor que los no fumadores (Lindquist et al., 1996). En línea con esta observación, varios estudios posteriores informaron de una fuerte asociación entre el tabaquismo y

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la periimplantitis. En un estudio de cohortes de 10 años, Karoussis y cols. encontraron que el 18% de todos los implantes en fumadores desarrollaron periimplantitis, mientras que solo el 6% de los implantes en no fumadores se vieron afectados (Karoussis et al., 2003). Tres estudios transversales confirmaron estos hallazgos, informando razones de odd de 32 (Rinke et al., 2011), 3 (Becker et al., 2017) y 5 (Roos-Jansåker, Lindahl, et al., 2006) respectivamente. Sin embargo, la mayoría de las publicaciones no identificaron el tabaquismo como un indicador de periimplantitis. Aguirre-Zorzano y cols. examinaron a 239 pacientes con un seguimiento medio de 5 años y encontraron una prevalencia general de periimplantitis del 15%, en el cual los fumadores no tenían un riesgo mayor (Aguirre-Zorzano et al., 2015). Los resultados de otros estudios transversales confirmaron sus hallazgos (Casado et al., 2013; Dalago et al., 2017; Koldsland et al., 2011; Marrone et al., 2013). Esto indica que el tabaquismo puede verse afectado por otras variables, por ejemplo, antecedentes de periodontitis. Las razones de los hallazgos contradictorios y la aparente asociación débil entre el tabaquismo y la periimplantitis no se comprenden actualmente, pero pueden estar relacionadas con las diferencias en la categorización de fumadores y no fumadores. Además, todos los estudios identificados se basaron únicamente en la información notificada por los pacientes para la evaluación del estado de tabaquismo.

Por lo que actualmente no hay evidencia concluyente de que el tabaquismo constituya un factor de riesgo/indicador de periimplantitis.

- **Diabetes:** estudios han indicado que los pacientes con diabetes tienen un mayor riesgo de periimplantitis. Ferreira y cols. registraron periimplantitis en el 24% de los pacientes que tomaban medicación para el control de la glucemia o presentaban un nivel de azúcar en sangre en ayunas ≥126 mg/dl, mientras que solo el 7 % de los pacientes no diabéticos fueron diagnosticados de periimplantitis, con una razón de odd de 1,9 (Ferreira et al., 2006). En otro estudio que incluyó a 96 pacientes con 225 implantes demostraron, después de un seguimiento medio de 11 años, un riesgo 3 veces mayor de periimplantitis en pacientes a los que se les diagnosticó diabetes en el momento de la colocación del implante. Sin embargo, este análisis no se ajustó por posibles factores de confusión (Daubert et al., 2015). Tawil y cols. realizaron un seguimiento de 42 meses (1-12 años) a 45 pacientes con diabetes, en los pacientes con un nivel medio de HbA1c ≤7%, no se diagnosticó periimplantitis en ningún implante, mientras que en aquellos con niveles elevados de HbA1c (7% a 9%), seis de 141 implantes desarrollaron periimplantitis (Tawil et al., 2008). Otros estudios no lograron identificar la diabetes como un riesgo de

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periimplantitis. En el estudio retrospectivo de Costa y cols. los pacientes con diabetes diagnosticados con mucositis no tuvieron mayor riesgo de desarrollar periimplantitis en comparación con los no diabéticos (Costa et al., 2012). De manera similar, en la mayoría de los estudios transversales disponibles se informó de una falta de asociación entre la periimplantitis y la diabetes (Derks, Schaller, et al., 2016a; Dvorak et al., 2011; Marrone et al., 2013; Renvert et al., 2014; Rokn et al., 2017; Roos-Jansåker, Renvert, et al., 2006). Cabe señalar que la evaluación de la diabetes en todos los estudios, excepto en tres (Costa et al., 2012; Ferreira et al., 2006; Tawil et al., 2008), se basó únicamente en la información reportada por los pacientes. En dos de los tres se encontró una asociación entre la diabetes o los niveles de HbA1c y la periimplantitis. En un metaanálisis reciente sobre la prediabetes y la diabetes tipo 2 concluyeron que los pacientes diagnosticados con prediabetes y con diabetes tipo 2 no controlada presentan peores condiciones periimplantarias que aquellos individuos con diabetes tipo 2 controlada o sanos (Bencze et al., 2024).

Por lo que, la evidencia disponible no es concluyente en cuanto a si la diabetes es un factor de riesgo/indicador de periimplantitis.

1.1.5.2. Relacionados con el implante

- **Mucosa queratinizada:** Tanto el grosor como la cantidad de mucosa queratinizada son dos componentes clave del fenotipo del tejido periimplantario, pero las medidas que se necesitan de estos para mantener la estabilidad del tejido periimplantario y así prevenir la periimplantitis es un tema controvertido. La evidencia de que existe una necesidad de mucosa queratinizada (KM) para mantener la salud periimplantaria es aún limitada (Gobbato et al., 2013; Wennström & Derks, 2012). Dos revisiones sistemáticas han indicado que una KM de <2 mm se asocia con una mayor acumulación de placa e inflamación del tejido blando periimplantario en comparación con los implantes que estaban rodeados por una KM de ≥2 mm (Gobbato et al., 2013; Lin et al., 2013). Además, un metaanálisis mostró diferencias estadísticamente significativas en términos de control de placa, índice gingival modificado, recesión de la mucosa y pérdida de inserción a favor de implantes con mayor KM (Lin et al., 2013). Estos hallazgos también fueron respaldados por estudios observacionales (Canullo, Peñarrocha-Oltra, et al., 2016; Souza et al., 2016; Ueno et al., 2016).

  Si bien los estudios sugieren que la ausencia o un tamaño reducido de encía queratinizada puede afectar negativamente al control de placa, existe evidencia limitada de que este factor constituya un riesgo de periimplantitis.

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

- **Profundidad de vestíbulo:** Se ha sugerido que la reducción de la profundidad de vestíbulo (VD) es un factor que contribuye a la periimplantitis. En el estudio de Halperin-Sternfeld y cols. (Halperin-Sternfeld et al., 2016) los sitios con VD poco profundo presentaron una KM más baja en comparación con los sitios con VD adecuado (1,24 mm versus 2,38 mm, respectivamente). De hecho, un estudio transversal publicado recientemente (Isler et al., 2024) mostró que la ausencia de KM (odd ratio: 9,24), la ausencia de mucosa adherida (odd ratio:19,58) y una profundidad del vestíbulo reducida (<4 mm) (odd ratio:2,61) se asociaron con presencia de dehiscencia vestibular y periimplantitis. Por lo que puede ser una variable de confusión con la KM, ya que cuando hay una profundidad de vestíbulo reducida suele no haber KM.

  Por lo tanto, los estudios que abordan la falta de KM en los niveles de hueso marginal pueden presentar un factor de confusión importante como lo es VD, ya que la reducción de VD se asocia con una reducción o falta de KM.

- **Infección residual:** El concepto de periimplantitis retrógrada se define como una radiolucidez periapical localizada alrededor del implante, que puede o no estar asociada con signos clínicos de inflamación. Se encontró que estaba estrechamente relacionado con la presencia de patologías endodónticas de los dientes adyacentes (Schwarz et al., 2018). Además, en zonas donde se extrajeron dientes por infección endodóntica, se informó que se produciría una radiolucidez periapical en el 8,2 % al 13,6 % (odds ratio 7,2) de los casos (Lefever et al., 2013). Es importante desbridar meticulosamente el alvéolo de extracción para eliminar cualquier tejido patológico, especialmente al colocar implantes inmediatos, ya que la infección residual puede extenderse al implante y provocar una pérdida ósea periapical (Chrcanovic et al., 2015).

  Por tanto, hay evidencia que sugiere que la infección endodóntica residual es un factor de riesgo/indicador para desarrollar periimplantitis retrógrada.

1.1.5.3. Relacionados con la prótesis

- **Exceso de cemento:** Varios estudios observacionales han mostrado una correlación entre el exceso de cemento y la prevalencia de las enfermedades periimplantarias. Se sugirió que la presencia de exceso de cemento estaba estrechamente relacionada con la aparición de mucositis periimplantaria o periimplantitis (Korsch et al., 2014; Linkevicius et al., 2013). Esta posible asociación se debe a una reacción de los tejidos periimplantarios al

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denominado concepto de cuerpo extraño descrito por Wilson y cols. (Wilson et al., 2015), donde se observa un aumento de la inflamación crónica y el cemento rodeado de células inflamatorias. Sin embargo, las proporciones de implantes con periimplantitis que mostraban exceso de cemento variaron considerablemente entre los estudios y oscilaron entre el 9% y el 81%. En consecuencia, numerosos implantes con exceso de cemento no mostraban mayor probabilidad de periimplantitis (Korsch et al., 2014; Linkevicius et al., 2013). Además, no se encontró que las prótesis cementadas tuvieran un mayor riesgo de periimplantitis en comparación con las prótesis atornilladas (Daubert et al., 2015; Derks, Schaller, et al., 2016a; Kotsakis et al., 2016; Marrone et al., 2013). Sin embargo, una revisión sistemática enfatizó que la superficie rugosa del implante junto con los restos de cemento puede facilitar la retención y la formación de biopelículas (Staubli et al., 2017).

Por lo tanto, no hay una evidencia clara sobre si el exceso de cemento es un factor/ indicador de riesgo de periimplantitis.

- **Restauraciones sobrecontorneadas:** Un estudio mostró que las restauraciones con un ángulo de emergencia de más de 30° tenían una prevalencia dos veces mayor de periimplantitis que las restauraciones con ángulos de emergencia más estrechos (31% vs. 15%), especialmente en el implante con superficie rugosa (Katafuchi et al., 2018). Esto podría deberse en parte a un implante mal posicionado o a un ángulo de emergencia mayor (superior a 30°), lo que genera dificultad para acceder a la plataforma del implante para el control de la placa. Esto fue respaldado por una revisión sistemática donde se concluye que un perfil de emergencia mayor y la conexión externa de la prótesis están relacionados con una incidencia mayor de periimplantitis (Papavasiliou et al., 2023).

  Por tanto, hay evidencia moderada que sugiere que la restauración sobrecontorneada es un indicador para el desarrollo de periimplantitis.

1.1.5.4. Relacionados con el operador

- **Factores iatrogénicos:** El informe del 7th *Workshop* de periodoncia reconoció que la aparición y progresión de la periimplantitis puede verse influida por factores iatrogénicos como " una adaptación inadecuada de los pilares de la prótesis, un contorno excesivo de las prótesis o una mala posición de los implantes" (Lang & Berglundh, 2011). La posición del implante afecta a la función y estética a largo plazo, influye en la

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

preservación de los tejidos duros y blandos periimplantarios, el perfil de emergencia y el control efectivo de la placa (Jepsen et al., 2015). En un análisis retrospectivo, se observó que la periimplantitis estaba relacionada con la mala posición del implante (OR 48) (Canullo, Tallarico, et al., 2016). Además, en otro estudio retrospectivo se observó que los implantes con expiras expuestas debido a la remodelación ósea inicial tienen 3.77 veces más riesgo de periimplantitis (Ravidà et al., 2023).

Por tanto, parece razonable sugerir que la posición del implante es un posible indicador de riesgo de periimplantitis.

1.1.6. Relación entre la periimplantitis y la inflamación sistémica

1.1.6.1. Concepto de inflamación sistémica de grado bajo

Recientemente, algunos autores que estudian la contribución de la inflamación a las enfermedades crónicas más comunes, como la diabetes, la obesidad, las enfermedades cardiovasculares y neurológicas, han introducido el concepto de "inflamación de grado bajo" (LGI) (Barbaresko et al., 2013; Danesh et al., 2004; Devaux et al., 1997). La LGI se caracteriza por una producción sistémica crónica de grado bajo de factores inflamatorios. Hasta la fecha, la LGI se reconoce como un factor de riesgo para una serie de enfermedades crónicas, incluidas las enfermedades cardiovasculares, cerebrovasculares, neurodegenerativas y el cáncer (Coussens & Werb, 2002; Engström et al., 2003; Kaptoge et al., 2014; Lind, 2003; Samuels, 2004). También se ha sugerido que la LGI puede aumentar el riesgo de resistencia a la insulina y diabetes tipo 2 (Kolb & Mandrup-Poulsen, 2010). La evaluación de la LGI se realiza mediante la evaluación de biomarcadores circulantes (p. ej., PCR, fibrinógeno) o biomarcadores celulares (p. ej., recuento de leucocitos y plaquetas) (Arcari et al., 2008; Bonaccio et al., 2014; Danesh et al., 2004; Kaptoge et al., 2010), aunque es una condición que aún no se ha definido o medido de manera consistente.

1.1.6.2. Relación entre la periodontitis y la inflamación sistémica de grado bajo

Se han formulado hipótesis sobre la relación entre la periodontitis y LGI, ya que parece que la periodontitis puede contribuir a inducir y/o mantener el estado sistémico de LGI y, además, la LGI también puede ser un factor de riesgo para la periodontitis (Forner et al., 2006; Gamonal et al., 2000; Teeuw et al., 2015). El concepto de LGI podría explicar el vínculo existente entre la periodontitis y ciertas comorbilidades sistémicas (Hajishengallis, 2022).

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La periodontitis es una enfermedad inflamatoria crónica asociada a la microbiota oral (Bartold & Van Dyke, 2013). En la cual, la agresión microbiana no es suficiente por si sola para inducir la aparición de la enfermedad (Page & Kornman, 1997; Page et al., 1997), su desarrollo también se debe a una susceptibilidad individual vinculada a una base genética (Loos et al., 2005) y factores de riesgo asociados (especialmente tabaquismo y mala higiene bucal) que permiten a las bacterias expresar su potencial patógeno (Heitz-Mayfield, 2005). La acumulación de placa, activa una respuesta inmunitaria local a nivel del periodonto, con la intervención de la inmunidad innata (p. ej., macrófagos, células dendríticas, neutrófilos) y la inmunidad adaptativa (p. ej., linfocitos B y T) con la consiguiente liberación de moléculas proinflamatorias (p. ej., interferón-gamma, interleucina-17, factor de necrosis tumoral, interleucina-1, interleucina-6) y enzimas (p. ej., colagenasas como las metaloproteinasas de la matriz) (Page, 1991). La secreción inadecuada de estas citocinas, ya sea en términos de tipo o cantidad, caracteriza una respuesta inmune desregulada que conduce a la destrucción irreversible del periodonto con signos clínicos de periodontitis como bolsas periodontales, pérdida de inserción, recesiones gingivales, movilidad dental, migración dental y pérdida de dientes (Madianos et al., 2005). El área de la bolsa periodontal en contacto directo con la biopelícula subgingival, representa la interfaz a través de la cual la inflamación local y las bacterias periodontopatógenas pueden afectar a la salud sistémica (Hujoel et al., 2001). Por un lado, el epitelio de la bolsa proporciona una entrada para las bacterias periodontopatógenas a través de la cual puede dar lugar a una bacteriemia, ya que se ha visto que estas bacterias tienen la capacidad de colonizar localizaciones distantes (Haraszthy et al., 2000). Además, los componentes bacterianos como los lipopolisacáridos (LPS) también pueden diseminarse en el torrente sanguíneo, estos junto con los antígenos bacterianos pueden desencadenar procesos inflamatorios sistémicos significativos. En consecuencia, los glóbulos blancos (p. ej., PMN) y los reactantes de fase aguda (APR) de las células endoteliales (EC) y los hepatocitos pueden producir mediadores proinflamatorios. Por otro lado, los mediadores proinflamatorios producidos localmente, como la interleucina-1 (IL-1), la interleucina-6 (IL-6), el factor de necrosis tumoral alfa (TNF-α) y la prostaglandina E2 (PGE2), pueden pasar a la circulación sistémica y, posteriormente, ejercer efectos sobre órganos distantes y aumentar y/o perpetuar un estado inflamatorio (Hajishengallis, 2015; Moutsopoulos & Madianos, 2006). Estas observaciones han mostrado que la inflamación local causada por la periodontitis puede extenderse a un nivel sistémico influyendo en la carga inflamatoria del sujeto (Beck et al., 1998; Ioannidou et al., 2006; Page, 1998). Por lo que, la EP provoca un estado inflamatorio sistémico de grado bajo.

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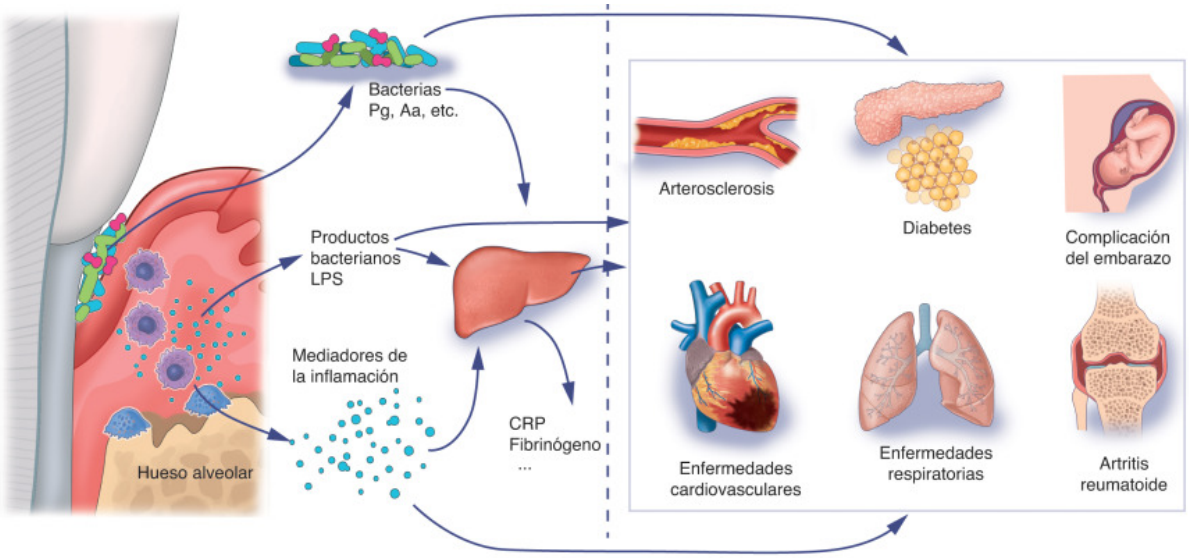


Figura 4. Medios de conexión entre la periodontitis y la inflamación sistémica (imagen copyright © Sojod y cols. Enfermedad periodontal y salud general 2022, reproducida con permiso de Elsevier).

1.1.6.3. Evidencia de la relación de la periimplantitis con la inflamación sistémica

En la periimplantitis, la presencia de patógenos subgingivales provoca una respuesta inflamatoria local, que se caracteriza por mayores proporciones de leucocitos polimorfonucleares y macrófagos. Además, esta respuesta inflamatoria se amplifica debido a la producción de citocinas proinflamatorias y prostaglandinas. La liberación de éstas en el torrente sanguíneo estimula un mayor reclutamiento de mediadores proinflamatorios y leucocitos (Gualini & Berglundh, 2003). Esta respuesta inflamatoria local es más pronunciada en los tejidos periimplantarios que en los tejidos periodontales (Berglundh et al., 2011). El epitelio gingival ulcerado permite que estos mediadores inflamatorios producidos localmente ingresen al torrente sanguíneo e induzcan una reacción de fase aguda en el hígado con una mayor producción de reactantes de fase aguda como la proteína C reactiva (PCR), contribuyendo así a la carga inflamatoria sistémica general (Hajishengallis, 2015). Si tenemos en cuenta las similitudes fisiopatológicas de la periimplantitis y la periodontitis, un estado inflamatorio periimplantario persistente también podría tener un impacto en la inflamación sistémica. Si este proceso inflamatorio agudo no se resuelve, puede conducir eventualmente a un estado inflamatorio sistémico crónico de grado bajo (LGI). Recientemente, un estudio de casos y controles mostró que los sujetos con enfermedad cardiovascular (ECV) tenían una prevalencia más alta de periimplantitis moderada a grave que aquellos con implantes sanos (≈50 % frente a ≈30 %) (Wang, Ou, et al., 2022). Además, hay evidencia clínica y experimental reciente donde se demuestra un vínculo potencial entre

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la periimplantitis y la inflamación sistémica (Chaushu, Tal, et al., 2020b; Chaushu et al., 2021; Ustaoğlu & Erdal, 2020; Wang, Sugai, et al., 2022). Los pacientes con periimplantitis mostraron niveles más altos de algunos marcadores de inflamación sistémica como el TNF-α y los leucocitos en comparación con sujetos con implantes sanos (Chaushu, Tal, et al., 2020a; Chaushu, Tal, Sculean, Fernández-Tomé, et al., 2020; Ustaoğlu & Erdal, 2020). En una revisión sistemática reciente se mostró que los sujetos con periimplantitis muestran niveles más altos de PCR, IL- 6 y recuento de glóbulos blancos en comparación con individuos sanos (Yan et al., 2023). Además, también se observó un estado dislipidémico en individuos con periimplantitis (niveles sanguíneos elevados de colesterol total y lipoproteínas de baja densidad, así como triglicéridos) (Ustaoğlu & Erdal, 2020; Wang, Sugai, et al., 2022). En pacientes con ECV, la periimplantitis también se asoció con niveles elevados de citocinas proinflamatorias (Wang, Sugai, et al., 2022). Todos estos hallazgos clínicos preliminares fueron respaldados por estudios previos en animales donde las concentraciones de leucocitos y otros mediadores inflamatorios aumentaron después de inducir una periimplantitis experimental. Cabe destacar que, el tratamiento de las lesiones periimplantarias revirtió los niveles de marcadores inflamatorios a valores normales (Chaushu, Tal, Sculean, Fernández-Tomé, et al., 2020).

1.1.7. Tratamiento de la periimplantitis

El tratamiento de la periimplantitis tiene como objetivo la resolución de la inflamación de los tejidos blandos periimplantarios a la vez que detener la pérdida ósea periimplantaria e incluso la reconstrucción de la estructura ósea perdida. En términos clínicos se considera que tenemos resolución de la enfermedad, y por lo tanto éxito en el tratamiento, cuando se consigue una profundidad de sondaje menor o igual a 5 mm, presencia de un punto o ausencia de sangrado al sondaje y ausencia de progresión de la pérdida ósea radiográfica (Tonetti et al., 2023). A fin de lograr estos objetivos, se pueden emplear tratamientos no quirúrgicos y quirúrgicos.

En base a la guía de prevención y práctica clínica de las enfermedades periimplantarias (Herrera et al., 2023), una vez que se ha establecido un diagnóstico de periimplantitis, se deben reconocer dos puntos:

- La periimplantitis es irreversible; por lo tanto, incluso después de una terapia de periimplantitis exitosa, se asigna un diagnóstico de periimplantitis “estable”.

- Los resultados del tratamiento de la periimplantitis dependen de una multitud de factores (características del implante y la prótesis, factores del paciente, factores locales, gravedad de la enfermedad, configuración del defecto óseo). En

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consecuencia, se utilizan intervenciones personalizadas dirigidas específicamente a uno o varios de los factores anteriores en su manejo. Por lo que los resultados del tratamiento de estas intervenciones son variables.

Según esto, el manejo de la periimplantitis debe abarcar los siguientes pasos:

- Tras el diagnóstico, se debe valorar si el implante afectado es tratable.
- De ser así, se realiza un paso inicial de terapia no quirúrgica, que incluye instrumentación submarginal.
- Después del paso no quirúrgico, la reevaluación de los resultados clínicos (después de 6-12 semanas), basada en un conjunto de criterios preestablecidos para el éxito, guiará la decisión de si el implante está estable y por lo tanto el paciente entra en terapia de cuidado y soporte periodontal, o de proceder con el paso quirúrgico, siempre que el implante afectado siga considerándose tratable.
- El paso quirúrgico del tratamiento de la periimplantitis siempre debe incluir instrumentación submarginal después de elevar un colgajo.
- Después de la evaluación de los resultados clínicos después del paso quirúrgico, y siempre que se cumpla un conjunto de criterios preestablecidos para el éxito, el paciente pasa a la fase de terapia de cuidado y soporte periodontal.

1.1.7.1. Tratamiento no quirúrgico de la periimplantitis

Se ha demostrado que la causa principal de la periimplantitis es la acumulación de biopelículas bacterianas alrededor del implante dental. Por ello, el objetivo principal del tratamiento será la eliminación de éstas (Schwarz et al., 2018). En este contexto, las terapias utilizadas a lo largo del tiempo se basan en la evidencia existente para el tratamiento de la periodontitis. Por lo que, independientemente del grado de progresión y severidad de la enfermedad, el tratamiento no quirúrgico representa el primer paso para su resolución.

El objetivo del tratamiento no quirúrgico se basa en el control de las biopelículas bacterianas y la resolución de la inflamación periimplantaria, y por lo tanto, el tratamiento se centra en la instrumentación submarginal, un control óptimo de la placa realizado por el paciente, además de un control de los factores de riesgo, como una periodontitis mal controlada, modificación de la prótesis para buen acceso a la higiene (Herrera et al., 2023).

Aunque el tratamiento no quirúrgico puede ser efectivo en el control de la mucositis periimplantaria (Suárez-López Del Amo et al., 2016), los resultados de este tratamiento en la

USC SANTIAGO DE COMPOSTELA

periimplantitis han resultados contradictorios. La dificultad de este tratamiento para realizar el desbridamiento alrededor de los implantes dentales con perdida ósea reside en la presencia de una superficie rugosa, la posición del implante y prótesis que implican una dificultad en el acceso.

Se han investigado distintos dispositivos de descontaminación mecánica en el tratamiento no quirúrgico de la periimplantitis, y se ha evaluado su efectividad en diferentes ensayos clínicos:

- **Curetas y ultrasonidos** (Karring et al., 2005; Persson et al., 2010; Renvert et al., 2009) (tabla 2): Existen diferentes tipos de curetas para el desbridamiento mecánico de la superficie del implante (plástico, titanio, PTFE, fibra de carbono, acero), y de ultrasonidos. El objetivo de la instrumentación es realizar un desbridamiento subgingival con un daño mínimo de la superficie del implante. Aunque la evidencia sobre el tratamiento sólo con estes dispositivos muestran resultados muy limitados en la reducción de la inflamación, son dispositivos recomendados por la guía de práctica clínica para esta primera fase del tratamiento (Cosgarea et al., 2023).

Tabla 2. Estudios tratamiento no quirúrgico sólo de la periimplantitis (RCTs)

Autor (año)	Tamaño muestral	seguimiento	intervención	PS inicial	PS final	BoP inicial	BoP final	Ganancia ósea radiográfica
Karring (2005)	11	6 meses	Curetas fibra de carbono	6,2	6,3	72,7	81,8	--
	11		ultrasonidos	5,8	5,8	63,6	36,4	--
Persson (2010)	17	6 meses	Curetas titanio	4,0	4,0	1,7	1,2	--
	14		Ultrasonidos	4,3	3,9	1,7	1,4	--
Renvert (2009)	17	6 meses	Curetas titanio	4,0	4,0	1,7	1,2	--
	14		ultrasonidos	4,3	3,9	1,7	1,4	--

- **Aeropulidores** (Persson et al., 2011; Renvert et al., 2011; Sahm et al., 2011) (tabla 3): Se han propuesto como un enfoque de tratamiento alternativo a la instrumentación manual y los dispositivos ultrasónicos con el objetivo de eliminar de manera eficiente la biopelícula y descontaminar la superficie del implante sin dañarla, ya que se ha visto que modificar la superficie del implante puede provocar una rápida recolonización por biopelículas bacterianas (Cao et al., 2018). Las investigaciones in vitro han demostrado que estos dispositivos parecen tener un buen potencial de limpieza, mostrando un acceso suficiente a las roscas de los

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implantes sin causar un daño significativo a la superficie de titanio (Moharrami et al., 2019). Pero, por otro lado, las investigaciones clínicas no han podido demostrar su superioridad en comparación con el desbridamiento mecánico. Los polvos más utilizados son el bicarbonato de sodio y los polvos de glicina, se ha demostrado que el polvo de glicina, un aminoácido de baja abrasión, es menos abrasivo para la superficie del implante en comparación con el bicarbonato de sodio (Petersilka et al., 2003). Basándose en los resultados limitados del uso de estos dispositivos, no habiendo un claro beneficio para el paciente y el aumento de riesgo de enfisema subcutáneo, la guía de práctica clínica no recomiendo el uso de estos dispositivos en esta fase del tratamiento (Cosgarea et al., 2023).

Tabla 3. Estudios tratamiento no quirúrgico de la periimplantitis con aeropulidores (RCTs)

Autor (año)	Tamaño muestral	seguimiento	intervención	PS inicial	PS final	BoP inicial	BoP final	Ganancia ósea radiográfica
Renvert (2011)	21	6 meses	aeropulidor	Reducción: 0,8		No BoP: 25%		--
	21		Er:YAG laser	Reducción: 0,9		No BoP: 30,9%		--
Sahm (2011)	15	6 meses	Curetas fibra carbono + CHX	4,0	3,5	95,3	84,3	--
	15		Aeropulidor glicina	3,8	3,2	94,6	51,1	--
Persson (2011)	21	6 meses	Aeropulidor	6,2	6,2	--	--	--
	21		Er:YAG laser	5,9	5,9	--	--	--

- **Láser** (Abduljabbar et al., 2017; Alpaslan Yayli et al., 2022; Arısan et al., 2015; Persson et al., 2011; Renvert et al., 2011; Roccuzzo et al., 2022; Schwarz et al., 2005) (tabla 4): la implementación de este dispositivo tiene como objetivo detener la actividad bacteriana y disminuir por tanto la inflamación periimplantaria, este se utiliza de manera complementaria al tratamiento mecánico convencional. Existen diferentes tipos de láser, los que se han evaluado en el tratamiento de la periimplantitis son el láser de diodo, Er:YAG , Nd:YAG, Cr: YSGG. Según los resultados de los estudios, en algunos se observa que el uso complementario del láser puede aportar un beneficio adicional frente al desbridamiento mecánico sólo, pero sin ser suficiente en la mayoría de los casos para la resolución de la enfermedad, además de que en hay poca evidencia sobre la estabilidad ósea radiográfica y un seguimiento limitado. Por lo que, teniendo en cuenta estos resultados limitados con el uso de estos dispositivos, no mostrando resultados superiores significativos frente a la instrumentación mecánica por sí sola, no son recomendados por la guía de práctica clínica (Cosgarea et al., 2023).

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Tabla 4. Estudios tratamiento no quirúrgico de la periimplantitis con láser (RCTs)								
Autor (año)	**Tamaño muestral**	**seguimiento**	**intervención**	**PS inicial**	**PS final**	**BoP inicial**	**BoP final**	**Ganancia ósea radiográfica**
Abduljabbar (2017)	32	6 meses	Curetas plástico	5,6	4	48,6	8,8	0,1
	31		Nd:YAG láser	5,3	2,5	50,3	10,5	0,1
Alpaslan (2022)	17	6 meses	Curetas titanio	4,14	3,62	72,02	60,71	--
	16		Láser diodo	4,14	3,28	88,09	61,90	--
	17		Er, Cr:YSGG	4,48	3,33	100	51,19	--
Arisan (2015)	5	6 meses	Curetas plástico + láser diodo + suero	4,71	4,54	100	95,8	-0,67
	5		Curetas plástico + suero	4,38	4,17	100	100	-0,28
Persson (2011)	21	6 meses	aeropulidor	6,2	6,2	--	--	--
	21		Er:YAG láser	5,9	5,9	--	--	--
Renvert (2011)	21	6 meses	aeropulidor	Reducción: 0,9		No BoP: 25%		--
	21		Er:YAG láser	Reducción: 0,9		No BoP: 30,9%		--
Rocuzzo (2022)	12	6 meses	Curetas titanio-acero + suero + láser diodo	Reducción: 1,28		Reducción: 15,3		0,04
	13		Curetas titanio-acero + suero	Reducción: 1,47		Reducción: 15,4		0,03
Schwarz (2005)	9	6 meses	Curetas plástico + CHX	5,5	4,8	80	58	--
	10		Er:YAG láser	5,4	4,6	83	31	--

- **Terapia fotodinámica** (Alasqah, 2022; Wang et al., 2019) (tabla 5): este tratamiento se basa en la activación de un fotosensibilizador que es absorbido por los microorganismos. Se han utilizado diferentes fotosensibilizadores para el tratamiento de la periimplantitis, incluido el azul de toluidina y el azul de metileno. La evidencia que hay sobre su uso en el tratamiento no quirúrgico de la periimplantitis es muy escasa, el seguimiento es muy corto y la muestra insuficiente. Debido a la falta de datos suficientes para valorar su eficacia, no es un dispositivo que se recomiende (de Waal et al., 2023).

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Tabla 5. Estudios tratamiento no quirúrgico de la periimplantitis con terapia fotodinámica (RCTs)								
Autor (año)	**Tamaño muestral**	**seguimiento**	**intervención**	**PS inicial**	**PS final**	**BoP inicial**	**BoP final**	**Ganancia ósea radiográfica**
Alasqah (2022)	25	6 meses	Curetas plástico	5,1	3,7	44,3	15,5	-0,4
	26		Curetas plástico+ aPDT azul metileno + laser diodo	4,8	3,1	43,3	11	0,2
Wang (2019)	66	6 meses	Aeropulidor + suero	5,07	4,62	100	100	--
	66		Aeropulidor + aPDT azul toluidina	4,93	3,06	100	46	--

En la mayoría de los estudios, estos dispositivos se han combinado con el uso de antimicrobianos, con el objetivo de reducir la carga bacteriana en las áreas más profundas y porosas de la superficie rugosa del implante, inaccesibles para los métodos mecánicos:

- **Antisépticos** (John et al., 2015; Merli et al., 2020; Renvert et al., 2006; Renvert et al., 2008; Sahm et al., 2011) (tabla 6): El agente químico más evaluado es el digluconato de clorhexidina aplicado en gel, en enjuague o aplicación a través del concepto de desinfección de boca completa. Los resultados de los estudios han mostrado un beneficio clínico limitado, la reducción de la desinflamación es similar al tratamiento no quirúrgico sólo (beneficio adicional de 0,5mm), no aportando su uso un beneficio adicional, debido a estos resultados y el costo adicional que implican, no es recomendado su uso (de Waal et al., 2023).

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Tabla 6. Estudios tratamiento no quirúrgico de la periimplantitis con antisépticos (RCTs)								
Autor (año)	**Tamaño muestral**	**seguimiento**	**intervención**	**PS inicial**	**PS final**	**BoP inicial**	**BoP final**	**Ganancia ósea radiográfica**
Merli (2020)	16	6 meses	US	4,4	4,2	3,3	2,9	0,2
	16		US + Hyben X	5,0	4,5	2,9	2,5	0,1
	16		US + aeropulidor	5,1	4,8	3,6	2,8	-0,4
	16		US + aeropulidor+ Hyben X	4,9	4,0	3,6	2,7	0,1
Renvert (2006)	14	12 meses	Curetas fibra de carbono + CHX	3,9	3,9	86	78	--
	16		Curetas fibra de carbono + minociclina	3,85	3,55	89,2	63,5	--
Renvert (2008)	58 implantes	12 meses	Curetas fibra de carbono + CHX	3,87	3,72	86,5	48,1	--
	37 implantes		Curetas fibra de carbono + minociclina	3,85	3,55	89,2	63,5	--
Sahm (2011)	15	6 meses	Curetas fibra carbono + CHX	4,0	3,5	95,3	84,3	--
	15		Aeropulidor glicina	3,8	3,2	94,6	51,1	--
John (2015)	12	12 meses	Aeropulidor glicina	3,7	3,2	99	57,8	--
	13		Curetas de fibra carbono + CHX	3,9	3,5	94,7	78,1	--

- **Antimicrobianos locales** (Ahmed et al., 2020; Bassetti et al., 2014; Machtei et al., 2012; Machtei et al., 2021; Renvert et al., 2006; Renvert et al., 2008; Schär et al., 2013) (Tabla 7): La aplicación local de éstos como complemento se han propuesto como métodos de descontaminación en el tratamiento de la periimplantitis, buscando evitar los efectos adversos de los antibióticos sistémicos (es decir, susceptibilidad/resistencia a los antimicrobianos). Se han evaluado microesferas de minociclina, gel de metronidazol y chips de clorhexidina. Los resultados no han mostrado una resolución de la enfermedad en términos clínicos ni radiográficos. Se recomienda su uso en localizaciones que no responden al tratamiento o zonas residuales, pero no como primera fase del tratamiento, además muchos de estos no están disponibles en algunos países como España y al ser un beneficio limitado no compensa su coste elevado (Liñares et al., 2023).

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Tabla 7. Estudios tratamiento no quirúrgico de la periimplantitis con antibióticos locales (RCTs)								
Autor (año)	Tamaño muestral	seguimiento	intervención	PS inicial	PS final	BoP inicial	BoP final	Ganancia ósea radiográfica
Ahmed (2020)	20	6 meses	US + gel (MTZ 400mg+ AMX 500mg + CHX)	6,6	3,9	55,8	15,6	1,2
	20		US+ láser diodo + CHX	6,8	4,0	52,6	14,5	0,9
	20		US	6,9	4,7	46,6	19,8	0,6
Bassetti (2014)	20	12 meses	Curetas titanio+ aeropulidor + aPDT	4,19	4,08	4,03	1,74	--
	20		Curetas titanio + aeropulidor + minociclina	4,39	3,83	4,41	1,55	--
Machtei (2012)	30	6 meses	Desbridamiento subgingival + chip CHX 12 semanas	7,6	5,48	100	42,8	--
	30		Desbridamiento subgingival + placebo	7,2	5,48	100	54,5	--
Machtei (2021)	146	6 meses	Desbridamiento subgingival + chips CHX 12 semanas	6,2	4,40	100	50	--
	144		Desbridamiento subgingival + supragingival 12 semanas	6,1	4,52	100	45	--
Renvert (2006)	14	12 meses	Curetas fibra de carbono + CHX	3,9	3,9	86	78	--
	16		Curetas fibra de carbono + minociclina	3,85	3,55	89,2	63,5	--
Renvert (2008)	58 implantes	12 meses	Curetas fibra de carbono + CHX	3,87	3,72	86,5	48,1	--
	37 implantes		Curetas fibra de carbono + minociclina	3,85	3,55	89,2	63,5	--
Schär (2013)	20	6 meses	Curetas titanio + aeropulidor + láser diodo	4,19	3,83	4,03	1,51	--
	20		Curetas titanio + aeropulidor + minociclina	4,39	3,90	4,41	2,10	--

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- **Probióticos** (Laleman et al., 2020; Tada et al., 2018) (tabla 8): se ha investigado cepas de *Lactobacillus reuteri* como complemento al tratamiento no quirúrgico administrado durante un periodo de 15 o 30 días. La evidencia actual sobre este tratamiento es muy limitada, los resultados muestran una reducción media de la profundidad de sondaje de 0,5mm – 1 mm sin ser suficiente para la resolución de la enfermedad. Debido a esta escasa evidencia y el coste adicional que supone para el paciente no se recomienda su uso complementario (Liñares et al., 2023).

Tabla 8. Estudios tratamiento no quirúrgico de la periimplantitis con probióticos (RCTs)

Autor (año)	Tamaño muestral	seguimiento	intervención	PS inicial	PS final	BoP inicial	BoP final	Ganancia ósea radiográfica
Laleman (2020)	11	6 meses	US + curetas titanio+ aeropulidor + probiótico local + probiótico 10 días	5,2	4,2	87	28	--
	12		US + curetas titanio+ aeropulidor + placebo local + placebo 10 días	5,5	4,2	87	34	--
Tada (2018)	15	6 meses	Desbridamiento supra + azitromicina + probiótico 6 meses	3,6	3,2	38,8	13,3	--
	15		Desbridamiento supra + azitromicina + placebo	3,5	3,4	45,5	15,7	--

- **Antibióticos sistémicos** (Carrillo de Albornoz et al., 2024; Estefanía-Fresco et al., 2019; Mombelli & Lang, 1992; Nart et al., 2020) (tabla 9): Con el objetivo de mejorar el resultado de la terapia no quirúrgica, se ha evaluado el uso coadyuvante de antibióticos sistémicos. Hasta el momento sólo teníamos evidencia de series de casos donde se muestra el uso complementario de ornidazol, amoxicilina junto con metronidazol y metronidazol sólo. Esta serie de casos mostraron buenos resultados en términos de resolución de la enfermedad, donde se observan unas medias en la reducción de la profundidad de sondaje de entre 2-3 mm, reducción del sangrado al sondaje del 40-50% y ganancia ósea radiográfica de 1-2mm. Estas series de casos mostraron resultados prometedores en términos de resolución de la enfermedad, y abrieron una vía de investigación para realizar ensayos clínicos para evaluar su eficacia. Hasta ahora, tenemos dos ensayos clínicos que evalúen la eficacia del tratamiento no quirúrgico de la periimplantitis con el uso complementario de antibiótico sistémico (Almohareb et al., 2020; Shibli et al., 2019) (tabla 10).

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Tabla 9. Estudios tratamiento no quirúrgico de la periimplantitis con antibióticos sistémicos (series de casos)								
Autor (año)	**Tamaño muestral**	**seguimiento**	**intervención**	**PS inicial**	**PS final**	**BoP inicial**	**BoP final**	**Ganancia ósea radiográfica**
Monbelli (1992)	9	12 meses	Desbridamiento subgingival + ornidazol 1000mg 10 días	5,89	3,43	89	43	--
Estefanía (2019)	37	12 meses	Desbridamiento subgingival + amoxicilina 500mg + metronidazol 500mg 7 días	6,80	4,61	22,4	10,8	0,91
Nart (2020)	21	12 meses	curetaje + metronidazol 500mg 7 días	5,34	3,69	78,78	21,22	1,31
Albornoz (2024)	117	12 meses	Curetaje+ US + aeropulidor + metronidazol 500 mg 7 días o azitromicina 500mg 3 días o amoxicilina 7 días	6,3	3,5	79,6	17,1	1,2

Tabla 10. Estudios tratamiento no quirúrgico de la periimplantitis con antibióticos sistémicos (RCTs)								
Autor (año)	**Tamaño muestral**	**seguimiento**	**intervención**	**PS inicial**	**PS final**	**BoP inicial**	**BoP final**	**Ganancia ósea radiográfica**
Shibli (2019)	20	12 meses	Curetas teflón + metronidazol 400 mg + amoxicilina 500mg 14 días	7,0	3,9	86,6	50,6	0,4
	20		Curetas teflón + placebo	5,5	3,7	85	44,7	0,5
Almohareb (2020)	20	12 meses	PDT + desbridamiento mecánico	5,2	3,9	43,8	26,7	--
	20		Desbridamiento mecánico + amoxicilina 500 mg + metronidazol 400mg 7 días	5,4	4,1	45,3	18,1	--

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Los ensayos clínicos que evaluaron la eficacia de estos protocolos mostraron un impacto limitado en la reducción de la profundidad de sondaje, aunque el efecto sobre el sangrado al sondaje fue más notorio. La mayor reducción en la profundidad de sondaje registrado fue menor a 2 mm, mientras que, en la mayoría de los estudios, las puntuaciones de sangrado al sondaje siguieron siendo superiores al 50%. Además, este tipo de tratamientos no mostraron efectos sobre los niveles de pérdida ósea. Por lo tanto, el tratamiento no quirúrgico sólo o con medidas complementarias (antimicrobianos locales, antisépticos) o alternativas (terapia fotodinámica, aeropulidores, láser), ha demostrado tener una eficacia limitada para obtener la resolución de la enfermedad, no es efectiva en un porcentaje significativo de casos, especialmente en aquellos con patología más avanzada y configuración de defectos periimplantarios más complejos (Renvert & Polyzois, 2018). Los únicos estudios que muestran resultados prometedores son aquellos en los que se evalúa el tratamiento no quirúrgico con el uso complementario de antibióticos sistémicos, pero hasta el momento no había ensayos clínicos suficientes que pudiesen respaldar su efectividad.

1.1.7.2. Tratamiento quirúrgico de la periimplantitis

El objetivo del abordaje quirúrgico en el tratamiento de la periimplantitis es proporcionar acceso al implante para facilitar la descontaminación de la superficie y así lograr la resolución de la lesión inflamatoria. Se debe realizar en aquellos implantes que presentan signos persistentes de patología después de la terapia no quirúrgica, es decir, bolsas profundas (>5mm) junto con más de una localización con sangrado, supuración y progresión de la pérdida ósea (Herrera et al., 2023). Esta fase del tratamiento se recomienda sólo en aquellos pacientes que consiguen o mantienen hábitos de higiene oral adecuados, ya que se ha visto resultados desfavorables tras este tratamiento en aquellos pacientes con mal control de placa (Koldsland et al., 2018).

El procedimiento quirúrgico consiste en, además de la elevación del colgajo y la eliminación del tejido inflamado, la limpieza/descontaminación de la superficie del implante. Los procedimientos adicionales en el tratamiento quirúrgico de la periimplantitis pueden incluir: (I) el manejo de los defectos óseos periimplantarios utilizando enfoques reconstructivos, (II) métodos adicionales para la descontaminación de la superficie del implante y (III) el uso complementario de antibióticos locales/sistémicos (Herrera et al., 2023).

- **Eficacia del tratamiento quirúrgico con cirugía de acceso o cirugía resectiva:** este procedimiento incluye la elevación del colgajo, la eliminación de los tejidos inflamados y el desbridamiento/descontaminación de la superficie del implante. En la cirugía de acceso, los colgajos de tejido blando simplemente se

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reposicionan, mientras que los abordajes resectivos se desplazan apicalmente los colgajos a través de la remodelación del tejido blando y/o del tejido duro. La reducción estimada de la profundidad de sondaje es de 2,2 mm, la reducción de media del sangrado al sondaje es del 27% y la ganancia ósea media es de 0,2mm. La supervivencia de los implantes varía entre el 85,7% y el 100% a los 12 meses (Karlsson et al., 2023). Se recomienda este procedimiento en aquellos implantes donde no se ha alcanzado la resolución de la enfermedad con la primera fase del tratamiento no quirúrgico (Herrera et al., 2023).

- **Eficacia del tratamiento quirúrgico con cirugía reconstructiva:** Los procedimientos reconstructivos tienen como objetivo regenerar el defecto óseo, lograr la reintegración ósea y limitar la recesión de los tejidos blandos periimplantarios (Jepsen et al., 2019). La terapia reconstructiva de los defectos óseos periimplantarios incluye el uso de injertos óseos, injertos de reemplazo óseo, membranas de barrera, agentes bioactivos (factores de crecimiento, concentrados plaquetarios autólogos y amelogeninas) o combinaciones de los mismos. Independientemente de los biomateriales aplicados, la reducción media de la profundidad de sondaje varía entre 2,0 y 4,5 mm y se observa una reducción media del sangrado entre el 44,8% y el 86% a los 12 meses. La supervivencia del implante a los 12 meses oscila entre el 92% y el 100% (Donos et al., 2023). Este procedimiento se recomienda en implantes con defectos intraóseos ≥3 mm (Herrera et al., 2023).

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2

Justificación e Hipótesis

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2. JUSTIFICACIÓN E HIPÓTESIS

2.1. JUSTIFICACIÓN

En las últimas décadas la implantología dental se ha convertido en una de las mejores alternativas de tratamiento para rehabilitar a pacientes total o parcialmente edéntulos. De hecho, esta área de la odontología ha tenido un gran avance en vista de las mejoras en la calidad de vida que ofrece, en particular para pacientes con problemas de masticación o estéticos. Hasta la fecha, los implantes dentales han mostrado altas tasas de supervivencia de hasta el 99% en 10 años (Howe et al., 2019). Sin embargo, no se ha dado un énfasis adecuado en las complicaciones que pueden ocurrir después de la rehabilitación protésica. De las cuales, las complicaciones biológicas se consideran una de las principales causas de la pérdida de los implantes dentales.

Uno de los principales problemas ha sido una comprensión limitada de los innumerables factores que pueden poner a los pacientes en riesgo a padecer estas complicaciones biológicas, las denominadas enfermedades periimplantarias, que provocan un deterioro de los tejidos blandos y/o duros en los implantes. Además, la falta de consenso sobre las enfermedades periimplantarias ha contribuido aún más a la falta de un buen diagnóstico y tratamiento adecuado. Debido a esto, en los últimos años se ha puesto especial énfasis en investigar estas enfermedades que provocan problemas a nivel funcional y estético en los implantes dentales.

Las modalidades actuales para el tratamiento de la periimplantitis parecen dar lugar a resultados moderadamente efectivos, por lo que es urgente investigar estrategias de tratamiento para obtener mejores beneficios para el paciente en términos de salud. El tratamiento sigue siendo un desafío. Un estudio reciente con 5 años de seguimiento mostró un 44 % de recurrencia/progresión de la periimplantitis, y un 27 % de pérdida del implante después del tratamiento. La PS residual ≥ 6 mm fue el principal factor de riesgo de recurrencia y progresión de la periimplantitis (Carcuac et al., 2020), otros estudios han mostrado resultados similares con una recurrencia de la enfermedad que varía entre el 20-50% (Heitz-Mayfield et al., 2018; Monje & Nart, 2024; Stiesch et al., 2023), lo que destaca la necesidad de una intervención adecuada.

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Hasta el momento el tratamiento no quirúrgico había demostrado ser ineficaz para el control de esta enfermedad. Pero, una serie de publicaciones de casos han mostrado el posible beneficio adicional del tratamiento no quirúrgico en combinación con antibiótico sistémico. Teniendo en cuenta estos resultados clínicos prometedores, llevamos a cabo esta investigación para comprobar la hipótesis de si este procedimiento puede ser efectivo en la resolución de la enfermedad, y además, debido a las similitudes entre la periodontitis y la periimplantitis, también abordamos su posible asociación con la inflamación sistémica y cómo el tratamiento de esta enfermedad puede afectar a los parámetros inflamatorios sistémicos.

2.2. HIPÓTESIS

2.2.1. Hipótesis Nula

- No existe un beneficio adicional en términos de resolución de la periimplantitis cuando realizamos tratamiento no quirúrgico de las lesiones en combinación con la administración de metronidazol sistémico.
- No existe una respuesta inflamatoria sistémica en pacientes que presentan periimplantitis.
- No existe impacto del tratamiento no quirúrgico de la periimplantitis con metronidazol sistémico en la inflamación sistémica.

2.2.2. Hipótesis Alternativa

- El tratamiento no quirúrgico de la periimplantitis en combinación con metronidazol sistémico produce beneficios adicionales en términos de resolución de la enfermedad.
- La periimplantitis se asocia a la presencia de inflamación sistémica de grado bajo.
- Tras el tratamiento de la periimplantitis hay una modificación de la respuesta inflamatoria sistémica.

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3
Objetivos

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3. OBJETIVOS

3.1. OBJETIVOS GENERALES

Evaluar la eficacia del tratamiento no quirúrgico de la periimplantitis junto con metronidazol y su posible asociación con la inflamación sistémica.

3.2. OBJETIVOS ESPECÍFICOS

Estudio #1

Mostrar en una serie de casos con más de 1 año de seguimiento, los cambios en las variables clínicas y radiográficas tras el tratamiento no quirúrgico de periimplantitis en combinación con metronidazol sistémico.

Estudio #2

El objetivo principal de este ensayo es evaluar los resultados clínicos, radiográficos y microbiológicos después del tratamiento no quirúrgico de las lesiones periimplantarias en combinación con metronidazol sistémico en comparación con un grupo control con placebo.

Estudio #3

Investigar la asociación entre la presencia de periimplantitis y la inflamación sistémica, así como con la dislipemia.

Estudio #4

Evaluar el efecto del tratamiento no quirúrgico en combinación con metronidazol de la periimplantitis en los marcadores inflamatorios séricos (PCR, IL-6, IL-10 y TNF-α) durante un periodo de 6 meses frente al tratamiento no quirúrgico sólo, y además investigar los cambios en las fracciones lipídicas y los recuentos sanguíneos diferenciales.

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4

Material y Métodos. Resultados

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4. MATERIAL Y MÉTODOS. RESULTADOS

La explicación de los material y métodos, así como los resultados obtenidos en el presente trabajo de investigación, han sido publicados en formato de artículos científicos, en cuatro publicaciones independientes con las siguientes referencias:

Estudio #1

Liñares A, Pico A, **Blanco C**, Blanco J. Adjunctive systemic metronidazole to nonsurgical therapy of peri-implantitis with intrabony defects: a retrospective case series study. Int J Oral Maxillofac Implants. 2019 sep/oct;34(5):1237-1245. doi: 10.11607/jomi.7343.

Estudio #2

Blanco C, Pico A, Dopico J, Gándara P, Blanco J, Liñares A. Adjunctive benefits of systemic metronidazole on non-surgical treatment of peri-implantitis. A randomized placebo-controlled clinical trial. J Clin Periodontol. 2022 Jan;49(1):15-27. doi: 10.1111/jcpe.13564.

Estudio #3

Blanco C, Liñares A, Dopico J, Pico A, Sobrino T, Leira Y, Blanco J. Peri-implantitis, systemic inflammation, and dyslipidemia: a cross-sectional biochemical study. J Periodontal Implant Sci. 2021 Oct;51(5):342-351. doi: 10.5051/jpis.2100920046.

Estudio #4

Liñares A, Dopico J, **Blanco C**, Pico A, Sobrino T, Blanco J, Leira Y. The systemic impact of non-surgical treatment of peri-implantitis with or without adjunctive systemic metronidazole: Secondary analysis of a randomized clinical trial. Clin Oral Implants Res. 2024 Aug 2. doi: 10.1111/clr.14339.

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4.1. ESTUDIO #1

Liñares A, Pico A, **Blanco C**, Blanco J. Adjunctive systemic metronidazole to nonsurgical therapy of peri-implantitis with intrabony defects: a retrospective case series study. Int J Oral Maxillofac Implants. 2019 sep/oct;34(5):1237-1245. doi: 10.11607/jomi.7343.

4.1.1. Objetivo

Mostrar los resultados clínicos y radiográficos de lesiones de periimplantitis tratadas de forma no quirúrgica con metronidazol sistémico coadyuvante con un seguimiento medio de 50 meses.

4.1.2. Material y métodos

Se incluyeron en este estudio sujetos con diagnóstico de periimplantitis (profundidad de sondaje ≥ 5 mm con sangrado concomitante al sondaje y/o supuración) con evidencia radiográfica de defectos intraóseos > 2mm. Los implantes afectados recibieron una sesión de desbridamiento mecánico no quirúrgico con curetas de acero y ultrasonidos. Se prescribió inmediatamente metronidazol sistémico durante 7 días. Se registraron variables clínicas y radiográficas al inicio y al final del seguimiento.

4.1.3. Resultados

Se incluyeron en esta investigación dieciocho pacientes y 25 implantes. Al inicio, el nivel óseo radiográfico medio y el componente intraóseo fueron de 4,52 ± 2,14 mm y 3,93 ± 1,51 mm, respectivamente. Después de un seguimiento medio de 54 meses (rango: 12 a 108), la reducción media del nivel óseo radiográfico fue de 2,6 ± 0,21 mm y la reducción del componente intraóseo fue de 2,85 ± 0,37 mm ($p < .05$). Se observó una reducción media de la profundidad de sondaje de 4,66 ± 1,33 mm ($p < .05$).

4.1.4. Conclusiones

Dentro de los límites de este estudio, el tratamiento no quirúrgico de la periimplantitis con la administración coadyuvante de metronidazol sistémico ha demostrado una eficacia potencial en términos de reducción de la profundidad de sondaje y del defecto óseo radiográfico después de un seguimiento medio de 54 meses.

Adjunctive Systemic Metronidazole to Nonsurgical Therapy of Peri-implantitis with Intrabony Defects: A Retrospective Case Series Study

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Carlota Blanco, DDS[1]/Juan Blanco, MD, DDS, MSc, PhD[1]

Purpose: *To show the clinical and radiographic results of intrabony peri-implantitis lesions treated nonsurgically with adjunctive systemic metronidazole with a mean follow-up of 50 months.* ***Materials and Methods:*** *Subjects diagnosed with peri-implantitis (probing depth ≥ 5 mm with concomitant bleeding on probing and/or suppuration) with radiographic evidence of intrabony defects > 2 mm were included in this study. Implants affected received one session of nonsurgical mechanical debridement with ultrasonic and steel curettes. Systemic metronidazole was immediately prescribed for 7 days. Clinical and radiographic variables were registered at baseline and at the end of follow-up.* ***Results:*** *Eighteen patients and 25 implants were included in this investigation. At baseline, the mean radiographic bone level and intrabony component were 4.52 ± 2.14 mm and 3.93 ± 1.51 mm, respectively. After a mean follow-up of 54 (range: 12 to 108) months, the mean radiographic bone level reduction was 2.6 ± 0.21 mm, and the intrabony component reduction was 2.85 ± 0.37 mm (P < .05). A mean probing depth reduction of 4.66 ± 1.33 mm was observed (P < .05).* ***Conclusion:*** *Within the limits of this study, nonsurgical treatment of peri-implantitis with the adjunctive administration of systemic metronidazole has shown potential effectiveness in terms of probing depth and radiographic defect reduction after a mean follow-up of 54 months.* Int J Oral Maxillofac Implants 2019;34:1237–1245. doi: 10.11607/jomi.7343

Keywords: *metronidazole, nonsurgical peri-implant therapy, peri-implantitis, radiographic bone loss*

Peri-implantitis is characterized by soft tissue inflammation accompanied by a rapid loss of hard tissues and pocket formation around dental implants.[1] Based on cross-sectional studies, moderate and severe stages of peri-implantitis occur in 15% to 20% of patients with dental implants.[2,3] Studies with more than 100 patients and more than 5 years of follow-up (8.6 mean years of follow-up) showed that peri-implantitis (bone loss ≥ 2 mm) occurs in 10% of implants and 21% at the patient level.[2–6]

Peri-implant and periodontal tissues have common clinical characteristics, but there are also structural differences that may influence host response against infection.[7,8] The results obtained from human biopsies have shown that peri-implantitis and periodontitis lesions present a large inflammatory infiltrate of connective tissue (ICT) lateral to a pocket epithelium, but the apical extension of this infiltrate in peri-implantitis is closer to the bone crest than in periodontitis. Another important consideration is the self-limiting process that occurs at teeth but not at implant sites where the ICT extends to the bone crest.[9,10] On teeth, the ICT is encapsulated and separated from apical bone for healthy connective tissue attached to the root surface. However, on implants, this ICT reaches the bone, and is more evident on rough implant surfaces.[10] Furthermore, peri-implantitis lesions progress in an accelerating pattern. The onset may be initiated within the first 3 years of function.[11] It has been shown that microbial colonization of the implant surface is the main causative factor in the pathogenesis of this disease.[12] Other factors that have been postulated as potential etiologic factors have been excessive occlusal overload[13] and excess of cement as a foreign body reaction.[14,15] Moreover, the work by Albrektsson's group postulates that progressive bone loss is related to a complicating

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factor resulting in an immuno-osteolytic reaction accounting for the ongoing bone resorption. This may be caused by numerous factors related to marginal bone level changes such as abutment height, insertion torque, implant position, poor oral hygiene, or absence of maintenance.[16,17] Moreover, a regularly supportive therapy program seems to be crucial to prevent peri-implantitis. Furthermore, the history of periodontal disease and smoking appear to be factors that increase the appearance of peri-implantitis.[18–20]

The composition of peri-implantitis microbiota causing inflammation and destruction of hard tissues is similar to periodontitis.[21] However, there are enough data showing that although periodontal and peri-implant diseases are similar with regard to the bacterial composition, this is not completely similar.[22] Great counts and proportions of gram-negative anaerobic bacteria and great prevalence of pathogens associated with periodontitis, clinically characterized implants with peri-implantitis.[23] The microbiologic profile of advanced peri-implantitis lesions is composed mainly by gram-anaerobic bacteria.[24,25] An important role is played by *Porphyromonas gingivalis*, and also a cluster of *Tannerella forsythia* and *Staphylococcus aureus*.[26] Moreover, studies have found the presence of *Staphylococcus aureus*, enteric rods, and Candida at peri-implantitis sites due to the attraction of titanium for such bacteria and fungi.[26]

Thus, the rationale of using a systemic antibiotic such as metronidazole as adjunctive to nonsurgical peri-implantitis therapy may be justified. In fact, it has been shown that there are added benefits to the treatment of refractory periodontitis after nonsurgical periodontal therapy.[27]

The treatment of peri-implantitis aims to control the infection and reduce bacterial load. The evidence on periodontal treatment is the basis for the treatment of peri-implantitis. Surgical and nonsurgical techniques have been developed in peri-implantitis, but nonsurgical treatment alone has been shown to be ineffective.[28] However, case series and cohort studies have shown added benefit to nonsurgical therapy when systemic antibiotics were used adjunctively.[29–32]

Recent publications have shown the potential of nonsurgical periodontal therapy in deep intrabony defects.[33,34] Moreover, the regression analysis showed a significant radiographic defect fill increase if systemic antibiotics were used as adjunctive to nonsurgical therapy.[34]

The present case series study shows radiographic and clinical outcomes after nonsurgical peri-implant treatment with adjunctive systemic metronidazole in advanced peri-implantitis lesions.

MATERIALS AND METHODS

Files and radiographs of patients with at least one implant diagnosed for peri-implantitis who had received nonsurgical treatment in combination with systemic metronidazole at a Specialist Private Practice in Periodontology (A Coruña, Spain) were analyzed. Patients with periodontitis were treated and included in the maintenance program before.

The diagnosis of peri-implantitis was based on the following parameters[35]:

- Probing depth > 5 mm
- Peri-implant sites with bleeding on probing (BOP+) and/or suppuration
- Radiographic evidence of intrabony defect > 2 mm

To be included, patients needed to meet the following criteria:

- Older than 18 years of age
- At least one implant initially diagnosed for peri-implantitis (probing depth > 5 mm with bleeding on probing [BOP+] and/or suppuration and radiographic evidence of intrabony defect > 2 mm)
- Had received nonsurgical treatment in combination with systemic metronidazole
- Full-mouth plaque score < 25%
- Full-mouth bleeding score < 25%
- Cemented or screw-retained single crowns or fixed dental prostheses
- A minimum follow-up of 12 months.

The following exclusion criteria were applied:

- Systemic pathology that contraindicates treatment
- History of taking systemic antibiotics in the last 3 months
- Uncontrolled periodontal disease
- Smoking more than 20 cigarettes per day
- Mobility of the implant

The study was performed in accordance with the principles stated in the Declaration of Helsinki. Oral informed consent for treatment was obtained.

Nonsurgical Treatment

After the diagnosis of peri-implantitis, patients were instructed in oral hygiene and motivation was reinforced. After that, one session of nonsurgical treatment consisting of supra- and submucosal mechanical debridement using ultrasound with a metal periodontal tip (EMS, Electro Medical Systems) was performed with no time restriction. Treatment was performed by an experienced periodontist (A.L.). Ultrasonic

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debridement was performed with concomitant irrigation of chlorhexidine of 0.12% (Perio AID, Dentaid). The tip removed granulation tissue and also touched the implant surface. After that, a steel curette Columbia 4R/4L (LM Instruments Oy) was used to remove granulation tissue and minor mucosa curettage. If oral hygiene was not allowed by prosthetic design, a contour correction was made. Immediately after treatment, patients were prescribed to apply a chlorhexidine gel in the area 2 times a day for 2 weeks, and systemic metronidazole 250 mg, 2 tablets every 8 hours for 7 days was also prescribed. The gel was applied by the patient on the peri-implant mucosa after brushing. No microbiologic testing was performed. After a follow-up of 8 to 10 weeks, a clinical re-evaluation was performed, and new periapical radiographs were taken. Long-cone parallel technique was performed for the digital radiographic evaluation.[36] After that, the patient entered into a 4- to 6-month recall program, consisting of oral hygiene reinforcement as needed, subgingival instrumentation with low power ultrasonics under anesthesia if required, and annual radiographic control.

Clinical Variables

Probing depth was measured to the closest millimeter with a manual PCP15 periodontal probe (Hu-Friedy) at six sites per implant, and the deepest site was recorded.

Demographic data (age, sex, history of periodontitis, smoking) and information related to the implant location, type of implant, implant restoration (cemented or screwed), and type of prosthesis were also recorded. History of periodontitis was determined by assessing the attachment loss using a periodontal probe. Patients with proximal attachment loss of ≥ 3 mm in ≥ 2 nonadjacent teeth were diagnosed with periodontitis.[37] Smoking status was classified as: nonsmoker (0 cigarettes/day), light smoker (0 to 10 cigarettes /day), and heavy smoker (> 10 to 20 cigarettes/day).

Radiographic Examination

With the long-cone technique, an intraoral radiograph was obtained at baseline, reevaluation, and at follow-up to evaluate crestal bone level. Those radiographs were imported to digital radiographic examination software (ImageJ 1.47 V Wayne Rasband, National Institutes of Health). All examinations were performed by two independent and calibrated examiners (A.L., A.P.) to the nearest 0.1 mm using ImageJ software, and the mean of the two measurements was calculated. The height of the dental implant was taken as reference for the calibration, which yielded a pixel/mm ratio. The implant shoulder was used as a fixed reference point. All radiographic measurements were made by a trained and calibrated examiner (A.P.).

The following measurements were recorded at the mesial and distal aspects:

- Radiographic bone level: distance between the implant shoulder and the bottom of the defect at bone-level implants. At tissue-level implants, the rough-smooth interface was used as the landmark; thus, the machined collar length was subtracted according to the macro design of the implant.
- Intrabony component: Distance between the bottom of the defect and the line connecting the mesial and distal interproximal bone crest
- Defect resolution: The percentage was calculated as follows:

$$\frac{\text{Defect resolution} \times 100}{\text{Depth of intrabony (baseline)}} = \text{\% of defect resolution}$$

- Intrabony defect angle: Radiographic angle of the defect was measured identifying the most apical extension of the intrabony destruction adjacent to the implant wall and the most coronal position of the alveolar bone crest of the intrabony defect.

As the radiographies were not standardized, the distortion between follow-up and baseline was estimated as it was described in previous investigations.[38] In order to calculate this distortion, a fixed distance as the implant length (distance from the implant shoulder to the implant apex [IS-IA]) was measured on the radiographs, and then a correction factor was calculated as follows:

IS-IA (baseline) / IS-IA (follow-up) = Correction factor

When the implant length could not be measured, the implant width was assessed (measured at the implant shoulder). Implant length was obtained from the surgical report at implant placement.

Data Analysis

Clinical (probing pocket depth) and radiographic variables (radiographic bone level, intrabony component, and intrabony defect angle) were measured at baseline and at the last follow-up examination and averaged to represent changes over time; significance of differences between follow-up and diagnosis were compared.

After application of the Shapiro-Wilk test to verificate the normality assumptions, parametric paired *t* test was applied to analyze probing pocket depth and intrabony defect angle. A nonparametric test (Wilcoxon signed-rank test) was used to analyze differences in radiographic bone level and intrabony component variables. The statistical analysis was performed by an author (A.P.) using SPSS software (Version 20.0 SPSS). The level of significance was set at $P < .05$. The unit of analysis was patient level.

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Table 1 Sample Description

Characteristic	No.
Age (y)	60 (32–79)
Sex	10 men/8 women
Smoking	4 smokers/14 nonsmokers
Systemic diseases	16 healthy/2 diabetic
Type of implant	14 tissue level/11 bone level
History of periodontitis	8 patients with chronic periodontitis
Retention	20 screw-retained / 5 cemented
Type of superstructure	13 FPP/7 single crowns/5 full-arch
Location	16 mandible/9 maxilla
Follow-up (mo)	54 (12–108)

FPP = fixed partial dental prosthesis.

Table 2 Clinical and Radiographic Parameters (mean ± SD) at Baseline and at End of Follow-up: Patient Level Analysis

	Baseline	Follow-up	Difference	*P* value
PD (mm)	8.72 ± 2.13	4.06 ± 0.8	4.66 ± 1.33	< .05
RBL (mm)	4.52 ± 2.14	1.92 ± 1.93	2.6 ± 0.21	< .05
IC (mm)	3.93 ± 1.51	1.08 ± 1.14	2.85 ± 0.37	< .05
IDA (%)	33.50 ± 9.59	67.80 ± 19.04	34.3 ± 9.45	< .05

PD = pocket depth; RBL = radiographic bone level; IC = intrabony component; IDA = intrabony defect angle.

RESULTS

Study Sample

Eighteen patients and 25 implants were included in this study (Table 1). The mean age was 60 (range: 32 to 79) years. Two patients were smokers. Sixteen patients were systemically healthy. Two patients were diabetics. Eight patients were diagnosed with chronic periodontitis and treated before implant placement. At the diagnosis of peri-implantitis, four patients also needed to be treated for periodontitis.

Fourteen tissue-level and 11 bone-level implants, all with rough surface, were diagnosed and treated. The tissue-level implants had a 1.8-mm smooth collar length. Eleven patients had one implant with peri-implantitis, and seven patients had two implants affected. The majority (16 implants) were placed in the mandible. Twenty were screw-retained restorations, while only five were cemented. All implants were placed in pristine bone since no guided bone regeneration technique was performed previously. A total of 13 implants were included in fixed partial restorations, seven in single crowns, and five in full-arch prostheses. The mean period of implant function at baseline was 79 (range: 4 to 276) months with a mean follow-up of 54 (range: 12 to 108) months after therapy. In 21 implants, peri-implantitis was diagnosed at least 1 year after implant placement, while in four implants, the diagnosis was made before.

Clinical Data

At the end of follow-up, a mean probing depth reduction of 4.66 ± 1.33 mm was observed ($P < .05$). After treatment, mean probing depth changed from 8.72 ± 2.13 mm at baseline to 4.06 ± 0.8 mm (Table 2).

Radiographic Data

At diagnosis, the mean radiographic bone level was 4.52 ± 2.14 mm and the intrabony component (IC) was 3.93 ± 1.51 mm. After a mean follow-up of 54 (range: 12 to 108) months, the mean radiographic bone level was 1.92 ± 1.93 mm, and the intrabony component was 1.08 ± 1.14 mm ($P < .05$). The mean radiographic bone level improved 2.6 ± 0.21 mm ($P < .05$). The mean intrabony component was reduced 2.85 ± 0.37 mm ($P < .05$), from 3.93 ± 1.51 mm at the diagnosis to 1.08 ± 1.4 mm at the end of follow-up. This means a 62.63% radiographic defect resolution. The mean angle of the intrabony defects was augmented after treatment. A statistically significant difference was observed (34.3 ± 9.45 degrees; $P < .05$) between the two time points (Table 2). No differences were observed between mesial and distal locations for any of the parameters analyzed. Examples of radiographic outcomes are displayed in Fig 1. Clinical and radiographic outcomes are also shown in Figs 2 and 3.

DISCUSSION

The present cases series study shows the potential successful clinical and radiographic outcomes following nonsurgical peri-implant treatment with adjunctive systemic metronidazole. The adjunctive use of systemic antibiotics could be justified based on the rapid progression of peri-implantitis and the differences between advanced peri-implantitis lesions and periodontitis lesions against the recognized putative pathogens.[9–11] The capacity of certain bacteria to invade soft tissues in periodontal lesions has been shown in classic studies.[39,40] No studies have addressed the potential of bacterial invasion in peri-implant lesions. However, studies have shown that peri-implantitis lesions presented pocket epithelium ulceration with potential invasion of the subepithelial connective tissue.[41–43] This may be a reason why conventional nonsurgical therapy has no improvements in treating

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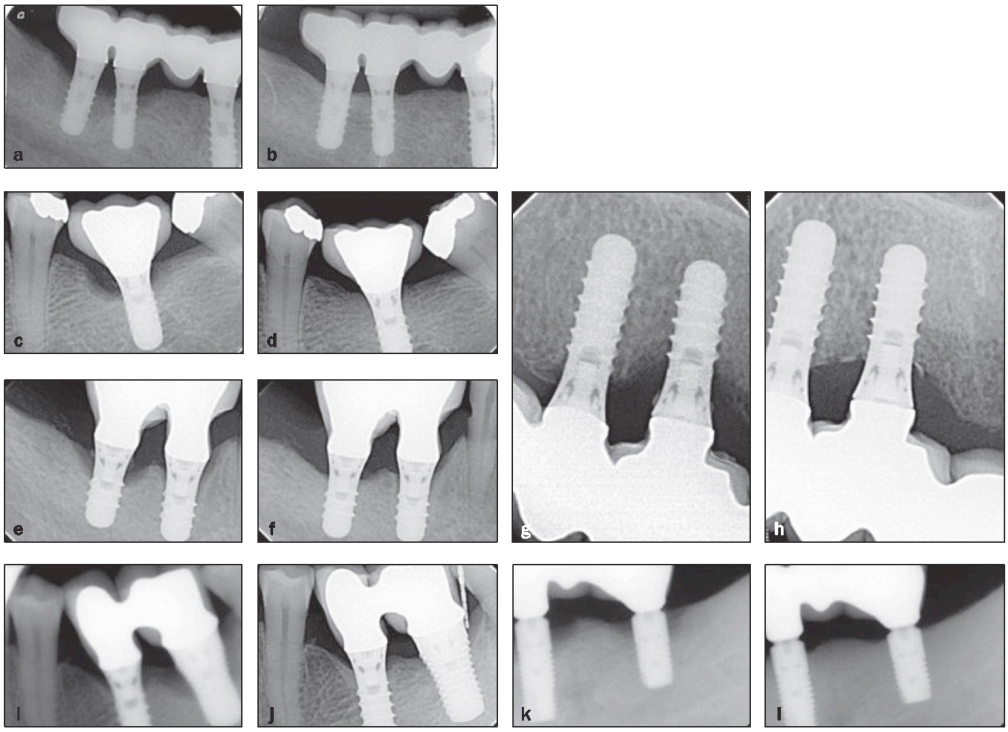


Fig 1 Radiographic outcome cases included in the study. *(a)* Baseline radiograph in a male nonsmoker 69 years of age. *(b)* 9-year follow-up radiograph. Note radiographic bone fill on distal implants. *(c)* Baseline radiograph of a female nonsmoker 72 years of age. *(d)* 6-year follow-up radiograph. *(e)* Baseline radiograph of a male nonsmoker 75 years of age. *(f)* 5-year follow-up. *(g)* Baseline radiograph of a male diabetic nonsmoker 60 years of age. *(h)* 9 years after therapy. *(i)* Baseline radiograph of a peri-implantitis lesion in a male nonsmoker 40 years of age. *(j)* Follow-up radiograph taken 5 years after therapy. *(k)* Baseline radiograph of a male light smoker 68 years of age. *(k)* 2-year follow-up radiograph.

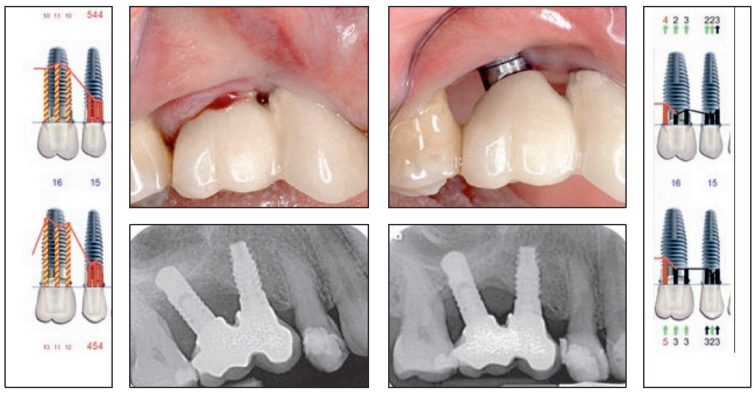


Fig 2 Case 1. *(Left)* Female patient 72 years of age. Right maxillary first molar implant with advanced peri-implantitis showing bleeding, suppuration, and deep probing depths, with evidence of radiographic bone loss. *(Right)* 18 months later with reduced probing depth and radiographic bone gain. After nonsurgical therapy, patient was set in a 6-month recall program.

peri-implantitis, since infection may be present not only within the pocket but also within the connective tissue. This feature of bacteria invasion may be more severe on implants with rough surfaces since the inflammatory infiltrate is larger when compared with the lesions in the periodontium and reaches the bone.[10]

In the consensus report from the Sixth European Workshop on Periodontology, it was concluded that surgical therapy is usually required due to the incapacity of nonsurgical treatment to resolve the majority of peri-implantitis lesions.[44] The review provided by Renvert and coworkers identified just one randomized controlled clinical trial on nonsurgical mechanical debridement of peri-implantitis with no clinical changes after 6 months of treatment.[28,45] Thus, it seems that conventional nonsurgical peri-implant therapy alone

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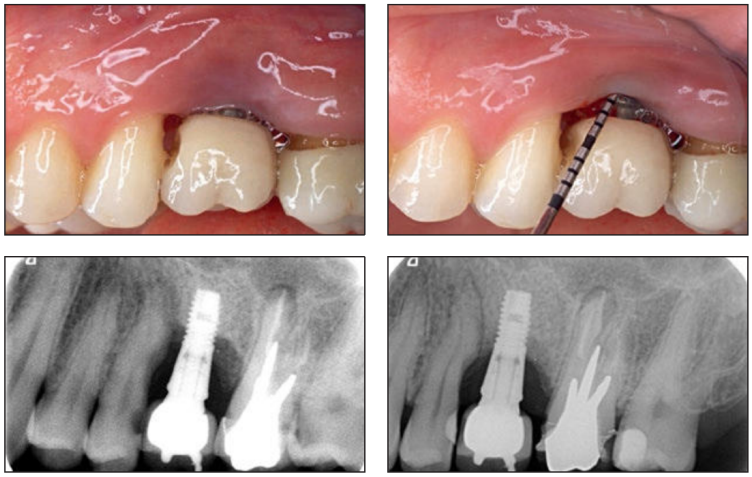


Fig 3 Case 2. A woman 30 years of age, systemically healthy with advanced peri-implantitis lesion at left maxillary first molar. Decay at left maxillary second premolar and radiolucency at left maxillary second molar. Note situation 1 year after nonsurgical therapy of peri-implantitis lesion with decreased inflammation and evidence of radiographic bone gain.

is unable to reduce peri-implantitis lesions. Adjunctive therapy to nonsurgical mechanical debridement has been studied, such as laser, local, and systemic antibiotics (for review, see Renvert et al [2008]).[28] Some minor improvements have been observed when local antibiotics were applied adjunctively. The use of lasers showed almost null improvements. A recent randomized controlled trial studied the adjunctive use of light-activated disinfection (LAD) therapy with mechanical cleaning of implants affected by peri-implantitis. After a year of follow-up, the results showed that there was not any improvement in clinical outcomes compared with mechanical cleaning alone.[46] However, Mettraux et al, in a retrospective case series study, evaluated the clinical effect of nonsurgical mechanical therapy of peri-implantitis in combination with the repeated application of a diode laser.[55] After 2-year follow-up, a significant reduction in probing pocket depth and in the percent of implants with ≥ 1 site with bleeding on probing was observed, showing the need for randomized clinical trials to obtain more evidence on this topic.

On the other hand, promising results were observed in case series studies when systemic antibiotics were used in combination with nonsurgical mechanical debridement.

Mombelli and Lang observed a significant reduction of probing depths and microbial parameters after nonsurgical treatment and systemic antimicrobial therapy (1,000 mg ornidazole for 10 consecutive days) of implants affected by a marked bone loss. After 12 months of treatment, probing pocket depth was reduced from 5.9 to 3.4 mm. Gram-anaerobic rods were also reduced from 40% to 16%. Moreover, in some cases, a radiographic bone gain was observed.[29] Other case series showed probing depth reduction of 2.5 mm and radiographic bone fill of 1.6 mm after nonsurgical treatment of peri-implantitis with different systemic antibiotics according to a susceptibility test.[31] A recent study analyzed the clinical outcomes of nonsurgical treatment with adjuvant povidone-iodine application and an adjuvant administration of systemic antibiotics. The nonsurgical therapy consisted of the use of ultrasonic devices with metal tips, the use of curettes to remove the mucosal tissues facing implant surfaces, and glycine powder air polishing accompanied by repeated submucosal application of povidone-iodine. In such patients diagnosed with severe periodontitis, amoxicillin and metronidazole were prescribed for 7 days. After 12 months of follow-up, implants treated without antibiotics showed significant reductions of mean pocket depth (1.4 ± 0.7 mm), clinical attachment level (1.3 ± 0.8 mm), and bleeding on probing. In the deepest pocket, the analysis revealed more pronounced changes in comparison with shallow pockets. There were no significant changes in clinical outcomes in the group of antibiotics. However, the presence of implants with deep pockets and bleeding on probing after therapy was lower in patients taking systemic antibiotics than in those without (31.8% ± 12.6% vs 20.8% ± 14.7%).[32] It is important to mention that in that study the mean probing depth at baseline was 4.8 ± 0.9 mm. This is substantially smaller than the baseline mean probing depth presented in the present investigation (8.72 ± 2.13 mm). Thus, the potential added benefit of systemic antibiotics may be related to disease severity as also occurs in periodontitis.[48] In the present study, it was shown that metronidazole as adjunctive to nonsurgical therapy of peri-implantitis has the potential to improve clinical/radiographic outcomes.

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Some improvements have been shown when nonsurgical therapy was combined with local antibiotics (for review, see Renvert et al [2008]).[28] No controlled clinical trials have tested the potential adjunctive benefits of systemic antibiotics in the nonsurgical therapy of peri-implantitis. However, three case-series studies have shown a clear improvement in terms of clinical and radiographic outcomes.[29–31] The rationale behind why clinical and radiographic improvements were achieved in those studies remains unclear. It is important to point out that peri-implantitis lesions (particularly rough surfaces) reach the bone and are much more aggressive than periodontitis.[10] Moreover, the histology of peri-implantitis lesions has shown clear signs of epithelium ulceration.[41,42] It can be hypothesized that bacterial invasion of subepithelial connective tissue may be present in peri-implantitis lesions. This concept of bacterial invasion was first described by Listgarten (1965) with human biopsies of acute necrotizing periodontitis lesions.[39] Later on, bacterial invasion in localized aggressive and advanced chronic periodontitis lesions was shown.[40,41] Thus, mechanical debridement alone may leave an important colony of bacteria within the connective tissue. In fact, studies performed in localized aggressive periodontitis lesions and advanced chronic periodontitis showed that scaling alone could not reduce the number of *Aggregatibacter actinomycetemcomitans*; however, with gingival curettage or flap surgery, *Aggregatibacter actinomycetemcomitans* numbers could be decreased.[41,49] This is also the rationale of performing minor peri-implant mucosa curettage. Moreover, systemic antibiotics have been shown to improve clinical outcomes in aggressive forms of periodontitis.[47,48] Diffusion of antibiotics within the subepithelial connective tissue may be achieved after systemic administration. The rationale of using metronidazole as adjunctive to nonsurgical therapy comes from the microflora of peri-implantitis lesions, where gram-anaerobic bacteria are predominant. Thus, it is the hypothesis that metronidazole could be the antibiotic of choice in treating advanced peri-implantitis lesions. Not only is there a lack of controlled clinical trials with systemic antibiotics, but also of those comparing different antibiotics and/or regimens. Thus, the potential benefit of other forms of systemic antibiotics cannot be discarded. Care should be taken with metronidazole in avoiding alcohol intake during treatment, and patients under anticoagulant therapy drugs, since metronidazole may increase the international normalized ratio (INR) of those patients. Another advantage of metronidazole is low resistance profile. A big concern is occurring nowadays with the increase of bacteria resistance to some systemic antibiotics.[50] Moreover, some clinical data of using systemic antibiotics after surgical therapy have shown no added benefits in treating peri-implantitis lesions on implants with a smooth surface.[51] However, that study showed a clear benefit in treating rough surfaces surgically with adjunctive systemic antibiotics. Successful outcomes at 1 year were almost double in the group treated surgically plus systemic antibiotics compared with those of the no antibiotic group. This may be explained due to a less aggressive form of lesion in smooth surfaces,[9] and it may be hypothesized that bacteria invasion in those peri-implantitis lesions of smooth surfaces may not be present. This is a reason for a classification proposal of peri-implantitis lesions into aggressive forms (mainly in rough surfaces and rapid progression), and chronic peri-implantitis lesions (smooth surfaces and slow progression).

Although there was significant improvement in clinical and radiologic parameters obtained in this study, differences in length of follow-up, radiographic standardization, and the absence of a control group without systemic antibiotics need to be taken into account. However, data from clinical trials of nonsurgical therapy without antibiotics have shown no improvements. The radiographic improvement of the present cases series may be related to four important points: *(1)* improvement in oral hygiene; *(2)* debridement and curettage of the defect; *(3)* elimination of pathogenic bacteria with antibiotics; and *(4)* the stability of clot formation after debridement may lead to improvement of radiographic bone fill. In fact, clot stability may be a key point in periodontal regeneration.[52] This feature may be related to defect morphology. In periodontal studies, surgical and nonsurgical treatments of intrabony defects have shown that the narrower the defect angle, the higher the chance to obtain more defect resolution.[53] Moreover, it was shown that defect configuration on surgical treatment of peri-implantitis plays an important role in clinical and radiographic outcomes. Self-contained crater defects showed a higher chance of resolution than defects that present some missing bony wall.[54]

Case-series studies are important to create new research hypotheses. Thus, randomized controlled clinical trials are needed to test the null hypothesis that nonsurgical treatment of peri-implantitis with or without systemic antibiotics shows no difference.

CONCLUSIONS

Within the limits of this study, nonsurgical treatment of peri-implantitis with adjunctive administration of systemic metronidazole has shown favorable probing depth reduction and radiographic defect reduction in patients with good oral hygiene and maintenance. Controlled studies are needed to test this proof of principle treatment protocol.

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4.2. ESTUDIO #2

Blanco C, Pico A, Dopico J, Gándara P, Blanco J, Liñares A. Adjunctive benefits of systemic metronidazole on non-surgical treatment of peri-implantitis. A randomized placebo-controlled clinical trial. J Clin Periodontol. 2022 Jan;49(1):15-27. doi: 10.1111/jcpe.13564.

4.2.1. Objetivo

Estudiar los resultados clínicos, radiográficos y microbiológicos después de la terapia no quirúrgica de la periimplantitis con o sin metronidazol sistémico coadyuvante.

4.2.2. Material y métodos

Se llevó a cabo un ensayo clínico aleatorizado controlado con placebo en 32 sujetos (62 implantes) diagnosticados con periimplantitis. Los implantes recibieron una sesión de desbridamiento mecánico no quirúrgico y metronidazol sistémico o placebo. Los resultados clínicos, radiográficos y microbiológicos se evaluaron al inicio, a los 3, 6 y 12 meses.

4.2.3. Resultados

Después de 12 meses, el grupo test resultó en una reducción significativamente mayor de la PS (2,53 frente a 1,02 mm) y ganancia de CAL (2,14 frente a 0,53 mm) ($p < 0,05$) en comparación con el grupo placebo. El grupo test también obtuvo una ganancia ósea radiográfica adicional (2,33 frente a 1,13 mm) en comparación con el grupo placebo ($p < 0,05$). Se observó una disminución significativamente mayor en los recuentos de *Porphyromonas gingivalis*, *Tannerella forsythia* y *Campylobacter rectus* en comparación con el grupo control ($p < 0,05$). Al final del seguimiento, el 56,3% de los pacientes cumplieron los criterios de éxito en el grupo test y el 25% en el grupo control.

4.2.4. Conclusiones

El uso de metronidazol sistémico como complemento al tratamiento no quirúrgico de la periimplantitis resultó en mejoras adicionales significativas en los parámetros clínicos, radiográficos y microbiológicos después de 12 meses de seguimiento.

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ORIGINAL ARTICLE

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Adjunctive benefits of systemic metronidazole on non-surgical treatment of peri-implantitis. A randomized placebo-controlled clinical trial

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Abstract

Aim: To study clinical, radiographic, and microbiological outcomes after non-surgical therapy of peri-implantitis with or without adjunctive systemic metronidazole.

Materials and Methods: A randomized placebo-controlled clinical trial was carried out in 32 subjects (62 implants) diagnosed with peri-implantitis. Implants received a mechanical non-surgical debridement session and systemic metronidazole or placebo. Clinical, radiographic, and microbiological outcomes were evaluated at baseline, 3, 6, and 12 months.

Results: After 12 months, the test treatment resulted in significantly greater PPD reduction (2.53 vs. 1.02 mm) and CAL gain (2.14 vs. 0.53 mm) (p value <.05) in comparison with placebo. The test treatment also resulted in additional radiographic bone gain (2.33 vs. 1.13 mm) compared with placebo (p value <.05). There was a significantly greater decrease in *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Campylobacter rectus* counts compared with the control group (p value <.05). At the end of follow-up, 56.3% of patients met the success criteria in the test group and 25% in the control group.

Conclusions: The use of systemic metronidazole as an adjunct to non-surgical treatment of peri-implantitis resulted in significant additional improvements in clinical, radiographic, and microbiological parameters after 12 months of follow-up.

This study is registered in ClinicalTrials.gov (NCT03564301).

KEYWORDS
antibiotic, metronidazole, non-surgical, peri-implantitis, treatment

Clinical Relevance

Scientific rationale for study: Recent case series studies have shown improvements in clinical and radiographic parameters with non-surgical treatment and systemic adjunctive antibiotics in the treatment of peri-implantitis. However, RCTs to confirm these findings are lacking.

Principal findings: As initial therapy, systemic metronidazole as an adjunct to non-surgical therapy in peri-implantitis lesions achieved significant additional improvements in terms of clinical,

Carlota Blanco, Alex Pico, and Jose Dopico contributed equally to this manuscript.

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radiographic, and microbiological outcomes compared with placebo. Despite these promising results, only 53.6% of the patients treated with adjunctive antibiotic met the success criteria. *Practical implications*: In light of the results of this RCT, modifications in treatment protocols for peri-implantitis could be implemented.

1 | INTRODUCTION

Peri-implantitis is defined as a "pathological condition associated with plaque that occurs in the tissues surrounding dental implants, characterized by inflammation of the peri-implant mucosa and the subsequent progressive loss of bone" (Berglundh et al., 2018). Although survival of dental implants is high (Howe et al., 2019), the prevalence of peri-implant diseases is also very significant. Using the case definition criteria proposed by Sanz and Chapple (Sanz & Chapple, 2012), a recent systemic review showed a prevalence of 18.5% at patient level and 12.8% at implant level (Dreyer et al., 2018). A study in a Spanish population, with data from 474 implants in 275 patients, showed an implant-level peri-implantitis prevalence of 20% (bone loss ≥2 mm) and 24% at patient level (Rodrigo et al., 2018). Considering the case definitions proposed at the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (Renvert et al., 2018) (bone loss ≥3 mm), 14% of patients and 11% of implants presented peri-implantitis in the aforementioned Spanish study (Rodrigo et al., 2018).

It is widely accepted that poor oral hygiene, history of periodontitis, and tobacco smoking are well-documented risk factors for peri-implantitis. Other factors such as diabetes, alcohol consumption, and genetic traits may also increase the risk of peri-implantitis (Schwarz et al., 2018).

Peri-implantitis and periodontitis have common clinical features. However, marked differences exist. It has been shown that lesions of both pathologies show large amounts of inflammatory infiltrate, spreading to a more apical level in peri-implantitis (Berglundh et al., 2011; Carcuac et al., 2013). Moreover, the microbiota associated with peri-implantitis is characterized by a mixed anaerobic infection, with a composition similar to the subgingival microbiota of periodontitis lesions, but greater complexity, composed of predominantly non-cultivable gram-negative species (Lafaurie et al., 2017).

There is no consensus on standards of care or clinical protocols for the management of peri-implant diseases (Renvert et al., 2013). In addition, different available therapeutic approaches have shown moderately successful outcomes (Renvert & Polyzois, 2018). It has been shown that non-surgical treatment is effective for peri-implant mucositis (Suárez-López Del Amo et al., 2016). In contrast, in peri-implantitis, non-surgical therapy alone is not effective in a significant proportion of cases (Renvert et al., 2008). Despite the fact that the clinical endpoint for success may not be achieved in part of the cases, especially those with more advanced pathology, published case series studies have shown promising additional benefits when using systemic antibiotics as an adjunct to non-surgical therapy (Mombelli & Lang, 1992; Estefanía-Fresco et al., 2019; Liñares et al., 2019; Nart et al., 2020). Non-surgical treatment of advanced peri-implantitis lesions with intra-bony defects in combination with systemic metronidazole resulted in reduction in probing depth of 4.6 and 2.6 mm in radiographic bone gain after 54 months of follow-up (Liñares et al., 2019).

To date, no randomized clinical trials have been conducted to assess the effects of systemic metronidazole as an adjunct to non-surgical treatment of peri-implantitis. The main aim of this trial is to assess clinical, radiographic, and microbiological outcomes after non-surgical treatment of peri-implant lesions in combination with adjunctive systemic metronidazole.

2 | MATERIALS AND METHODS

2.1 | Experimental design

This study was a triple-blind, randomized, placebo-controlled, clinical trial with 12 months follow-up. The study was carried out in accordance with the principles described in the Declaration of Helsinki on experimentation with human beings (Order SCO/256/2007), and was approved by the Ethical Committee of Galicia (2017/508). It is registered in ClinicalTrials.gov (NCT03564301).

2.2 | Patient screening

Subjects eligible for the study were identified from patients referred to the Periodontology Unit of the University of Santiago de Compostela between January 2018 and July 2019. The study included subjects with (I) ≥ 18 years of age, (II) presence of at least one implant diagnosed with peri-implantitis defined as presence of bleeding on probing and/or suppuration, probing depth ≥6 mm and ≥3 mm of detectable bone loss after initial re-modelling (Berglundh et al., 2018), and (III) absence of implant mobility. Subjects were excluded from the study if they (I) had history of allergy to metronidazole, (II) had received treatment with bisphosphonates, (III) were pregnant or breast-feeding, (IV) had received antibiotic treatment in the previous 3 months, or (V) had systemic conditions that contraindicated treatment.

2.3 | Sample size calculation

Sample size calculation was made for the primary outcome variable, probing pocket depth (PPD). Due to the absence of previous RCTs,

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the 6 months visit data of the first 25 patients recruited for the study were used to estimate sample size. Standard deviation (SD) was 1.703 for the test group and 1.803 for the control group. The mean difference was 1.214 mm. A sample of 32 patients, 16 per group, was estimated to provide 80% power with an α of .05, accounting for 10% attrition.

2.4 | Randomization and allocation concealment

Subject numbers were assigned in ascending order at the enrolment visit. Subjects were randomly assigned by a computer-generated table to receive one of the two treatments. A balanced random permuted block approach (4-unit block size) was used to prepare the randomization tables in order to avoid unequal balance between treatments. Restricted randomization (minimization) was performed, stratifying for smoking habits (yes or no) and history of periodontitis (yes or no). A randomization table was sent to the pharmacy, to prepare the medication for the first 25 subjects (12 tests and 13 controls). Twenty-five plastic bags containing metronidazole or placebo were sent back to the study coordinator (J.B.), who was not involved in the examination of patients, provision of the clinical intervention or data analysis, and was the only person who had access to them. Consequently, the study coordinator completed the treatment assignment and matched the code of the plastic bags with the subject number. The research nurse provided each subject with their corresponding plastic bag. Once 6 months data were available, sample size calculation was made, and medication or placebo was prepared in the same way as for the first 25 patients for the remaining seven subjects (four tests, three controls) and sent to the study coordinator (J.B.), who again was the only person who had access to them. The research nurse provided each remaining participant with their allocated plastic bag.

Allocation concealment was only broken by the study coordinator (J.B.) for sample size calculation purposes and was not broken again until all data were collected and analysed. Thus, the treatment group was concealed to the patient, the clinical examiner, the treatment provider, and the statistician.

2.5 | Examiner calibration

One examiner (J.D.) carried out all clinical measurements. The examiner was calibrated in measurement of PPD, CAL, and REC (Dopico et al., 2016). The measurement of radiographic bone levels was carried out by a different examiner (A.P.). The examiner was trained and calibrated in the measurement of radiographs using ImageJ software (ImageJ 1.47 V Wayne Rasband, National Institutes of Health) by another examiner (A.L.), who had been previously calibrated (Liñares et al., 2019) and represented the "gold standard". Inter-examiner agreement was evaluated as the standard error of the mean difference of the measurements performed by the examiner (A.P.) and those performed by the "gold standard" examiner (A.L.) in 10 radiographs. The examiner showed 98.2% reproducibility (Liñares et al., 2019).

2.6 | Clinical parameters

Clinical parameters were assessed using a UNC-15 periodontal probe by a calibrated examiner at six sites per implant. Data were collected at baseline, 3, 6, and 12 months. In case an implant-supported restoration did not allow adequate access to the implant, it was removed for clinical assessment at each appointment.

Probing pocket depth (PPD) was calculated as the distance from the gingival peri-implant margin to the bottom of the peri-implant pocket (Mombelli & Lang, 1994).

Recession (REC) was measured as the distance from the free marginal mucosa to the most apical portion of the crown.

Clinical attachment level (CAL) was calculated as the sum of PPD and REC (distance from the most apical portion of the crown to the bottom of the periodontal pocket).

Bleeding on probing (BoP) was assessed dichotomously in six sites per implant (Heitz-Mayfield, 2008).

Full-mouth plaque score (FMPS) was calculated by assigning a binary score to each surface (1 for plaque present, 0 for absent) and calculating the percentage of total tooth/implant surfaces that revealed the presence of plaque detected by a periodontal probe (Tonetti & Claffey, 2005).

Full-mouth bleeding score (FMBS) was recorded by assigning a binary score to each surface (1 for bleeding present, 0 for absent) and calculating the percentage of total tooth/implant surfaces that bled upon probing (Tonetti & Claffey, 2005).

Mean values and confidence intervals for PPD, CAL, REC, deepest PPD per implant, BoP, FMPS, and FMBS were calculated.

2.7 | Radiographic parameters

Intra-oral phosphor plate, long-cone parallel technique periapical radiographs were taken with the aid of custom-made holders silicone index (Griffiths et al., 1996) to evaluate peri-implant marginal radiographic bone levels at baseline, 3, 6, and 12 months. The same custom-made holders for each specific implant were used in all visits. Those radiographs were imported to a digital radiographic examination software (ImageJ 1.47 V Wayne Rasband, National Institutes of Health). All examinations were performed by an independent and calibrated examiner (A.P.) to the nearest 0.1 mm using IMAGE J software. The scale was set and calibrated by the height of the dental implant, which yielded a pixel/mm ratio. The implant shoulder was used as a fixed reference point. To assess linear changes at inter-proximal alveolar crestal bone height, the distance from the implant shoulder to the most coronal bone to implant contact (RBL) was determined both at the mesial and distal aspect of each implant and expressed as the mean of both measurements in millimetres.

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2.8 | Microbiological parameters

Microbiological testing was performed in the deepest peri-implant pocket of each subject at baseline, 3, 6, and 12 months. A commercially available microbiological test was used (Guidor Perio-implant diagnostic test – Sunstar). Following elimination of the supragingival biofilm, samples were taken with two consecutive sterile medium paper points (Maillefer, Ballaigues, Switzerland). The paper points were kept in place for 10 s and transferred into one empty sterilized 1.5 ml Eppendorf tube. Subsequently, samples were sent for analysis by quantitative PCR (qPCR) for detecting and quantifying bacterial DNA. Standard curves for each bacterium were prepared by determining the Cq values of serial 10-fold dilutions of purified genomic DNA from each bacterium. Standard curves were constructed by plotting Cq values generated from qPCR against *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Fusobacterium nucleatum*, and *Campylobacter rectus* (log CFU ml^{-1}).

The reduction of CFU counts of each group was calculated and the interaction of the microbiological status (presence or absence of studied bacterial species) with the treatment effect (test or control).

2.9 | Other parameters

Age, gender, history of periodontitis, and smoking status were recorded. Subjects presenting with inter-dental CAL at ≥2 non-adjacent teeth were diagnosed with a history of periodontitis (Papapanou et al., 2018).

Patients were classified as current smokers or former/never smokers.

Data on the type of restoration (implant-supported single restoration, fixed partial denture, overdenture, or fixed complete denture), and retention (screw- or cement-retained) were also collected.

Adverse events and compliance with the prescribed treatment were also recorded.

2.10 | Success criteria

A case was considered successfully treated if PPD was reduced to 5 mm with no BoP or to <5 mm irrespective of BoP, and no further bone loss was detected between baseline and 1 year (Carcuac

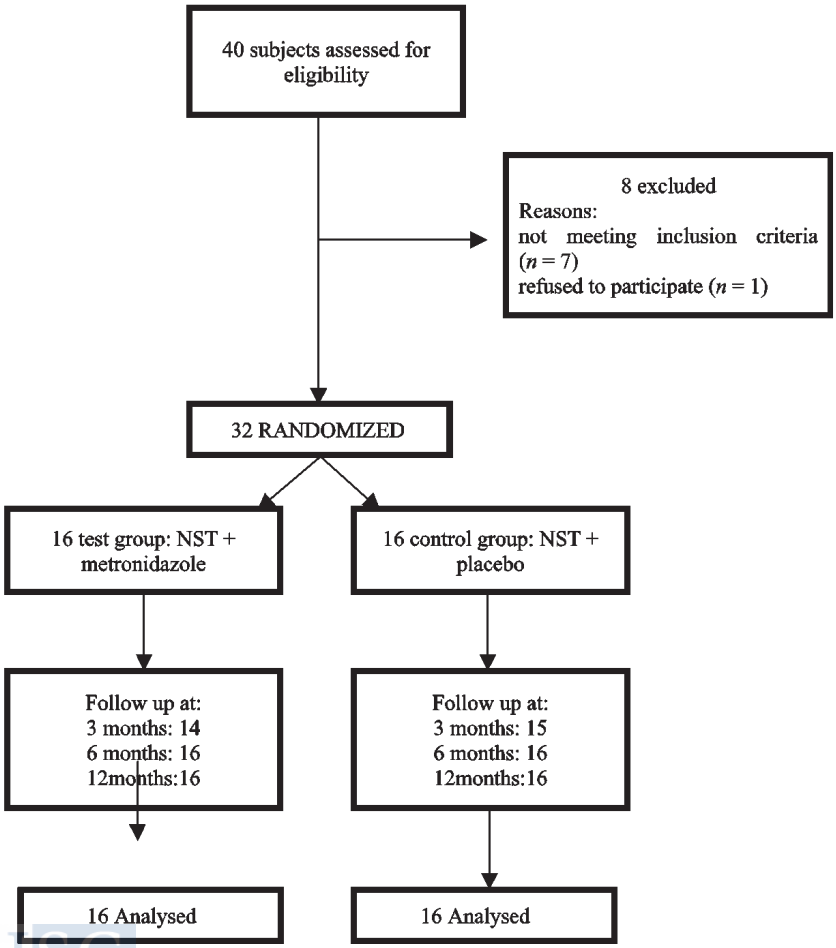


FIGURE 1 Flow chart for study patients

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et al., 2016). This was evaluated both at patient and implant level. In cases where success criteria were not met upon completion of the study, further treatment was provided according to individual needs.

2.11 | Pre-treatment visits

These visits were scheduled in order to help patients to achieve and maintain adequate self-performed plaque control. Supragingival debridement and elimination/reduction of plaque-retentive factors, including modification of existing restorations, were performed (de Tapia et al., 2019). Oral hygiene instructions were provided until an FMPS ≤20% was achieved (Gabay et al., 2015).

2.12 | Baseline examination

Baseline examination took place on a separate appointment after pre-treatment visits were completed.

2.13 | Intervention

Both groups received one session of non-surgical debridement as described previously (Liñares et al., 2019) by an experienced periodontist (A.L.). Implant-supported restorations were, if possible, removed during treatment and relocated at the end of the treatment session. Before instrumentation, patients rinsed with 0.12% chlorhexidine digluconate (Perio-aid; Dentaid, Spain). Non-surgical treatment under local anaesthesia consisting of supra- and submucosal mechanical debridement using ultrasonic stainless steel scaling inserts (EMS®, Electro Medical Systems) was performed in one treatment session with no time restrictions. Ultrasonic debridement was performed with simultaneous irrigation of 0.12% chlorhexidine digluconate (Perio-aid, Dentaid, Spain). After that, a stainless steel Columbia 4R/4L curette (LM Instruments Oy) was used to remove granulation tissue and minor mucosal curettage. Then, peri-implant pockets were irrigated with 0.12% chlorhexidine digluconate (Perio-aid, Dentaid, Spain). Immediately after the treatment session, patients initiated a course of two tablets three times a day, for 7 days, consisting of metronidazole 250 mg (test) or placebo pills (control).

2.14 | Post-treatment visits

Follow-up visits took place 1 week, 3, 6, and 12 months after the treatment session. In the post-treatment visits, oral hygiene advice and support were provided, early healing events were assessed and monitored, and any adverse events or additional medications were recorded. In the 1-week post-treatment visit, subjects were asked to return any medication not taken and/or the empty bottles. The number of pills not taken by the subject was recorded.

2.15 | Re-assessment visits

Re-assessment visits were scheduled 3, 6, and 12 months after treatment. During these appointments, the examiner recorded any changes in medical history. Clinical measurements, radiographs, and microbiological samples were taken. At the end of the re-assessment appointment, a session of supra-gingival debridement was performed. Sites with residual PPD ≥5 mm also received ultrasonic submucosal debridement as described above.

2.16 | Statistical analysis

IBM SPSS Statistics (version 24.0) was used to carry out statistical analyses. The Shapiro–Wilk test was applied to confirm if variables followed a normal distribution. A subject-level analysis was performed by computing a subject-level variable for each parameter. Numerical data were summarized as means and confidence intervals (CIs) for normally distributed continuous variables, categorical data were summarized as percentage. Means were calculated for PPD, REC, CAL, and RBL at patient, implant, and site level. Means for PPD, CAL, REC, and BoP were calculated at site

TABLE 1 Subject and clinical characteristics at baseline

Parameter		Test ($n = 16$)	Control ($n = 16$)	p value
Smoking	Never/former smoker	12/16 (75%)	11/16 (69%)	.50 ($\chi 2$)
	Current smoker	4/16 (25%)	5/16 (31%)	
History of periodontitis	Yes	9/16 (56%)	13/16 (81%)	.12 ($\chi 2$)
	No	7/16 (44%)	3/16 (19%)	
Gender	Male	9/16 (56%)	4/16 (25%)	.74 ($\chi 2$)
	Female	7/16 (44%)	12/16 (75%)	
Age		58.31 (51.46–65.16)	60.74 (55.09–65.84)	.71 (t-test)
Systemic diseases	Yes	3/16 (19%)	1/16 (6%)	.1 ($\chi 2$)
	No	13/16 (81%)	15/16 (94%)	
Number of implants (included/total)		1.75 (1–4)/4.29 (1–16)	2.12 (1–5)/4.47 (1–12)	.36 (t-test)

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TABLE 2 Mean clinical outcomes for baseline, 3, 6, and 12 months at subject level

	Test ($n = 16$)				Control ($n = 16$)			
Parameter	Baseline ($n = 16$)	3 months ($n = 14$)	6 months ($n = 16$)	12 months ($n = 16$)	Baseline ($n = 16$)	3 months ($n = 15$)	6 months ($n = 16$)	12 months ($n = 16$)
PPD (mm)	6.86 (5.78–7.94)	4.59 (3.99–5.19)*	4.42 (3.69–5.14)*	4.33 (3.64–5.01)*	5.89 (5.23–6.65)	5.04 (4.24–5.84)*	4.98 (4.18–5.77)*	4.87 (4.00–5.74)
CAL (mm)	7.29 (6.20–8.40)**	5.36 (4.78–5.95)*	5.09 (4.32–5.86)*	5.16 (4.48–5.83)*	6.08 (5.42–6.74)**	5.79 (5.00–6.57)	5.56 (4.75–6.37)	5.54 (4.72–6.37)
REC (mm)	0.44 (−0.06–0.93)	0.78 (0.40–1.16)	0.67 (0.23–1.11)	0.83 (0.35–1.31)	0.19 (0.02–0.35)	0.75 (0.38–1.11)*	0.59 (0.28–0.90)*	0.68 (0.47–0.88)*
ΔPPD (mm)		2.27 (1.17–3.37)**	2.44 (1.33–3.54)**	2.53 (1.37–3.69)**		0.85 (0.39–1.31)**	0.92 (0.46–1.37)**	1.02 (0.06–1.99)**
ΔCAL (mm)		1.93 (0.92–2.94)**	2.21 (1.00–3.41)**	2.14 (0.97–3.30)**		0.29 (−0.16–0.75)**	0.51 (0.09–0.94)**	0.53 (−0.33–1.39)**
FMPS (%)	20.92 (18.68–23.16)	28.31 (15.09–41.52)	27.38 (21.69–33.08)	30.77 (23.15 38,.39)	21.20 (19.41–22.99)	38.87 (27.18–50.55)	30.93 (19.87–41.99)	33.60 (23.89–43.31)
FMBS (%)	39.85 (24.37–55.32)	17.77 (11.08–24.45)**	20.92 (14.47–27.38)**	20.77 (13.72–27.82)	50.47 (36.92–64.02)	34.40 (20.89–47.91)**	33.00 (23.20–42.80)**	29.47 (15.82–43.11)
RBL (mm)	6.31 (5.39–7.22)	5.84 (4.93–5.76)*	4.66 (3.79–5.53)*	3.97 (3.16–4.79)*	5.54 (4.39–6.69)	5.22 (3.95–6.49)	4.72 (3.49–5.96)*	4.41 (3.36–5.46)
ΔRBL (mm)		0.46 (0.18–0.75)	1.65 (0.98–2.31)**	2.33 (1.58–30.9)**		0.32 (−0.01–0.65)	0.82 (0.34–1.29)**	1.13 (0.31–1.95)**

Abbreviations: CAL, clinical attachment level; FMBS, full-mouth bleeding score; FMPS, full-mouth plaque score; PPD, probing pocket depth; RBL, radiographic bone level; REC, recession.
*p value <.05 for intra-group comparisons; **p value <.05 for inter-group comparisons.

level. Site-level data were divided into two subgroups according to PPD, in moderately deep (5–6 mm) and deep (>6 mm) sites to further explore the treatment effects within each of the subgroups. This later approach was also applied for another exploratory analysis on presence or absence of specific bacterial species in test and control groups.

Independent samples t-test were performed for inter-group comparisons of numerical variables. Repeated measures ANOVA was used for intra-group comparisons of numerical variables. Chi-squared test was used for categorical variables. All tests were performed at a significance level of $\alpha = .05$.

3 | RESULTS

3.1 | Subject accountability

Forty subjects were assessed for their eligibility before entering the study. Eight subjects were excluded: seven because they did not meet the inclusion criteria, while the other one was not willing to participate (Figure 1). Thus, 32 subjects (62 implants) were enrolled and randomly allocated to the test and control groups. All participants received the allocated intervention. The last treatment session took place in January 2020. Three patients, two from the test and one from the placebo group did not attend the 3-month visit because of reasons unrelated to the study (mobility restrictions related to COVID-19 pandemic). An intention-to-treat approach (ITT) was followed and all participants were included in the analysis (Figure 1). At the 3 months follow-up, the available data were analysed. No effort was made to input the missing data since the reason for not attending the follow-up appointment was unrelated to the study. Furthermore, data from later follow-up appointments was available.

3.2 | Subject characteristics at baseline

Baseline characteristics of the 32 participants are displayed in Table 1. The mean age of the participants was 58.31 (51.46–65.16) and 60.74 (55.09–65.84) for the test and placebo groups, respectively. Twenty-five percentage of subjects in the test group and 31% in the placebo group were current smokers. Fifty-six percentage of patients had history of periodontitis in the test group and 81% in the control group. Nineteen percentage of patients in the test group and 6% in control group had systemic diseases (cardiovascular disease in all cases). None of these parameters showed statistically significant differences between groups (p value >.05).

Regarding the type of restoration, in both groups, there were 10 implant-supported single restorations, 20 fixed partial dentures (2–4 units), three overdentures, and three fixed complete full-arch dentures. The majority of them were screw-retained (78%) versus cemented-retained (22%). All implants included had a moderately rough surface.

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TABLE 3 Mean clinical outcomes for baseline, 3, 6, and 12 months at implant level

	Test ($n = 28$)				Control ($n = 34$)			
Parameter	Baseline ($n = 28$)	3 months ($n = 26$)	6 months ($n = 28$)	12 months ($n = 28$)	Baseline ($n = 34$)	3 months ($n = 33$)	6 months ($n = 34$)	12 months ($n = 34$)
maxPPD (mm)	8.41 (7.62–9.21)	5.87 (5.25–6.50)*,**	5.62 (4.97–6.28)*,**	5.12 (4.52–5.73)*,**	8.36 (7.62–9.11)	7.15 (6.41–7.89)*,**	6.94 (6.10–7.78)*,**	6.85 (6.01–7.68)*,**
PPD (mm)	6.78 (5.95–7.62)	4.65 (4.18–5.13)*,**	4.54 (3.97–5.11)*,**	4.34 (3.79–4.94)*,**	6.32 (5.70–6.95)	5.74 (5.09–6.38)*,**	5.56 (4.85–6.23)*,**	5.43 (4.81–6.06)*,**
CAL (mm)	7.24 (6.43–8.05)	5.55 (5.07–6.04)*	5.48 (4.90–6.06)*	5.51 (4.92–6.11)*	6.59 (5.97–7.02)	6.47 (5.81–7.13)	6.19 (5.50–6.88)	6.09 (5.47–6.70)
REC (mm)	0.46 (0.16–0.76)	0.90 (0.60–1.21)*	0.94 (0.51–1.36)*	1.15 (0.65–1.65)*,**	0.26 (0.12–0.40)	0.74 (0.47–1.00)*	0.62 (0.40–0.84)*	0.65 (0.46–0.84)*,**
ΔmaxPPD (mm)		2.54 (1.75–3.33)**	2.79 (2.06–3.53)**	3.29 (2.30–4.28)**		1.21 (0.65–1.78)**	1.42 (0.73–2.12)**	1.52 (0.75–2.28)**
ΔPPD (mm)		2.13 (1.42–2.85)**	2.24 (1.49–3.00)**	2.42 (1.53–3.30)**		0.59 (0.13–1.04)	0.76 (0.33–1.20)**	0.89 (0.14–1.64)**
ΔCAL (mm)		1.69 (1.06–2.32)**	1.76 (1.00–2.52)**	1.73 (1.01–2.45)**		0.11 (−0.36–0.58)**	0.40 (0.00–0.80)**	0.50 (−0.18–1.18)**
RBL (mm)	6.31 (5.55–7.06)	5.91 (5.17–6.66)*	4.99 (4.24–5.73)*	4.16 (3.39–4.94)*	6.00 (5.19–6.81)	5.77 (4.92–6.62)	5.20 (4.33–6.06)*	5.05 (4.19–5.92)*
ΔRBL (mm)		0.40 (0.20–0.59)	1.32 (0.8–1.84)	2.15 (1.51–2.78)**		0.24 (0.05–0.42)	0.81 (0.39–1.22)	0.95 (0.39–1.51)**

Abbreviations: CAL, clinical attachment level; maxPPD, deepest probing pocket depth; PPD, probing pocket depth; RBL: radiographic bone level; REC, recession.
*p value <.05 for intra-group comparisons; **p value <.05 for inter-group comparisons.

3.3 | Adverse events and compliance

At the 1-week follow-up visit, six subjects (38%) in the test group and five subjects (31%) in the control group reported adverse events. Two patients reported gastrointestinal disorder (one test/one control), four patients reported headache (two test/two control), two patients reported metallic taste (one test/one control), and two patients (two test/zero control) had oral tissue alterations (peri-implant bleeding). All subjects returned the medication bottles. Fifteen subjects (94%) in the test group and 14 subjects (88%) in the placebo group completed the course of systemic medication as indicated. The reason for non-compliance in all cases was forgetting to take the medication. One subject in the control group missed 21 pills, and two subjects in the test group missed eight and six pills, respectively. An ITT approach was followed and no subjects were excluded from the analysis.

No implants were lost during the study.

3.4 | Clinical outcomes

3.4.1 | Subject-level analysis

Clinical outcomes at baseline, 3, 6, and 12 months are displayed in Table 2. At baseline, significant differences were observed in CAL between groups (7.29 mm test vs. 6.08 mm control) (p value <.05). In all follow-up visits, mean PPD (4.33 mm test vs. 4.87 mm control) and CAL (5.16 mm test vs. 5.54 mm control) were not significantly different between groups (p value >.05), but the amount of PPD reduction (2.53 mm test vs. 1.02 mm control) and CAL gain (2.14 mm test vs. 0.53 mm control) were significantly greater in the test group at the end of the study (p value <.05). Although a significant reduction can be observed in both groups, FMBS results were significantly different between groups at 3 (17.77% test vs. 34.40% control) and 6 months (20.92% test vs. 33.00% control) (p value <.05). Intra-group analysis showed that significant clinical improvements were present in both treatment groups. The test group achieved statistically significant improvements in PPD and CAL in all visits compared with baseline (p value <.05), while the clinical improvements in the control group only reached statistical significance at 3 and 6 months regarding PPD (p value <.05). REC in the test group increased, but the differences were not statistically significant (from 0.44 mm to 0.83 mm) (p value >.05). In contrast, the control group had a statistically significant increase in REC (from 0.19 mm to 0.68 mm) (p value <.05). FMPS remained stable throughout the duration of the study, and significant differences between groups were not found (p value >.05).

3.4.2 | Implant-level analysis

Implant-level clinical outcomes at baseline, 3, 6, and 12 months are displayed in Table 3. At baseline, there were no significant

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TABLE 4 Mean clinical outcomes for baseline, 3, 6, and 12 months at sites level

		Test				Control				
	Parameter	Baseline ($n = 87$)	3 months ($n = 83$)	6 months ($n = 87$)	12 months ($n = 87$)	Baseline ($n = 83$)	3 months ($n = 83$)	6 months ($n = 83$)	12 months ($n = 83$)	
Deep sites (>6 mm)	PPD (mm)	8.65 (8.30–9.01)	5.36 (5.01–5.71)*,**	5.38 (5.02–5.75)*,**	5.04 (4.64–5.43)*,**	8.54 (8.14–8.94)	6.86 (6.37–7.34)*,**	6.75 (6.19–7.30)*,**	5.95 (5.51–6.39)*,**	
	CAL (mm)	8.95 (8.60–9.30)	6.39 (6.75–6.35)*,**	6.19 (5.79–6.59)*,**	6.29 (5.85–6.72)*	8.65 (8.24–9.06)	7.30 (6.83–7.77)*,**	7.23 (6.69–7.76)*,**	6.63 (6.19–.06)*	
	REC (mm)	0.30 (0.11–0.49)	1.02 (0.79–1.26)*,**	0.81 (0.56–1.05)*,**	1.25 (0.89–1.61)*,**	0.11 (0.03–0.18)	0.45 (0.25–0.64)*,**	0.48 (0.29–0.66)*,**	0.67 (0.47–0.88)*,**	
	ΔPPD (mm)		3.29 (2.88–3.69)**	3.27 (2.79–3.74)**	3.61 (3.07–4.16)**		1.69 (1.33–2.05)**	1.80 (1.40–2.19)**	2.59 (2.02–3.16)**	
	ΔCAL (mm)		2.57 (2.16–2.98)**	2.76 (2.29–3.23)**	2.66 (2.18–3.15)		1.35 (0.98–1.72)**	1.42 (1.02–1.82)**	2.02 (1.45–2.60)	
	BoP (%)	87.4**	66.3**	63.2**	48.3**	96.4**	81.9**	85.5**	75.9**	
	Parameter	Baseline ($n = 51$)	3 months ($n = 45$)	6 months ($n = 51$)	12 months ($n = 51$)	Baseline ($n = 70$)	3 months ($n = 51$)	6 months ($n = 65$)	12 months ($n = 70$)	
Moderate sites (5–6 mm)	PPD (mm)	5.76 (5.62–5.89)	4.07 (3.77–4.36)*,**	3.78 (3.45–4.10)*,**	3.93 (362–4.24)*,**	5.55 (5.43–5.68)	5.00 (4.60–5.40)*,**	4.58 (4.23–4.93)*,**	4.85 (4.37–5.32)*,**	
	CAL (mm)	6.64 (6.29–7.00)**	5.07 (4.70–5.43)*,**	5.22 (5.69–5.25)*	5.22 (4.83–5.62)*	5.89 (5.70–6.09)**	6.15 (5.65–6.66)**	5.54 (5.13–5.94)*	5.60 (5.05–6.08)*	
	REC (mm)	0.89 (0.53–1.25)**	1.00 (0.64–1.35)	1.44 (0.99–1.90)	1.29 (0.92–1.65)**	0.34 (0.17–0.51)**	1.15 (0.86–1.45)*	0.95 (0.68–1.22)*	0.72 (0.46–0.98)*,**	
	ΔPPD (mm)		1.69 (1.40–1.97)**	1.98 (1.65–2.31)**	1.82 (1.53–2.12)**		0.55 (0.16–0.95)**	0.97 (0.61–1.33)**	0.71 (0.21–1.20)**	
	ΔCAL (mm)		1.58 (1.16–2.00)**	1.42 (0.93–1.92)**	1.42 (0.95–1.89)**		−0.26 (−0.69–0.16)**	0.35 (−0.1–0.72)**	0.32 (−0.16–0.80)**	
	BoP (%)	84.30	40**	49.00	31.4**	94.30	69.2**	62.90	57.1**	

Abbreviations: BoP, bleeding on probing; CAL, clinical attachment level; PPD, probing pocket depth; REC, recession.
*p value <.05 for intra-group comparisons; **p value <.05 for inter-group comparisons.

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TABLE 5 Mean microbiological outcomes for baseline, 3, 6, and 12 months

	Treatment group	Baseline positive (%)/>10^6 (%)	3 months positive (%)/>10^6 (%)	6 months positive (%)/>10^6 (%)	12 months positive (%)/>10^6 (%)
Aa	Test	0/16 (0%)	0/16 (0%)	0/14 (0%)	0/15 (0%)
	Control	0/16 (0%)	0/16 (0%)	1/14 (7%)	1/16 (6%)
	p value	.7	.7	.5	.3
Pg	Test	15/16 (94%)	5/12 (42%)*	3/14 (21%)*	4/15 (27%)*
	Control	9/16 (56%)	6/15 (40%)	6/14 (43%)	7/16 (44%)
	p value	**.01**	.6	.4	.3
Tf	Test	14/16 (86%)	4/12 (33%)*	4/14 (29%)*	5/15 (33%)*
	Control	14/16 (86%)	6/15 (40%)*	8/14 (57%)	13/16 (81%)
	p value	.7	.7	.3	**.001**
Fn	Test	15/16 (94%)	9/12 (75%)	13/14 (93%)	11/15 (73%)
	Control	16/16 (100%)	13/15 (87%)	14/14 (100%)	16/16 (100%)
	p value	.3	.2	.3	.06
Cr	Test	13/16 (81%)	6/12 (46%)*	4/14 (28%)*	3/15 (2%)*
	Control	11/16 (69%)	9/15 (60%)	6/14 (43%)	16/16 (100%)
	p value	.3	.3	.3	**.04**

Abbreviations: Aa, *Aggregatibacter actinomycetemcomitans*; Cr, *Campylobacter rectus*; Fn, *Fusobacterium nucleatum*; Pg, *Porphyromonas gingivalis*; Tf, *Tannerella forsythia*.
**p* value <.05 for intra-group comparisons.

differences between test and control groups in any of the studied variables (*p* value >.05). The results favoured the test group in all visits. Mean PPD (4.34 mm test vs. 5.43 mm control), deepest PPD (5.12 mm test vs. 6.85 mm control), PPD reduction (2.42 mm test vs. 0.89 mm control), deepest PPD reduction (3.29 mm test vs. 1.52 mm control), and CAL gain (1.73 mm test vs. 0.50 mm control) showed statistically significant differences between groups at 12 month favouring the test group (*p* value <.05). Intra-group analysis showed that test group achieved statistically significant improvements in all studied clinical parameters in all visits compared with baseline (*p* value <.05). Statistically significant improvements in the control group were only present in mean PPD, maxPPD, and REC (*p* value <.05).

3.4.3 | Site-level analysis

Clinical outcomes at moderately deep (5–6 mm) and deep (>6 mm) pocket categories at baseline, 3, 6, and 12 months are displayed in Table 4. At moderately deep sites, there were statistically significant differences favouring the test group in all variables except REC at 3 and 6 months (*p* value <.05), all favouring the test group. At deep sites, all the studied variables presented statistically significant differences favouring the test group (*p* value <.05). Intra-group analysis showed statistically significant clinical improvements compared with baseline in both groups at moderately deep and deep sites in all the studied variables (*p* value <.05).

3.5 | Radiographic outcomes

At baseline, there were no significant differences between test and control groups, both at patient and implant level (*p* value >.05). At subject level, the amount of RBL gain was significantly greater in the test group at 6 (1.65 mm test vs. 0.82 mm control) and 12 months (2.33 mm test vs. 1.13 mm control) (*p* value <.05) (Table 2). At implant level, there was significantly greater radiographic bone gain at 12 months in the test group compared with the control group (2.15 mm test vs. 0.95 mm control) (*p* value <.05) (Table 3).

3.6 | Microbiological outcomes

The number and percentage of subjects who tested positive to detectable levels of the studied species at baseline, 3, 6, and 12 months are displayed in Table 5. There was a statistically significant difference between groups in the detection of *Porphyromonas gingivalis* at baseline (15 test/9 control). At 12 months, *Tannerella Forsythia* and *Campylobacter rectus* was detected in significantly less patients in the test group compared with the control group (*p* value <.05).

CFU counts at baseline, 3, 6, and 12 months are displayed in Table 6. Differences in mean total *Tannerella forsythia* counts between groups were found at 12 months (*p* value <.05). Regarding quantitative reduction of the studied bacterial species, statistically significant differences favouring the test group were found between baseline and 6 months in *Porphyromonas gingivalis* (*p* value <.05) and between baseline and

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TABLE 6 Mean microbiological outcomes for baseline, 3, 6, and 12 months

	Treatment group	Baseline Log10 CFU/ml (95% CI)	3 months Log10 CFU/ml (95% CI)	6 months Log10 CFU/ml (95% CI)	12 months Log10 CFU/ml (95% CI)	*p* value differences Δbaseline – 3 months	*p* value differences Δbaseline – 6 months	*p* value differences Δbaseline –12 months
Aa	Test	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	.8	.7	.7
	Control	0 (0, 0)	0 (0, 0)	5.8 (−6.05, 6.4)	5.4 (−5.5, 5.9)			
	p value	.7	.7	.6	.6			
Pg	Test	8.1 (6.8, 8.3)	7.5 (−7.6, 8.1)*	5.7 (−5.1, 6.1)*	7.6 (−7.6, 8.1)*	.06	**.01**	**.04**
	Control	8.5 (−8.4, 8.9)	7.3 (−7.1, 7.7)*	7.9 (−7.9, 8.4)*	7.2 (−6.6, 7.6)*			
	p value	.1	.8	.6	.7			
Tf	Test	7.1 (−6.6, 7.5)	5.9 (−5.3, 6.3)*	5.6 (−5.2, 5.9)*	5.8 (−5.4, 6.2)*	.6	.7	**.03**
	Control	7.03 (5.8, 7.3)	5.9 (−5.5, 6.2)*	6.1 (−4.8, 6.4)*	7.1 (−6.5, 7.4)			
	p value	.9	.8	.1	**.01**			
Fn	Test	7.5 (−6.3, 7.8)	6.8 (5.8, 7.1)*	6.9 (6.4, 7.1)*	6.4 (−5.2, 6.7)*	.1	.4	.5
	Control	7.9 (6.1, 8.3)	7.1 (−5.3, 7.5)*	7.2 (6.9, 7.4)*	7.2 (6.3, 7.5)*			
	p value	.1	.2	.1	.1			
Cr	Test	7.7 (−7.6, 8.1)	6.1 (5.1, 6.4)*	5.9 (−5.6, 6.4)*	6.3 (−5.1, 6.7)*	.7	.8	.8
	Control	7.5 (−6.9, 7.9)	6.5 (5.6, 6.7)*	6.6 (5.8, 6.8)*	6.7 (−5.8, 7.1)*			
	p value	.8	.5	.2	.3			

Abbreviations: Aa, *Aggregatibacter actinomycetemcomitans*; Cr, *Campylobacter rectus*; Fn, *Fusobacterium nucleatum*; Pg, *Porphyromonas gingivalis*; Tf, *Tannerella forsythia*.
*p value <.05 for intra-group comparisons.

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12 months in *Porphyromonas gingivalis* and *Tannerella Forsythia* (p value <.05).

3.7 | Treatment success

After 1 year of follow-up, 56.30% of the test patients and 25% of the controls met the success criteria. At implant level, 57.1% of the implants in the test group and 23.5% of the implants in the control group met the success criteria. Subjects who did not meet the clinical endpoint for success at the end of the study underwent additional treatment according to their individual needs. Subjects meeting the success criteria after completion of the study were enrolled in an individually-tailored supportive periodontal therapy programme.

4 | DISCUSSION

To date, this was the first RCT designed to assess the effect of systemic metronidazole as an adjunct to non-surgical treatment of peri-implantitis. Data showed that the experimental therapy resulted in significant clinical, radiographic, and microbiological additional improvements after 1 year of follow-up.

Despite the paucity of RCTs investigating the effect of adjunctive systemic antibiotics in the treatment of peri-implantitis, the results in the present study are in line with the existing published data. PPD reduction at 12 months was 2.53 mm in the test group and 1.02 in the control group. Shibli and co-workers (Shibli et al., 2019) used adjunctive metronidazole plus amoxicillin, and found a PPD reduction of 3.1 mm in the antibiotic group against 1.8 mm in the control group at 12 months. In contrast, Stein and co-workers (Stein et al., 2017) failed to find differences in PPD reduction between test and control groups after a similar adjunctive antibiotic regime as described by Shibli (1.4 vs. 1.02 mm). This could be explained by the fact that PPD in the control group at baseline was shallower than the present investigation (7.6 mm control vs. 8.36 control). Thus, it seems that the impact of adjunctive antibiotics in non-surgical therapy of peri-implantitis may be influenced by the severity of disease.

A recently published study (De Waal et al., 2021) investigated the effect of chlorhexidine or amoxicillin/metronidazole as an adjunct to non-surgical therapy in bleeding scores and other clinical and microbiological parameters over a 3-month follow-up period. In contrast to the present study, although they found differences in clinical parameters favouring the use of adjunctive antibiotics, these differences did not reach statistical significance. The inclusion of initial peri-implantitis cases with shallow PPD (5.82 mm test, 5.63 mm control) and a short follow-up may explain the differences with the present study. Furthermore, sample size calculations in De Waal and co-workers study were made using differences in bleeding index in a previous study investigating the adjunctive use of amoxicillin plus metronidazole on periodontitis patients (Winkel et al., 2001). This may not fully apply to a study on peri-implantitis patients, and issues regarding statistical power may exist.

The observed PPD reduction was also comparable to that shown in different case series studies, where different antibiotic regimens were used (Mombelli & Lang, 1992; Estefanía-Fresco et al., 2019; Liñares et al., 2019; Nart et al., 2020). Up to 4.6 mm PPD reduction, and 2.6 mm radiographic bone gain after 54 months of follow-up have been reported after non-surgical therapy in combination with systemic metronidazole in advanced peri-implant lesions with associated intra-bony defects (Liñares et al., 2019).

In the present study, a mean radiographic bone gain of 2.33 mm was found in the test group and 1.13 mm in the control group at 12 months. The results in the test group are comparable to those reported by Liñares and co-workers (Liñares et al., 2019). The amount of radiographic bone gain exceeds that shown in previously published studies, where an average of 0.5 mm was observed (Stein et al., 2017; Shibli et al., 2019). This may be explained by the type of implants treated by Shibli and co-workers (machined), and moderate disease severity at the Stein and co-workers study. It has been shown that surgical therapy of peri-implantitis plus adjunctive systemic antibiotics was more successful in moderately rough surfaces compared with machined surfaces (Carcuac et al., 2016). Peri-implantitis lesions in rough-surface implants may be more aggressive, and may extend deeper to the bone than those present in implants with machined surfaces (Carcuac et al., 2013). This may explain the greater impact of adjunctive systemic antibiotics when treating peri-implantitis lesions in rough-surface implants. The additional benefits of the antibiotic regarding radiographic bone gain (2.33 mm) may be comparable to those obtained with reconstructive surgical therapy (1.9 mm) (Tomasi et al., 2019). The rationale behind these improvements could be related to the reduction/elimination of pathogenic bacteria with metronidazole in the present investigation and the stability of clot formation after non-surgical debridement. It has been shown that defect configuration on surgical treatment of peri-implantitis plays an important role in clinical and radiographic outcomes (Schwarz et al., 2010). Although defect configuration has not been evaluated in the present study, the potential influence of the inclusion of more favourable defects than in previously publishes studies cannot be ruled out.

Non-surgical therapy significantly decreased BoP in both groups to a similar extent to that observed in a previously published clinical trial (Stein et al., 2017). The amount of post-treatment recession was in line with existing studies (0.5 mm) (Faggion Jr. et al., 2014).

In this study, 500 mg of metronidazole three times a day during 7 days was prescribed. This treatment regime as an adjunct to non-surgical treatment of peri-implantitis has not been investigated in previous clinical trials. The rationale behind the use of metronidazole is based on the reported high prevalence of anaerobic pathogens in peri-implantitis lesions (Charalampakis & Belibasakis, 2015) and the relatively low rates of bacterial resistance (Soares et al., 2012). Some authors have advocated that the choice of an antibiotic regime should be based on the detection of certain bacterial species, and therefore a possible rationale for the use of amoxicillin plus metronidazole in periodontal therapy could be the presence of *Aa* (van Winkelhoff et al., 1992). In the present study, at baseline, *Aggregatibacter actinomycetemcomitans* (*Aa*) could not be detected in any sites and,

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therefore, the use of amoxicillin plus metronidazole may not be justified. Benefits in the long-term clinical stability of treated periodontitis patients have been shown with a combination of metronidazole plus amoxicillin. This adjunctive antibiotic regime has also been associated with a reduction in the need of periodontal surgery. Additional PPD reduction and CAL gain have also been shown with metronidazole alone in moderately deep and deep sites (Teughels et al., 2020).

Despite additional benefits of the use of adjunctive systemic antibiotics, due to the increase in antibiotic resistance in recent years (Soares et al., 2012), their use should be indicated on a one-to-one basis. It should be taken into account that significant improvements in clinical and microbiological parameters were also observed in the control group, and although a significantly lower proportion of cases achieved the endpoint of clinical success, adjunctive antibiotics may not be indicated in the initial stages of disease as clinical success may be achieved with non-surgical therapy only or in advanced cases where additional surgical therapy may be indicated regardless of the use of adjunctive antibiotics.

A critical question after completion of non-surgical therapy is related to residual pockets and the need for further treatment beyond supportive therapy. The presence of residual pockets ≥5 mm, bleeding on probing, and bone loss at re-assessment may be useful to predict further disease progression (Carcuac et al., 2016). Failure to achieve this clinical endpoint of success may be used as a rationale to provide further treatment. Previously published studies showed a success after non-surgical therapy around 50% (Stein et al., 2017; Estefanía-Fresco et al., 2019; Liñares et al., 2019; Nart et al., 2020). The results of the present study were in line with these data: it was observed that 57.10% of implants of test treatment met the success criteria versus 23.5% of the control at 1-year follow-up. In contrast, similar success rates after non-surgical therapy alone (55%) compared with adjunctive antibiotics (65%) have also been shown (Shibli et al., 2019). This may be explained by the fact that subjects in the control group had shallower PPD compared with the present study.

Lack of detailed information about the surface characteristics of the treated implants is a limitation of the present study. Also, a more comprehensive microbiological analysis may have helped to characterize the results much better.

Within the limitations of this study, the adjunctive use of systemic metronidazole as an adjunct to non-surgical treatment of peri-implantitis has resulted in significant additional improvements in clinical, radiographic, and microbiologic parameters after 12 months of follow-up. Adequately powered studies with longer follow-up periods are needed to confirm these findings in the long term.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS STATEMENT

The study was carried out in accordance with the principles described in the Declaration of Helsinki on experimentation with human beings (Order SCO/256/2007), and was approved by the Ethical Committee of Galicia (2017/508)

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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4.3. ESTUDIO #3

Blanco C, Liñares A, Dopico J, Pico A, Sobrino T, Leira Y, Blanco J. Peri-implantitis, systemic inflammation, and dyslipidemia: a cross-sectional biochemical study. J Periodontal Implant Sci. 2021 Oct;51(5):342-351. doi: 10.5051/jpis.2100920046

4.3.1. Objetivo

El objetivo de este estudio fue comparar el perfil inflamatorio y lipídico de pacientes con y sin periimplantitis.

4.3.2. Material y métodos

Se realizó un estudio transversal bioquímico en el que se recogieron muestras de sangre de 16 pacientes con periimplantitis y de 31 sujetos con implantes sanos. Se obtuvieron parámetros clínicos periimplantarios de todos los sujetos. Se midieron los niveles de factor de necrosis tumoral alfa e interleucina-10 (IL-10) en suero. También se evaluaron las fracciones lipídicas, los niveles de glucosa y creatinina y el hemograma completo.

4.3.3. Resultados

Después de controlar los antecedentes de periodontitis, se encontraron diferencias estadísticamente significativas entre los pacientes con periimplantitis y los controles para el colesterol total (diferencia media ajustada estimada, 76,4 mg/dl; intervalo de confianza [IC] del 95 %, 39,6; 113,2 mg/dl; $p < 0,001$), el colesterol de lipoproteínas de baja densidad (LDL) (diferencia media ajustada estimada, 57,7 mg/dl; IC del 95 %, 23,8; 91,6 mg/dl; $p < 0,001$), los glóbulos blancos (WBC) (diferencia media ajustada estimada, 2,8 × 103/µl; IC del 95 %, 1,6; 4,0 × 103/µl; $p < 0,001$) y la IL-10 (diferencia media ajustada estimada, −10,4 pg/ml; IC del 95 %, −15,8, −5,0 pg/mL; $p<0,001$). La PS se correlacionó positivamente con el colesterol total ($r=0,512$; $p<0,001$), el colesterol LDL ($r=0,463$; $p=0,001$) y los leucocitos ($r=0,519$; $p<0,001$). Se observó una correlación negativa moderada entre IL-10 y PS ($r=0,609$; $p<0,001$).

4.3.4. Conclusiones

Los sujetos sanos con periimplantitis mostraron un aumento de la inflamación sistémica de grado bajo y la dislipidemia.

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Peri-implantitis, systemic inflammation, and dyslipidemia: a cross-sectional biochemical study

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ABSTRACT

Purpose: The aim of this study was to compare the inflammatory and lipid profile of patients with and without peri-implantitis.
Methods: A cross-sectional biochemical study was carried out in which blood samples were collected from 16 patients with peri-implantitis and from 31 subjects with healthy implants. Clinical peri-implant parameters were obtained from all subjects. Levels of tumor necrosis factor-alpha and interleukin-10 (IL-10) were measured in serum. Lipid fractions, glucose and creatinine levels, and complete blood count were also assessed.
Results: After controlling for a history of periodontitis, statistically significant differences between peri-implantitis patients and controls were found for total cholesterol (estimated adjusted mean difference, 76.4 mg/dL; 95% confidence interval [CI], 39.6, 113.2 mg/dL; P<0.001), low-density lipoprotein (LDL) cholesterol (estimated adjusted mean difference, 57.7 mg/dL; 95% CI, 23.8, 91.6 mg/dL; P<0.001), white blood cells (WBC) (estimated adjusted mean difference, 2.8×10^3/μL; 95% CI, 1.6, 4.0×10^3/μL; P<0.001) and IL-10 (estimated adjusted mean difference, −10.4 pg/mL; 95% CI, −15.8, −5.0 pg/mL; P<0.001). The peri-implant probing pocket depth (PPD) was modestly positively correlated with total cholesterol (r=0.512; P<0.001), LDL cholesterol (r=0.463; P=0.001), and WBC (r=0.519; P<0.001). A moderate negative correlation was observed between IL-10 and PPD (r=0.609; P<0.001).
Conclusions: Otherwise healthy individuals with peri-implantitis showed increased low-grade systemic inflammation and dyslipidemia.

Keywords: Cardiovascular diseases; Dyslipidemias; Inflammation; Leukocytes; Peri-implantitis

INTRODUCTION

Peri-implantitis is a common immune-mediated inflammatory condition of bacterial origin, which is characterized by peri-implant soft tissue inflammation and bone loss around implants [1]. Recent epidemiological studies reported a high prevalence of this disease

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Author Contributions
Conceptualization: Yago Leira, Juan Blanco; Formal analysis: Yago Leira; Investigation: Carlota Blanco, Antonio Liñares, Jose Dopico, Alex Pico, Tomás Sobrino, Yago Leira; Methodology: Antonio Liñares, Tomás Sobrino, Yago Leira; Project administration: Antonio Liñares, Yago Leira, Juan Blanco; Writing - original draft: Carlota Blanco, Yago Leira; Writing - review & editing: Carlota Blanco, Antonio Liñares, Jose Dopico, Alex Pico, Tomás Sobrino, Yago Leira, Juan Blanco.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

worldwide, affecting between 24% and 45% of individuals with implants [2-5]. When compared to periodontitis, peri-implant lesions might be considered as "more invasive," as an increased immune response and osteoclastogenesis are present; furthermore, as a result of the lack of epithelial lining between the peri-implant lesion and the apical portion of the peri-implant pocket, infection can reach the alveolar bone [6].

Recent animal studies have shown elevation of peripheral levels of pro-inflammatory biomarkers (e.g., total protein, albumin, and white blood cells [WBC]) after ligature-induced experimental peri-implantitis [7,8]. It is worth mentioning that the surgical treatment of experimental peri-implantitis by means of open flap debridement led to a reduction of these systemic inflammatory parameters, which reached similar values to baseline [7,8]. It could be hypothesized that similarly to periodontitis, the inflamed and ulcerated peri-implant pocket epithelium allows the entrance of locally produced inflammatory mediators (e.g., leukocytes and cytokines) into the bloodstream, evoking a systemic immune and acute inflammatory response that subsequently could interact with lipid metabolism, thereby elevating blood levels of total cholesterol and low-density lipoprotein (LDL) cholesterol, which in turn may increase the risk of atherosclerotic disease. This is supported by previous experimental studies where long-term oral infection with lipopolysaccharide from *Porphyromonas gingivalis* in B6 Apoehl mice was associated with elevated very-low LDL, LDL, and total cholesterol levels, as well as reduced high-density lipoprotein levels due to an increase in liver-produced pro-inflammatory mediators, such as interleukin-6 (IL-6) [9]. There is also evidence that infection and inflammation may contribute to a pro-atherogenic lipid profile by overproduction of oxidized LDL [10]. Based on this, patients with peri-implantitis could present a similar systemic state to that seen in periodontitis patients. To our knowledge, there is a lack of clinical studies evaluating whether patients diagnosed with peri-implantitis have an exacerbated systemic pro-inflammatory state with dyslipidemia.

The aim of the present investigation was 2-fold: firstly, to investigate the relationship between peri-implantitis and systemic inflammation; and secondly, to analyze whether this systemic inflammatory state in peri-implantitis is associated with dyslipidemia.

MATERIALS AND METHODS

A cross-sectional biochemical study was carried out following the STROBE guidelines [11]. The research was performed in accordance with the Declaration of Helsinki of the World Medical Association (2008) and was approved by the Ethics Committee of the Servizo Galego de Saúde and Xunta de Galicia (2016/399 and 2017/508). Written informed consent was obtained from each patient after a full explanation of the oral examination and blood sample collection.

Study population

Otherwise healthy individuals diagnosed with peri-implantitis were identified among the population referred for dental care to the School of Dentistry at the University of Santiago de Compostela between January 2018 and January 2019. Subjects with peri-implant health who were also in apparent good general health were identified from the University Clinical Hospital of Santiago de Compostela between October 2016 and April 2017.

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Peri-implantitis group

Peri-implantitis subjects were defined based on the 2018 Consensus Classification of Periodontal Diseases (presence of bleeding on probing [BoP] and/or suppuration, probing pocket depth [PPD] ≥6 mm and/or ≥3 mm of radiographic bone loss) [12]. The inclusion criteria were as follows: (I) ≥18 years of age; (II) presence of at least 1 implant diagnosed with peri-implantitis; (III) absence of implant mobility; (IV) absence of systemic pathology; (V) not taking any local and/or systemic host modulators such as anti-inflammatory drugs, lipid-lowering medications, immunosuppressants, or antibiotics in the last 6 months; and (VI) no active clinical signs of periodontitis.

Individuals diagnosed with peri-implantitis were identified among the population referred for dental care to the School of Dentistry at the University of Santiago de Compostela between January 2018 and January 2019. From the 22 subjects initially screened, 6 were excluded because they had systemic diseases (cardiovascular diseases, n=4; diabetes, n=1; rheumatoid arthritis, n=1). Hence, the case group consisted of 16 patients with peri-implantitis.

Peri-implant health group

Subjects with healthy implants were classified as controls according to the 2018 Consensus Classification of Periodontal Diseases (absence of erythema, BoP and/or suppuration, increased PPD, and bone loss) [12]. The inclusion criteria were as follows: (I) ≥18 years of age; (II) presence of healthy implants; (III) absence of systemic pathology; (IV) not taking any local and/or systemic host modulators such as anti-inflammatory drugs, lipid-lowering medications, immunosuppressants, or antibiotics in the last 6 months; and (V) no active clinical signs of periodontitis.

Control individuals were identified from the University Clinical Hospital of Santiago de Compostela between October 2016 and April 2017. From the 48 participants initially screened, 17 were excluded due to the presence of systemic diseases (diabetes, n=5; cardiovascular diseases, n=4), antibiotic use (n=1), diagnosis of peri-implantitis (n=2) or peri-implant-mucositis (n=4), or refusal to give a blood sample (n=1). The final sample of the control group consisted of 31 individuals.

Clinical and radiographic examination

Clinical peri-implant examinations were performed in all participants by previously trained and calibrated periodontists (examiners #1 and #2). Briefly, the calibration was completed before the start of the study at the Periodontology Unit, Faculty of Odontology (University of Santiago de Compostela) using 10 non-study patients suffering from peri-implantitis. Intra-examiner reliability and inter-examiner reliability were assessed using the intraclass correlation coefficient (ICC) for PPD of peri-implant pockets. The intra-examiner ICC values were 0.88 and 0.85 for examiners #1 and #2, respectively. The inter-examiner values were 0.84. Thus, the reliability of the measurements was satisfactory.

PPD (in mm) and BoP (% of sites that bleed upon probing) were measured in all implants present in the mouth. Measurements were recorded at 6 sites per implant (mesiobuccal, distobuccal, midbuccal, mesiolingual, distolingual, and midlingual) using a calibrated University of North Carolina periodontal probe (UNC 15; Hu-Friedy, Chicago, IL, USA). The number of implants in each group was also recorded.

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An intraoral radiograph was obtained from each implant to evaluate crestal bone level (in mm). The X-ray was taken following the long cone parallelism technique with the help of positioning splints manufactured for this purpose individually for each patient. Digital periapical radiographs were taken and viewed on a calibrated computer screen using a software program (Digora™, KaVo Dental, Biberach an der Riss, Germany). Marginal bone loss was defined as the distance from the widest supracrestal part of the implant to the alveolar crest.

History of periodontitis and smoking status

For both peri-implantitis patients and controls, history of periodontitis and tobacco consumption was recorded. We considered participants as having a previous history of periodontitis if they had received periodontal treatment at least once in their lives and if, at the time their peri-implant status was examined and blood samples were collected, no clinical signs of periodontitis were detected (absence of periodontal sites with PPD ≥4 mm with or without BoP and full-mouth BoP <10%). Current smokers were defined as those who smoked >10 cigarettes/day.

Serum samples collection and laboratory tests

Blood samples were obtained in the morning after the peri-implant examination was done. Briefly, 2 mL of venous blood was collected from the antecubital fossa by venipuncture using a 20-gauge needle with a 2-mL syringe. Blood samples were allowed to clot at room temperature and, after 1 hour, serum was separated from blood by centrifugation (15 minutes at 3000×g) and 0.5 mL of extracted serum was immediately transferred to 1.5-mL aliquots. Each aliquot was stored at −80°C until required for analysis. Serum levels of tumor necrosis factor-alpha (TNF-α) were determined using an immunodiagnostic IMMULITE® 1000 System (Siemens Healthcare Diagnostics, Munich, Germany). Serum levels of IL-10 were quantified using the enzyme-linked immunosorbent assay technique following manufacturer instructions (BioLegend, San Diego, CA, USA). Lipid fractions, glucose, and creatinine (all measured in serum), as well as the complete blood count, were determined by routine biochemical methods.

All determinations were performed in independent laboratories blinded to clinical data.

Statistical analysis

No formal sample size calculation was performed since this was a pilot study and there are no data in the literature regarding this topic. However, a *post hoc* power analysis based on the results obtained from the present study and using our primary outcome (i.e., WBC concentrations) confirmed a 90% power to detect a $2.0\times10^3/\mu L$ difference in WBC between study groups, with a standard deviation (SD) of $0.4\times10^3/\mu L$ (Macro !NSize for PASW Statistics, http://www.metodo.uab.cat/macros.htm).

SPSS version 24.0 (IBM Corp., Armonk, NY, USA) was used to carry out all statistical analyses. To identify variables that followed a normal distribution, the Kolmogorov-Smirnov test was applied. Mean values ± SD and median (P_{25}, P_{75}) were calculated for normally and non-normally distributed continuous variables, respectively. The statistical tests used to compare continuous data were the independent *t*-test or the Mann-Whitney *U* test. Categorical variables were reported as percentages and compared using the χ^2 test. General linear models for analysis of covariance were created to compare mean values of significant biomarkers between cases and controls adjusted for potential confounders (covariates).

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A mixed model analysis was used to account for the different number of implants in each patient (the different implants were considered as repeated measures), and the dependent variable was each biomarker. In addition, non-parametric correlation analysis between peri-implant clinical parameters and circulating biomarkers was performed using the Spearman rank correlation coefficient. All tests were performed at a significance level of α=0.05.

RESULTS

The peri-implantitis patients and controls were similar in terms of age and sex (P=0.995 and P=0.917, respectively). Although a higher percentage of current smokers were detected in the case group than in the control group, this difference was not statistically significant (P=0.472). Nevertheless, more than 3-quarters of the cases (13 of 16) presented a previous history of periodontitis in comparison to none of controls (0/31) (P<0.001). As expected, the values of clinical peri-implant parameters such as PPD and BoP were significantly higher in peri-implantitis patients (both P<0.001) (Table 1). These results did not differ when linear mixed analysis was performed, accounting for the number of implants per patient (Table 1). The total number of implants was 20 and 36 in the case and control groups, respectively. The mean number of implants per patient was similar between groups (1.2±0.7 vs. 1.1±0.4, P=0.985).

Raw (unadjusted) data for lipid fractions, metabolic parameters, complete blood count, and inflammatory biomarkers are displayed in Table 2. Patients with peri-implantitis exhibited higher circulating levels of cholesterol (P<0.001), LDL cholesterol (P=0.001), WBC (P<0.001), monocytes (P<0.001), and TNF-α (P=0.033) than healthy controls. In contrast, serum levels of IL-10 were lower in subjects with peri-implantitis than in controls (P<0.001). These results did not differ when linear mixed analysis was performed, accounting for the number of implants per patient (Table 2). Only the neutrophil concentration showed a statistically significant difference between groups (P=0.034).

After adjustment for a history of periodontitis, statistically significant differences between the peri-implantitis patients and controls remained for total cholesterol (estimated adjusted mean difference, 76.4 mg/dL; 95% confidence interval [CI], 39.6, 113.2 mg/dL; P<0.001), LDL cholesterol (estimated adjusted mean difference, 57.7 mg/dL; 95% CI, 23.8, 91.6; P<0.001), WBC (estimated adjusted mean difference, 2.8×10^3/μL; 95% CI, 1.6, 4.0×10^3/μL; P<0.001) and IL-10 (estimated adjusted mean difference, −10.4 pg/mL; 95% CI, −15.8, −5.0 pg/mL; P<0.001), but not for TNF-α (estimated adjusted mean difference, 7.6 pg/mL; 95% CI, −60.2, 75.5 pg/mL, P=0.821) and monocytes (estimated adjusted mean difference, 0.2×10^3/μL; 95% CI, −0.2, 0.6×10^3/μL; P=0.252).

Table 1. Study sample characteristics (n=47)

Parameter	Peri-implantitis (n=16)	Controls (n=31)	*P* value[a]	*P* value[b]
Age (yr)	57.4±10.0	57.4±9.1	0.995	-
Males	8 (50.0)	15 (48.4)	0.917	-
Current smokers	5 (31.2)	6 (19.4)	0.472	-
Previous history of periodontitis	13 (81.2)	0 (0.0)	**<0.001**	-
PPD (mm)	6.0±1.7	3.9±0.2	**<0.001**	**<0.001**
BoP (%)	89.9±21.0	0.0±0.0	**<0.001**	**<0.001**

Values are presented as mean±standard deviation or number (%). Significant results are reported in bold.
PPD: probing pocket depth, BoP: bleeding on probing.
[a]*P* values for univariate analysis; [b]*P* values for linear mixed model analysis.

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Table 2. Biochemical characteristics (n=47)

Parameter	Peri-implantitis (n=16)	Controls (n=31)	*P* value[a]	*P* value[b]
Total cholesterol (mg/dL)	212.0 (175.0, 231.0)	156.0 (143.0, 172.0)	**<0.001**	**<0.001**
Triglycerides (mg/dL)	80.0 (61.0, 127.0)	66.0 (44.0, 111.0)	0.205	0.119
HDL cholesterol (mg/dL)	61.0 (55.0, 90.0)	55.0 (44.0, 73.0)	0.138	0.112
LDL cholesterol (mg/dL)	120.0 (101.0, 134.0)	91.0 (80.0, 101.0)	**0.001**	**<0.001**
Total/HDL cholesterol ratio	3.0 (2.4, 3.7)	2.8 (2.1, 3.4)	0.111	0.077
LDL/HDL cholesterol ratio	2.0±1.0	1.6±0.4	0.154	0.063
Creatinine (mg/dL)	0.6 (0.5, 0.7)	0.7 (0.6, 0.9)	0.320	0.435
Glucose (mg/dL)	83.0 (73.0, 90.0)	81.0 (73.0, 88.0)	0.669	0.420
RBC (10^6/μL)	4.5 (4.2, 4.9)	4.6 (4.2, 5.0)	0.543	0.599
Platelets (10^3/μL)	231.2±57.6	222.7±52.3	0.612	0.605
WBC (10^3/μL)	5.8 (4.3, 6.6)	3.7 (3.3, 3.9)	**<0.001**	**<0.001**
Lymphocytes (10^3/μL)	1.9±0.7	1.7±0.6	0.474	0.465
Monocytes (10^3/μL)	0.4 (0.3, 0.5)	0.3 (0.2, 0.3)	**<0.001**	**0.001**
Neutrophils (10^3/μL)	3.0±1.2	2.4±0.7	0.085	**0.034**
Eosinophils (10^3/μL)	0.08 (0.05, 0.21)	0.15 (0.07, 0.21)	0.290	0.289
Basophils (10^3/μL)	0.04 (0.01, 0.05)	0.04 (0.02, 0.05)	0.821	0.276
TNF-α (pg/mL) (n=46)	93.2 (56.7, 166.0)	65.6 (44.9, 85.7)	**0.033**	**0.003**
IL-10 (pg/mL)	1.9 (1.9, 2.0)	13.7 (9.5, 15.8)	**<0.001**	**<0.001**

Values are presented as number (range) or mean±standard deviation. Significant results are reported in bold. HDL: high-density lipoprotein, LDL: low-density lipoprotein, RBC: red blood cells, WBC: white blood cells, TNF-α: tumor necrosis factor alpha, IL-10: interleukin-10.
[a]*P* values for univariate analysis; [b]*P* values for linear mixed model analysis.

While modest positive correlations were found between PPD and total cholesterol (r=0.512; *P*<0.001) (Figure 1A), LDL cholesterol (r=0.463; *P*=0.001) (Figure 1B) and WBC (r=0.519; *P*<0.001) (Figure 1D), a moderate negative correlation was found between IL-10 and PPD (r=0.609; *P*<0.001) (Figure 1C) in all participants. Similar, but slightly higher, estimates were observed for BoP and total cholesterol (r=0.602; *P*<0.001), LDL cholesterol (r=0.483; *P*=0.001), WBC (r=0.630; *P*<0.001), and IL-10 (r=−0.758; *P*<0.001).

DISCUSSION

To the best of our knowledge, this is the first study assessing the inflammatory profile of patients with peri-implantitis. The findings of this pilot study showed an enhanced systemic inflammatory state characterized by elevated levels of WBC as well as the presence of dyslipidemia in patients with peri-implantitis compared to individuals with healthy implants. We found moderate linear correlations of the depth of the peri-implant pockets and peri-implant bleeding with markers of inflammation (WBC and IL-10) and blood lipids (total cholesterol and LDL cholesterol).

In peri-implantitis, the presence of subgingival pathogens elicits a local inflammatory response, which is characterized by larger proportions of polymorphonuclear leukocytes and macrophages. Furthermore, this inflammatory response is amplified due to the production of pro-inflammatory cytokines and prostaglandins. The release of these substances into the bloodstream stimulates further recruitment of pro-inflammatory mediators and leukocytes at the local site. It should be highlighted that it has been demonstrated that this local inflammatory response is more pronounced in peri-implant tissues than in periodontal tissues [6]. The ulcerated gingival epithelium of severely periodontally affected patients allows these locally produced inflammatory mediators to enter the bloodstream and induce an acute-phase reaction in the liver, thereby contributing to the overall systemic inflammatory burden [13]. If we take into account the pathophysiological similarities of

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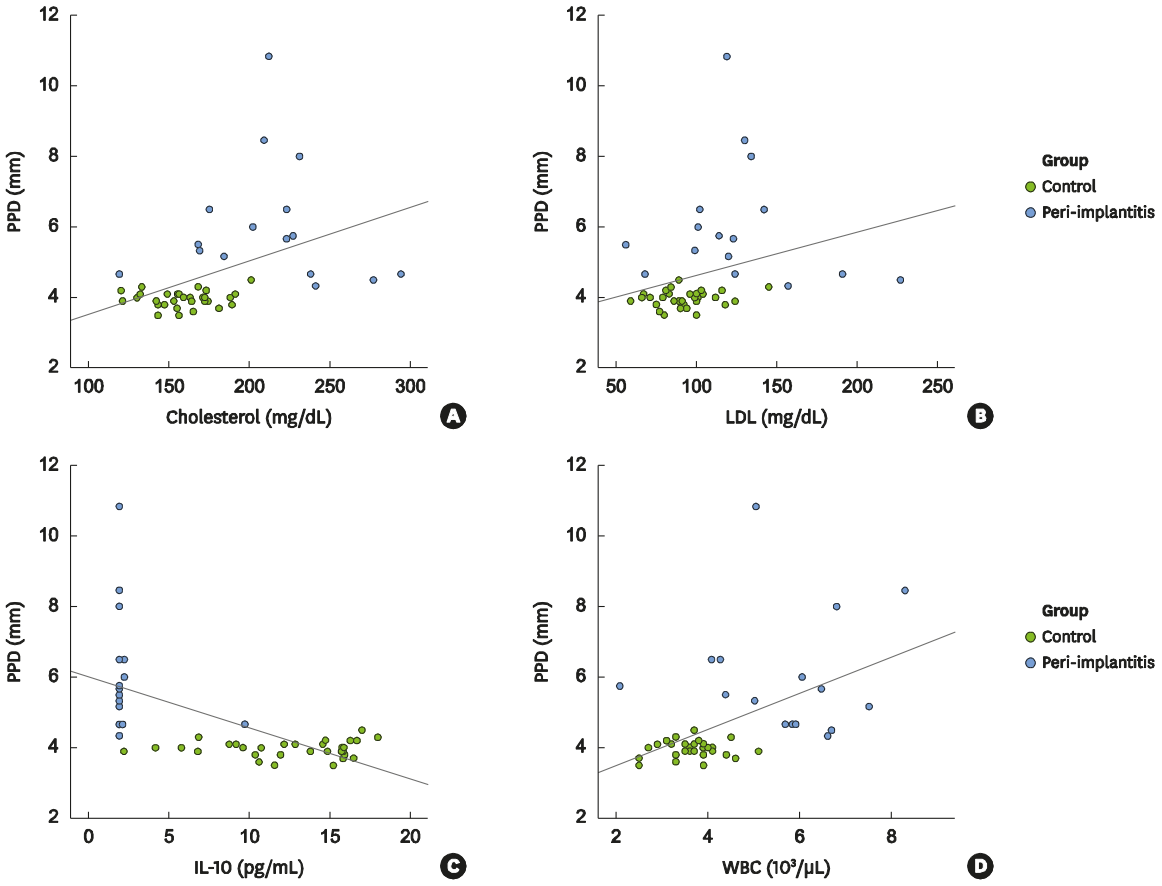


Figure 1. Scatter plots showing correlations between PPD (mm) and: (A) total cholesterol (mg/dL); (B) LDL cholesterol (mg/dL); (C) IL-10 (pg/mL); (D) WBC (10^3/μL). PPD: probing pocket depth, LDL: low-density lipoprotein, IL-10: interleukin-10, WBC: white blood cells.

both diseases, a persistent peri-implant inflammatory state might also have an impact on systemic inflammation. In the present study, patients with peri-implantitis had an increase in leukocytes (WBC), reflecting a possible chronic systemic inflammatory stimulus, which might have been caused by the persistent peri-implant disease, as has been shown recently in periodontitis [14]. A linear correlation was also found between clinical peri-implant inflammatory parameters and WBC levels. Along similar lines, recent animal studies have shown an increased systemic inflammatory response after ligature-induced experimental peri-implantitis that was characterized by high levels of total protein, albumin, and WBC, which reverted to baseline after surgical peri-implant treatment [7,8]. The systemic inflammatory state of peri-implantitis patients was confirmed by lower circulating levels of IL-10, a cytokine with important anti-inflammatory properties [15]. It has been suggested that decreased levels of IL-10 may favor a more inflammatory milieu since IL-10 has potent deactivating properties in macrophages and T-cells, and thus can act as a downregulator of cell-mediated immune responses, such as those potentially seen in peri-implantitis [15].

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Another relevant finding from this study is that the peri-implantitis patients exhibited dyslipidemia, as characterized by higher blood LDL cholesterol levels. This observation confirms previous results reporting higher LDL cholesterol and total cholesterol levels among periodontitis patients when compared to healthy controls [16-18]. A relationship between infections and lipid metabolism has been widely documented in the past decades. Chronic infectious diseases are now thought to have an impact on lipid plasma levels [19-21]. This dyslipidemia is thought to be part of a host response aimed at decreasing the toxicity of harmful microbiological agents [22]. The present investigation found an association between peri-implantitis and abnormal lipid levels, which may be mediated by the constant activation of the inflammatory process determined by the presence of periodontal pathogens in peri-implant pockets.

Based on the present results, one might speculate that peri-implantitis could be associated with atherosclerotic disease. The acute-phase response during peri-implant infection/inflammation protects the host from further infection. Changes in acute-phase proteins (e.g., C-reactive protein [CRP]) neutralize invading microorganisms such as periodontal bacteria, minimize the extent of tissue damage, participate in the local immune response and tissue regeneration, and replenish proteins used in the inflammatory process [22,23]. These changes, if present for a prolonged period of time, can lead to detrimental consequences to the host, such as the development of low-grade chronic systemic inflammation. In this sense, changes in acute-phase reactant synthesis are mediated by cytokines produced in response to a variety of stimuli in multiple cell types, including macrophages, monocytes, lymphocytes, and endothelial cells [24,25]. Cytokines responsible for the coordination of both immune and inflammatory responses such as ILs or TNF-α might induce alterations in lipid and lipoprotein metabolism that contribute to atherogenesis [22]. Due to the high prevalence of peri-implantitis and atherosclerotic vascular diseases such as coronary heart disease and stroke, future epidemiological studies should investigate whether individuals with peri-implantitis are at a high risk of having cardiovascular events.

Some shortcomings need to be acknowledged in relation to our investigation. Firstly, this was a pilot study and, therefore, the results are preliminary and hypothesis-generating. However, *post hoc* power calculation was performed, showing that our study had a power of 90% to detect clinically meaningful differences between peri-implantitis patients and controls in terms of WBC concentrations. Secondly, due to the cross-sectional nature of the study, causality cannot be demonstrated; hence, we cannot rule out the possibility that other factors could also be involved in the upregulation of peripheral inflammatory mediators and dyslipidemia seen in peri-implantitis patients. Although all participants were in apparent good general health, some of them could have suffered from undiagnosed medical conditions such as pre-hypertension, pre-diabetes, or obesity. In this sense, a recent study demonstrated that an extremely high body mass index (≥40 kg/m^2) was associated with worse peri-implant conditions, increased systemic pro-inflammatory state and dyslipidemia [26]. In the present investigation, an important factor that might have influenced the results was the previous history of periodontitis, as most of the peri-implant cases presented with successfully treated periodontal disease. Even after adjustment for this confounding factor, significance remained for levels of WBC, IL-10, cholesterol, and LDL. In addition, when the clinical peri-implant assessment was done and blood samples were collected, none of the patients had active signs of periodontitis, which therefore might not have had a strong impact at a systemic level. Another limitation is that commonly used serum biomarkers reflecting systemic pro-inflammatory processes such as CRP or IL-6 were not measured in

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this study. Nevertheless, WBC has been widely used in the literature as a surrogate marker of systemic inflammation [27]. We also included a well-known cytokine with anti-inflammatory action (IL-10) [15]. Our results showed not only that concentrations of WBC were elevated in peri-implantitis patients, but also that IL-10 serum levels were reduced when compared to subjects with healthy implants, thus supporting our initial hypothesis.

It can be concluded that otherwise healthy patients diagnosed with peri-implantitis presented with a low-grade inflammatory state (increased circulating levels of WBC) accompanied by dyslipidemia (increased blood levels of cholesterol and LDL). Further studies are warranted to confirm our preliminary results using large population-based cohorts. Experimental studies are also needed to investigate the potential biological mechanisms behind this link. Lastly, carrying out intervention studies will be of paramount interest to test whether non-surgical and surgical peri-implant therapy could have a beneficial systemic effect in terms of reducing the overall inflammatory burden in patients affected by peri-implantitis.

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4.4. ESTUDIO #4

Liñares A, Dopico J, **Blanco C**, Pico A, Sobrino T, Blanco J, Leira Y. The systemic impact of non-surgical treatment of peri-implantitis with or without adjunctive systemic metronidazole: Secondary analysis of a randomized clinical trial. Clin Oral Implants Res. 2024 Aug 2. doi: 10.1111/clr.14339.

4.4.1. Objetivo

El objetivo de este estudio fue evaluar el efecto sistémico del tratamiento no quirúrgico de la periimplantitis (NSPIT) con o sin la administración de metronidazol sistémico.

4.4.2. Material y métodos

En este análisis secundario de un ensayo clínico publicado previamente (NCT03564301), los pacientes con periimplantitis fueron asignados aleatoriamente a dos grupos: grupo test, que recibió NSPIT en combinación con 500 mg de metronidazol sistémico oral tres veces al día durante 7 días (n = 10); y grupo control, que recibió NSPIT más placebo (n = 11). Se obtuvieron muestras de sangre al inicio, 3 y 6 meses después de la terapia para determinar los niveles de biomarcadores inflamatorios, fracciones lipídicas y hemogramas completos.

4.4.3. Resultados

Ambas modalidades de tratamiento produjeron mejoras en los parámetros clínicos y radiográficos. Después de 6 meses de NSPIT, se observó una reducción de la proteína C reactiva (6,9 mg/dl; IC del 95 %: 3,7 a 9,9, $p < 0,001$) y del colesterol de lipoproteínas de baja densidad (21,8 mg/dl; IC del 95 %: −6,9 a 50,5, $p = 0,013$), así como un aumento los recuentos de neutrófilos (0,4 × 103/µl; IC del 95 %: −0,4 a 1,1, $p = 0,010$) en el grupo de control mientras que el grupo test mostró una reducción significativa del TNF-α (110,1; IC del 95 %: 38,9 a 181,4, $p = 0,004$).

4.4.4. Conclusiones

La NSPIT mostró un efecto sistémico beneficioso a corto plazo independientemente del uso coadyuvante de metronidazol sistémico.

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ORIGINAL ARTICLE

CLINICAL ORAL IMPLANTS RESEARCH WILEY

The systemic impact of non-surgical treatment of peri-implantitis with or without adjunctive systemic metronidazole: Secondary analysis of a randomized clinical trial

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Abstract

Objectives: The aim of this study was to evaluate the systemic effect of non-surgical peri-implantitis treatment (NSPIT) with or without the administration of systemic metronidazole.

Methods: In this secondary analysis from a previously published clinical trial (NCT03564301), peri-implantitis patients were randomized into two groups: test, receiving NSPIT plus 500 mg of oral systemic metronidazole three times a day for 7 days ($n = 10$); and control group, receiving NSPIT plus placebo ($n = 11$). Serum samples were obtained at baseline, 3 and 6 months after therapy to determine levels of inflammatory biomarkers, lipid fractions and complete blood counts.

Results: Both treatment modalities produced improvements in clinical and radiographic parameters. After 6 months from NSPIT, a substantial reduction in C-reactive protein (6.9 mg/dL; 95% CI: 3.7 to 9.9, $p < .001$) and low-density lipoprotein cholesterol (21.8 mg/dL; 95% CI: −6.9 to 50.5, $p = .013$) as well as a modest increase in neutrophils counts ($0.4 \times 10^3/\mu L$; 95% CI: −0.4 to 1.1, $p = .010$) was observed in the control group while the test group showed a significant reduction of TNF-α (110.1; 95% CI: 38.9 to 181.4, $p = .004$).

Conclusions: NSPIT showed a short-term beneficial systemic effect regardless of adjunctive use of systemic metronidazole.

KEYWORDS
antibiotic, cardiovascular disease, C-reactive protein, inflammation, peri-implantitis, treatment

1 | INTRODUCTION

Peri-implantitis is a chronic inflammatory infectious disease which affects the surrounding tissues of dental implants. It is estimated that at least one-quarter of people with implants will develop peri-implantitis at some point of their lives, what makes this oral condition highly prevalent in the adult population worldwide (Derks et al., 2016; Kordbacheh Changi et al., 2019; Matarazzo et al., 2018; Rodrigo et al., 2018). During

Antonio Liñares and Jose Dopico contributed equally to the manuscript as first authors.

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the last decade, several systematic reviews have shown that a wide range of pro-inflammatory mediators [i.e., interleukin 1 beta (IL-1β), IL-6 or tumor necrosis factor alpha (TNF-α) among others] can be detected in peri-implant crevicular fluids of patients with peri-implantitis mainly due to a strong inflammatory host response produced within the peri-implant tissues against bacterial challenge (Candel-Marti et al., 2011; Ghassib et al., 2019; Javed et al., 2011).

Similarly to periodontitis, it is plausible that the aforementioned locally produced inflammatory cytokines could gain access to the bloodstream through the ulcerated peri-implant epithelium leading to an acute-phase response in the liver with increased production of acute phase reactants such as C-reactive protein (CRP). If this acute inflammatory process is not resolved might eventually lead to a low-grade chronic systemic inflammatory state which can often be seen in some of the most prevalent and disabling non-communicable chronic conditions such as atherosclerotic vascular diseases, diabetes, rheumatic diseases, chronic kidney dysfunction or even Alzheimer's disease (Furman et al., 2019). Recently, a case–control study showed that subjects with cardiovascular disease (CVD) had a higher prevalence of moderate-to-severe peri-implantitis than those without infected dental implants (≈50% vs. ≈30%) (Wang, Ou, et al., 2021).

Moreover, recent clinical and experimental evidence have demonstrated a potential link between peri-implantitis and systemic inflammation (Blanco et al., 2021; Chaushu et al., 2020, 2021; Ustaoglu & Erdal, 2020; Wang, Sugai, et al., 2021). In two cross-sectional studies, patients with peri-implantitis showed higher levels of some markers of systemic inflammation such as TNF-α and leucocytes when compared to subjects with healthy implants (Blanco et al., 2021; Chaushu et al., 2020, 2021; Ustaoglu & Erdal, 2020). In addition, a dyslipidemic state was also observed in peri-implantitis individuals (elevated blood levels of total and low-density lipoprotein cholesterol as well as triglycerides) in these observational reports (Blanco et al., 2021; Ustaoglu & Erdal, 2020; Wang, Sugai, et al., 2021). In CVD patients, peri-implantitis was also associated with elevated levels of pro-inflammatory cytokines (Wang, Sugai, et al., 2021). All these preliminary clinical findings were supported by previous animal studies where circulating concentrations of leukocytes and other inflammatory mediators were increased after experimental peri-implantitis was induced by ligatures placement (Chaushu et al., 2020, 2021). It has to be highlighted that in these experiments, treatment of peri-implant lesions reverted levels of inflammatory markers to normal values (Chaushu et al., 2020, 2021).

Recently, our group published the results of a randomized clinical trial (RCT) suggesting that the use of systemic metronidazole could result in additional improvement of clinical, radiographic and microbiological parameters when used as adjunct to non-surgical treatment in patients with peri-implantitis (Blanco et al., 2022). On the other hand, several reports evaluated the potential systemic adjunctive benefit of administration of systemic antibiotics in the non-surgical periodontal therapy with conflicting results (Cosgarea et al., 2020; Giannopoulou et al., 2016; López et al., 2012). However, to our knowledge, no human intervention study has tested whether non-surgical peri-implantitis treatment (NSPIT) in conjunction with the use of systemic antibiotics could have a systemic anti-inflammatory effect in subjects diagnosed with peri-implantitis.

Therefore, the primary aim of this secondary analysis was to assess the effect of the use of systemic metronidazole in the NSPIT on serum inflammatory markers (CRP, IL-6, IL-10 and TNF-α) over a period of 6 months when compared to NSPIT alone. Secondly, the study investigated changes in lipid fractions and differential blood counts after NSPIT. Clinical and radiographic outcomes were also evaluated to validate the level of efficacy of NSPIT.

2 | MATERIALS AND METHODS

2.1 | Experimental design and study population

We have analyzed the changes in host-derived systemic biomarkers in the context of a 12-month single-center, parallel-arm, triple-blind, placebo-controlled RCT which evaluated the adjunctive effect of systemic metronidazole administration to non-surgical treatment of peri-implantitis (ClinicalTrials.gov NCT03564301) (Blanco et al., 2022). Recruitment and study flowchart are shown in Figure 1.

The aim was to include at least 20 consecutive patients with peri-implantitis recruited into the aforementioned trial for additional analyses of systemic biomarkers. Follow-up for this purpose was set at 6 months as in the majority of studies published in the field of Periodontal Medicine this is a commonly used time frame to assess changes in systemic biomarkers after non-surgical treatment. Participants were recruited among referral to the Periodontology Unit of the University of Santiago de Compostela (Spain) between January 2018 and July 2019. The trial included patients diagnosed with peri-implantitis presenting with at least one implant with bleeding on probing (BoP) and/or suppuration, probing pocket depth (PPD) ≥6 mm and ≥3 mm of detectable bone loss after initial remodeling (Berglundh et al., 2018; Renvert et al., 2018). Exclusion criteria included: (i) underage, (ii) previous history of allergy to metronidazole, (iii) implant mobility, (iv) pregnant or lactating females, (v) had received any pharmacological therapy within the 3 months before the start of the trial, or (vi) severe systemic illnesses or malignancies.

Ethical approval was obtained from the Research Ethics Committee of Santiago de Compostela/Lugo (2017/508) and the investigation was conducted in accordance with the principles outlined in the Declaration of Helsinki on experimentation involving human beings (Order SCO/256/2007). Informed consent was obtained from all individual participants included in the study. The present study was performed and reported according to the CONSORT guidelines for reporting parallel-group randomized clinical trials.

2.2 | Randomization, allocation concealment and masking

Randomization and masking procedures were published elsewhere (Blanco et al., 2022). In brief, following a baseline visit, each patient

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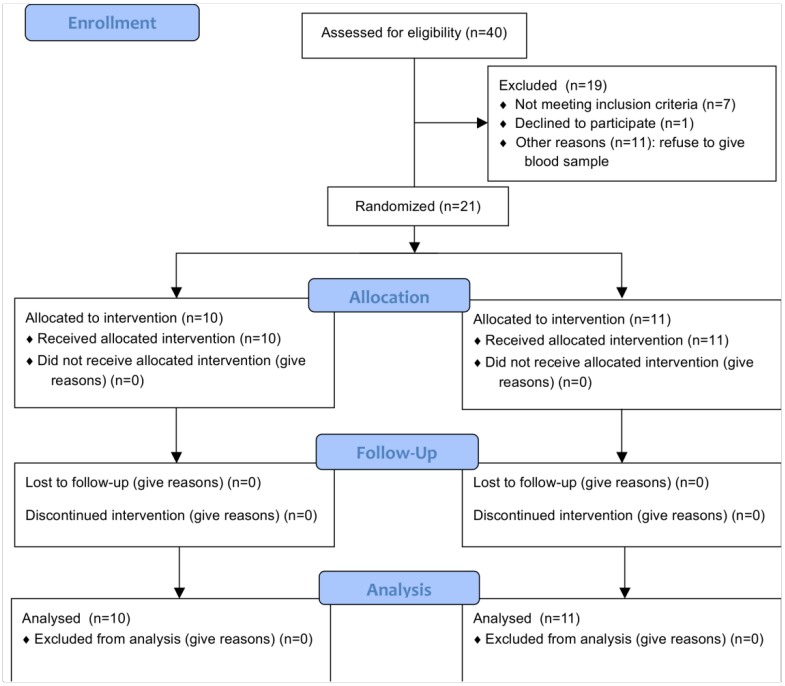


FIGURE 1 Flow chart of the recruitment and study protocol.

recruited into the trial was randomly allocated (using a computer-generated table) to receive either NSPIT + metronidazole ($n = 10$) or NSPIT + placebo ($n = 11$). Restricted randomization was performed (minimization), stratifying for smoking habits and history of periodontitis. Allocation to treatment was concealed in an opaque envelope. The patient, examiner, therapist and statistician were masked to the group allocation.

2.3 | Clinical outcomes

Clinical parameters were assessed using a UNC-15 periodontal probe (Hu-Friedy®, Chicago, IL, USA) by one calibrated examiner (JD) at six sites per implant (Blanco et al., 2022). These parameters were recorded at baseline, 3 and 6 months. In cases where the prosthesis did not allow adequate access to the implant, it was removed for clinical assessment at each appointment. PPD was calculated as the distance from the gingival peri-implant margin to the bottom of the peri-implant pocket (in millimeters). Peri-implant recession was measured as distance from the free gingival margin (more coronal portion of the free gingiva) to the more apical portion of the crown (in millimeters). BoP was assessed dichotomously also in six sites per implant (expressed in %).

2.4 | Radiographic outcomes

Intraoral phosphor plate long-cone parallel technique radiographs were taken with the aid of custom-made holders to evaluate peri-implant marginal radiographic bone levels at baseline, 3 and 6 months. The same custom-made holders for each specific implant were used in all visits. Those radiographs were analyzed using a digital radiographic software (ImageJ 1.47V Wayne Rasband, National Institutes of Health and Laboratory of Optical and Computational Instrumentation, University of Wisconsin, Wisconsin, USA). All examinations were performed by an independent and calibrated examiner (AP) to the nearest 0.1 mm using IMAGE J software (Blanco et al., 2022). The scale was set and calibrated by the height of the dental implant, which yielded a pixel/mm ratio. The implant shoulder was used as a fixed reference point. To assess linear changes at interproximal alveolar crestal bone height, the distance from the implant shoulder to the most coronal bone to implant contact (RBL) was determined both at the mesial and distal aspect of each implant and expressed in millimeters.

2.5 | Non-surgical peri-implant therapy (NSPIT)

Pre-treatment visits were scheduled to help the study subjects achieve and maintain adequate self-performed plaque control. Supragingival debridement and elimination/reduction of plaque-retentive factors, including modification of existing prosthesis were performed (de Tapia et al., 2019), and oral hygiene instructions were provided. After optimal plaque control was achieved (full-mouth plaque score < 20%), patients received one session of non-surgical debridement as described previously (Blanco et al., 2022) by an experienced periodontist. Prosthesis were removed during treatment, if possible, and relocated at the end of the treatment session. Before starting the instrumentation, the patient rinsed with 0.12% chlorhexidine digluconate (Perio-aid, Dentaid, Spain). Non-surgical

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treatment under local anesthesia consisting of supra- and submucosal mechanical debridement using ultrasound with a stainless steel periodontal tip (EMS®, Electro Medical Systems, Nyon, Switzerland) were performed in one treatment session with no time restriction. Ultrasonic debridement was performed with concomitant irrigation of chlorhexidine of 0.12% (Perio-aid, Dentaid, Spain). After that, a stainless steel curette Columbia 4R/4 L (LM Instruments Oy, Pargas, Finland) was used to remove the granulation tissue and minor mucosal curettage. Then, peri-implant pockets were irrigated with 0.12% chlorhexidine digluconate (Perio-aid, Dentaid, Spain). A regimen consisting of oral systemic metronidazole 500 mg for 7 days (three times/day) was prescribed in patients from the test group immediately after the treatment session while place pills were administered in the control group.

Follow-up visits were scheduled at 3 and 6 months after NSPIT. During these appointments, the examiner recorded any changes in medical history and adverse events. Clinical measurements, radiographs, and blood samples were taken at each of those visits. At the end of each appointment, oral hygiene instructions and motivation were provided together with a session of supragingival debridement. Sites with residual peri-implant pockets (sites with PPD ≥ 5 mm) also received submucosal debridement with same ultrasonic device described above.

2.6 | Biochemical analysis

Serial blood samples were collected before and 3 and 6 months after completion of therapy. Briefly, 2 mL of venous blood was collected from the antecubital fossa by venepuncture using a 20-gauge needle with a 2 mL syringe. Blood samples were allowed to clot at room temperature and, after 1 h, serum was separated from blood by centrifugation (15 min at 3000*g*) and 0.5 mL of extracted serum was immediately transferred to 1.5-mL aliquots. Each aliquot was stored at −80°C until required for analysis. Serum CRP concentrations were measured with a latex immunoassay namely MULTIGENT CRP Vario assay using the ARCHITECT cSystems (Abbott Laboratories, IL, USA). Serum levels of TNF-α were determined using an immunodiagnostic IMMULITE® 1000 Systems (Siemens Healthcare Diagnostics, Munich, Germany). Serum levels of IL-6 and IL-10 were quantified with enzyme-linked immunosorbent assay technique following manufacturer instructions (BioLegend, San Diego, CA, USA). Blood lipids and complete blood count were determined by routine biochemistry.

To minimize variability, all assays were performed at the end of the study, in duplicates and with the same kits at all timepoints by staff masked to study and treatment allocation.

2.7 | Statistical analysis

This is a secondary analysis of an RCT, hence, no formal sample size calculation was made. All data are presented as mean and standard deviation unless otherwise specified. Differences between two treatment groups at baseline were evaluated by Student *t* test and Fisher's exact test for continuous and categorical variables, respectively. An intention-to-treat, last value carried forward data analysis was performed in a conventional manner using two-way mixed analysis of variance (ANOVA) with post hoc comparison made by Bonferroni test and adjusted for potential confounders. Pearson´s correlation coefficient analysis was applied to assess correlations between changes in clinical/radiographic and systemic markers. All comparisons have been done at patient level. All statistical analyses were done using an appropriate statistical software (IBM SPSS Statistics version 24.0 for Windows, IBM Corporation, Armonk, NY, USA). The α value was set at 0.05.

3 | RESULTS

3.1 | Sample characteristics

No statistically significant differences were observed in subject characteristics by treatment group at baseline (Table 1). However, groups were notably unbalanced for gender, smoking habit, history of periodontitis and presence of systemic comorbidities. All subjects completed the trial and attended at each visit. Adverse events were similar between study groups being the most frequent gastrointestinal disorder (two participants, one per group), headaches (four participants, two per group), metallic taste (two participants, one per group), and oral tissue alterations (one participant from the test group). No major changes in patient's medical history were reported in either group over the study period.

3.2 | Effect of NSPIT on clinical and radiographic outcomes

NSPIT resulted in a marked improvement in clinical and radiographic parameters over the 6 months after therapy irrespectively of the treatment modality delivered (Table 2).

TABLE 1 Baseline characteristics of trial participants.

Parameter	Test ($n=10$)	Control ($n=11$)
Age (years)	59.6 (11.7)	58.6 (10.2)
Males, *n* (%)	6 (60.0)	2 (18.2)
Current smokers, *n* (%)	1 (10.0)	4 (36.4)
Presence of systemic condition, *n* (%)	4 (40.0)	1 (9.1)
Previous history of periodontitis, *n* (%)	6 (60.0)	10 (90.9)
Number of implants/patient	1.6 (1.1)	1.9 (1.4)
Prosthesis removed, *n* (%)	5 (50)	5 (45.5)
Re-instrumentation of residual pockets, *n* (%)	6 (60)	6 (54.5)

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TABLE 2 Changes in clinical and radiographic outcomes over time in each study group.

Group	Parameter	Baseline	3 months	6 months	Intragroup all groups (*p*-value)	Intragroup baseline versus 3 months (*p*-value)	Intragroup 3 months versus 6 months (*p*-value)	Intragroup baseline versus 6 months (*p*-value)	Time*treatment interaction (intergroup *p*-value)
Test ($n=10$)	PPD (mm)	6.5 (1.8)	4.6 (1.1)	4.3 (1.3)	**.014**	**.020**	1.000	**.009**	
Control ($n=11$)		5.7 (1.1)	4.7 (1.3)	4.5 (1.0)	.363	.761	1.000	.491	
	Intergroup (*p*-value)	.078	.497	.545					.471
Test ($n=10$)	maxPPD (mm)	8.5 (1.4)	6.2 (1.7)	5.6 (1.7)	**.003**	**.039**	.249	**.002**	
Control ($n=11$)		8.1 (1.8)	6.0 (2.1)	5.2 (1.2)	**.022**	**.049**	1.000	**.016**	
	Intergroup (*p*-value)	.263	.394	.698					.626
Test ($n=10$)	RBL (mm)	6.1 (1.6)	5.7 (1.6)	4.7 (1.6)	**.000**	.561	**.000**	**.004**	
Control ($n=11$)		5.4 (2.0)	5.0 (2.3)	4.7 (2.3)	.419	.566	1.000	.587	
	Intergroup (*p*-value)	.221	.268	.655					**.021**
Test ($n=10$)	Recession (mm)	0.5 (0.9)	0.8 (0.7)	0.7 (0.7)	.588	1.000	1.000	.961	
Control ($n=11$)		0.2 (0.3)	0.8 (0.7)	0.6 (0.6)	**.036**	**.040**	.555	.719	
	Intergroup (*p*-value)	.244	.788	.299					.454
Test ($n=10$)	BoP (%)	83	42	40	**.001**	**.001**	1.000	.064	
Control ($n=11$)		92	65	50	**.040**	.511	.629	.050	
	Intergroup (*p*-value)	.822	.108	.856					.181

Note: Statistically significant results are denoted in bold. *p*-values are adjusted for gender, smoking habit, presence of systemic diseases and previous history of periodontitis.
Abbreviations: BoP, bleeding on probing; PPD, probing pocket depth; RBL, radiographic bone level.

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Substantial reductions in PPD (mean decrease of 1.9 mm, 95% CI: 0.7 to 3.2 in the test group and mean decrease of 1.0 mm, 95% CI: −0.1 to 2.2 in the control group, $p=.497$ for intergroup comparison), maximum PPD (mean decrease of 2.3 mm, 95% CI: 0.1 to 4.6 in the test group and mean decrease of 2.1 mm, 95% CI: 0.0 to 4.2 in the control group, $p=.263$ for intergroup comparison), radiographic bone gain (mean increase of 0.4 mm, 95% CI: −0.1 to 1.0 in the test group and mean increase of 0.4 mm, 95% CI: −0.2 to 0.8 in the control group, $p=.268$ for intergroup comparison), and bleeding scores (mean decrease of 41%, 95% CI: 18 to 63 in the test group and mean decrease of 27%, 95% CI: 6 to 48 in the control group, $p=.108$ for intergroup comparison) were achieved in both groups 3 months after NSPIT. At 6 months, these improvements were more evident in the test group (for ΔPPD: 2.2 mm, 95% CI: 1.0 to 3.4, $p=.009$; for ΔmaxPPD: 3.4 mm, 95% CI: 1.3 to 5.5, $p=.002$; for ΔRBL: 1.4 mm, 95% CI: 0.7 to 2.2, $p=.004$; and for ΔBoP: 42%, 95% CI: 16 to 68, $p=.064$) than in the controls (for ΔPPD: 1.2 mm, 95% CI: 0.1 to 2.4, $p=.491$; for ΔmaxPPD: 2.4 mm, 95% CI: 0.4 to 4.3, $p=.016$; for ΔRBL: 0.7 mm, 95% CI: 0.0 to 0.4, $p=.587$; and for ΔBoP: 34%, 95% CI: 1 to 58, $p=.050$). However, time*treatment interaction for intergroup comparisons was only statistically significant for radiographic bone gain ($p=.021$). As expected, an increase in peri-implant recession was noted after therapy in both groups which reached statistical significance at 3 months in the control group (mean increase of 0.6 mm, 95% CI: 0.1 to 1.1, $p=.040$). No statistically significant differences were observed for any clinical parameter when participants who underwent re-instrumentation of residual peri-implant pockets were compared to those who have not.

3.3 | Effect of NSPIT on systemic outcomes

Comparisons for biomarkers are shown in Table 3. Time*treatment interaction was statistically significant for CRP ($p=.046$) and IL-6 ($p=.018$). Statistically significant differences between groups were noted for IL-6 (mean difference = 42.6 pg/mL; 95% CI: −122 to 167.2, $p=.012$) and TNF-α concentrations (mean difference = 0.7 pg/mL; 95% CI: −17.6 to 19.1, $p=.031$) at 3 months and for IL-6 (mean difference = 4.5 pg/mL; 95% CI: −11.9 to 20.9, $p=.019$) at 6 months after therapy.

Intragroup comparisons showed reductions in the control group for CRP at 6 months compared to baseline values (mean decrease of 6.9 mg/dL; 95% CI: 3.7–9.9, $p<.001$). With regards to the test group, a substantial decrease in TNF-α was found at 3 and 6 months after NSPIT (mean reduction at 3 months of 102.6; 95% CI: 24.2–181.1, $p=.006$ and mean reduction at 6 months of 110.1; 95% CI: 38.9–181.4, $p=.004$) compared to baseline. A trend towards an increase in peripheral IL-10 levels was also observed, albeit differences were not statistically significant.

Only a modest increase in platelets was observed in the test group between 3 and 6 months after NSPIT (mean increase of $29.2\times10^3/\mu L$; 95% CI: 9.1–49.4, $p=.040$) and in neutrophil counts in the test group between baseline and 6 months (mean increase = 0.4; 95% CI: −0.4 to 1.1, $p=.010$). Intergroup differences were observed for triglycerides levels at 6 months (mean difference = 13.6 mg/dL; 95% CI: −45.2 to 72.3, $p=.047$) and intragroup reductions in the control group for LDL cholesterol at 3 (mean decrease = 8.6 mg/dL; 95% CI: −18.7 to 35.9, $p=.012$) and 6 months (mean decrease = 21.8 mg/dL; 95% CI: −6.9 to 50.5, $p=.013$) compared to baseline. No substantial intra and intergroup changes were noted in other lipid fractions and the remaining hematological parameters. No statistically significant differences were observed for any clinical parameter when participants who received re-instrumentation of residual peri-implant pockets were compared to those who have not.

3.4 | Correlation analysis

A moderate positive correlation was found for reduction in TNF-α concentrations between baseline and 6 months and radiographic bone gain at 6 months (Figure 2) as well as baseline PPD (Figure 3). No other clinical or radiographic parameters were correlated with changes in systemic biomarkers.

4 | DISCUSSION

To our knowledge, this is the first human investigation evaluating the systemic impact of non-surgical treatment of peri-implantitis. Findings from this secondary analysis of an RCT suggest that NSPIT has a systemic anti-inflammatory effect (reduction in circulating levels of CRP, IL-6 and TNF-α) after 6 months of follow-up.

A potential association between peri-implantitis and systemic inflammatory state has recently been described (Blanco et al., 2021; Ustaoglu & Erdal, 2020). In these human studies, patients with peri-implantitis showed greater concentrations of WBCs and TNF-α than those subjects with healthy implants. These findings are in accordance with animal experiments where after induction of peri-implantitis by means of ligature placement, an increase in some inflammatory parameters such as total protein, albumin and WBCs was noticed (Chaushu et al., 2020, 2021). In the present study, we observed that after 6 months of NSPIT, levels of well-characterized inflammatory mediators (CRP, IL-6 TNF-α) were statistically significant reduced when compared to baseline values. In line with these results, previous animal studies demonstrated that treatment of experimentally induced peri-implantitis using a surgical conservative approach consisting of open flap debridement was able to revert concentrations of inflammatory biomarkers to baseline levels (Chaushu et al., 2020, 2021). Likewise the findings observed in the present clinical trial, plenty of investigations support a mid-term reduction of systemic inflammation (measured by CRP, IL-6, TNF-α and other inflammatory markers) after non-surgical periodontal therapy in patients with and without comorbidities (D'Aiuto et al., 2019; Iwamoto et al., 2003; Kamil et al., 2011; Marcaccini et al., 2009).

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TABLE 3 Changes in biochemical outcomes over time in each study group.

Group	Biomarker (reference values)	Baseline	3 months	6 months	Intragroup all groups (*p*-value)	Intragroup baseline versus 3 months (*p*-value)	Intragroup 3 months versus 6 months (*p*-value)	Intragroup baseline versus 6 months (*p*-value)	Time*treatment interaction (*p*-value)
Inflammatory mediators									
Test ($n=10$)	CRP (mg/L) (<0.5 mg/L)	7.6 (1.6)	4.2 (2.7)	4.0 (2.1)	.683	1.000	1.000	1.000	
Control ($n=11$)		9.9 (4.5)	6.1 (4.1)	3.1 (1.5)	**.000**	.307	.104	**.000**	
	Intergroup (*p*-value)	**.038**	.077	.695					**.046**
Test ($n=10$)	IL-6 (pg/mL) (<7 pg/mL)	5.3 (3.7)	4.8 (3.5)	2.6 (1.0)	.183	.649	.259	1.000	
Control ($n=11$)		4.6 (4.1)	3.9 (4.4)	2.2 (1.2)	**.004**	.286	**.016**	.058	
	Intergroup (*p*-value)	.054	**.012**	**.019**					**.018**
Test ($n=10$)	IL-10 (pg/mL) (<10 pg/mL)	2.5 (1.1)	2.3 (1.1)	2.3 (1.1)	.753	1.000	1.000	1.000	
Control ($n=11$)		1.9 (0.1)	2.0 (0.3)	3.5 (1.9)	.451	1.000	1.000	.792	
	Intergroup (*p*-value)	.922	.218	.585					.614
Test ($n=10$)	TNF-α (pg/mL) (<8 pg/mL)	117.5 (75.1)	14.9 (15.5)	7.4 (3.0)	**.007**	**.006**	.883	**.004**	
Control ($n=11$)		84.5 (66.5)	15.6 (19.2)	5.8 (1.6)	**.001**	.699	**.014**	.144	
	Intergroup (*p*-value)	.109	**.031**	.926					.091
Lipid fractions									
Test ($n=10$)	TC (mg/dL) (<255 mg/dL)	217.2 (44.1)	206.1 (28.9)	197.2 (25.1)	.978	1.000	1.000	1.000	
Control ($n=11$)		207.2 (47.9)	197.8 (35.8)	183.9 (34.7)	.057	.173	.393	.051	
	Intergroup (*p*-value)	.993	.499	.161					.422
Test ($n=10$)	Triglycerides (mg/dL) (<150 mg/dL)	91.6 (71.2)	121.5 (104.8)	106.7 (63.4)	.388	.551	.713	1.000	
Control ($n=11$)		106.3 (48.4)	112.2 (55.2)	93.2 (57.3)	.885	1.000	1.000	1.000	
	Intergroup (*p*-value)	.311	.651	**.047**					.732
Test ($n=10$)	HDL-C (mg/dL) (>40 mg/dL)	69.7 (23.4)	65.0 (16.4)	63.4 (20.9)	.219	.229	.732	1.000	
Control ($n=11$)		64.0 (19.9)	62.2 (13.4)	66.4 (19.5)	.963	1.000	1.000	1.000	
	Intergroup (*p*-value)	.097	.093	.088					.433
Test ($n=10$)	LDL-C (mg/dL) (<150 mg/dL)	131.2 (48.6)	121.6 (30.7)	114.1 (34.2)	.583	.903	1.000	1.000	
Control ($n=11$)		121.8 (33.7)	113.2 (23.8)	100.0 (28.7)	**.010**	**.012**	.640	**.013**	
	Intergroup (*p*-value)	.401	.675	.466					.085
Differential blood counts									
Test ($n=10$)	RBC (10^6/μL) ($4.5–5.5\times10^6$/μL)	4.5 (0.4)	4.5 (0.4)	4.6 (0.5)	.057	.075	.125	1.000	
Control ($n=11$)		4.5 (0.3)	4.5 (0.4)	4.6 (0.2)	.346	.411	1.000	1.000	
	Intergroup (*p*-value)	.987	.348	.857					.083
Test ($n=10$)	Platelets (10^3/μL) ($135.0–369.0\times10^3$/μL)	262.2 (44.1)	240.4 (33.8)	269.6 (31.0)	**.026**	.064	**.040**	1.000	
Control ($n=11$)		223.2 (65.1)	233.0 (62.5)	234.9 (68.2)	.238	.309	1.000	.430	

(Continues)

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TABLE 3 (Continued)

Group	Biomarker (reference values)	Baseline	3 months	6 months	Intragroup all groups (*p*-value)	Intragroup baseline versus 3 months (*p*-value)	Intragroup 3 months versus 6 months (*p*-value)	Intragroup baseline versus 6 months (*p*-value)	Time*treatment interaction (*p*-value)
	Intergroup (*p*-value)	**.010**	.064	**.027**					.063
Test ($n=10$)	WBC ($10^3/\mu L$) ($4.09–10.5\times10^3/\mu L$)	5.9 (1.1)	5.8 (1.3)	6.0 (1.6)	.858	1.000	1.000	1.000	
Control ($n=11$)		5.3 (1.6)	5.7 (0.8)	5.9 (1.3)	.287	.863	1.000	.321	
	Intergroup (*p*-value)	.960	.337	.470					.530
Test ($n=10$)	Lymphocytes ($10^3/\mu L$) ($0.7–4.67\times10^3/\mu L$)	2.2 (0.5)	2.1 (0.8)	1.9 (0.7)	.849	1.000	1.000	1.000	
Control ($n=11$)		1.9 (0.7)	2.1 (0.6)	1.9 (0.3)	.271	1.000	.296	.600	
	Intergroup (*p*-value)	.284	.184	.884					.489
Test ($n=10$)	Monocytes ($10^3/\mu L$) ($0.108–0.86\times10^3/\mu L$)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	.847	1.000	1.000	1.000	
Control ($n=11$)		0.6 (0.6)	0.5 (0.1)	0.5 (0.1)	.608	1.000	1.000	1.000	
	Intergroup (*p*-value)	.819	.251	.785					.734
Test ($n=10$)	Neutrophils ($10^3/\mu L$) ($1.7–7.33\times10^3/\mu L$)	3.1 (1.0)	3.0 (1.3)	3.4 (1.2)	.759	1.000	1.000	1.000	
Control ($n=11$)		2.7 (1.3)	3.0 (0.6)	3.3 (1.2)	**.008**	1.000	.135	**.010**	
	Intergroup (*p*-value)	.608	.946	.443					.089
Test ($n=10$)	Eosinophils ($10^3/\mu L$) ($0.02–0.6\times10^3/\mu L$)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	.168	1.000	.166	.344	
Control ($n=11$)		0.1 (0.1)	0.1 (0.0)	0.1 (0.1)	.111	1.000	.107	.188	
	Intergroup (*p*-value)	**.151**	.052	.840					.082
Test ($n=10$)	Basophils ($10^3/\mu L$) ($0.004–0.12\times10^3/\mu L$)	0.1 (0.0)	0.1 (0.1)	0.0 (0.0)		1.000	1.000	1.000	
Control ($n=11$)		0.1 (0.1)	0.1 (0.1)	0.1 (0.0)		1.000	1.000	1.000	
	Intergroup (*p*-value)	.972	.987	.899					.466

Note: Statistically significant results are denoted in bold. *p*-Values are adjusted for gender, smoking habit, presence of systemic diseases and previous history of periodontitis.

Abbreviations: CRP, C-reactive protein; HDL-C, high-density lipoprotein; IL-10, interleukin 10; IL-6, interleukin 6; LDL-C, low-density lipoprotein; RBC, red blood cells; TC, total cholesterol; TNF-α, tumor necrosis factor alpha; WBC, white blood cells.

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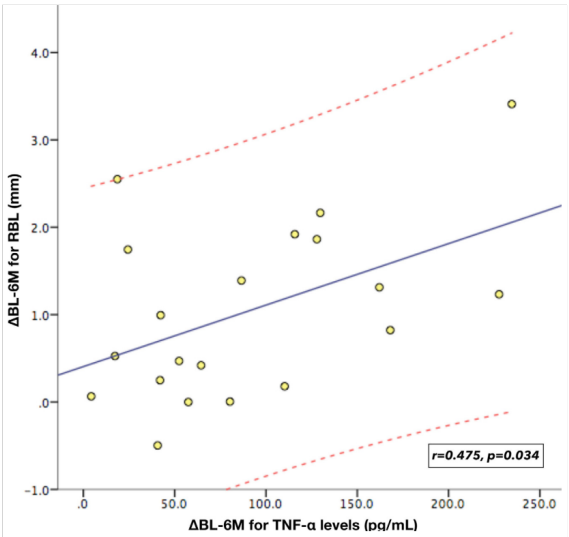


FIGURE 2 Scatter plot showing a positive correlation between radiographic bone fill (mm) and decrease in serum levels of TNF-α (pg/mL) after 6 months of non-surgical peri-implantitis treatment.

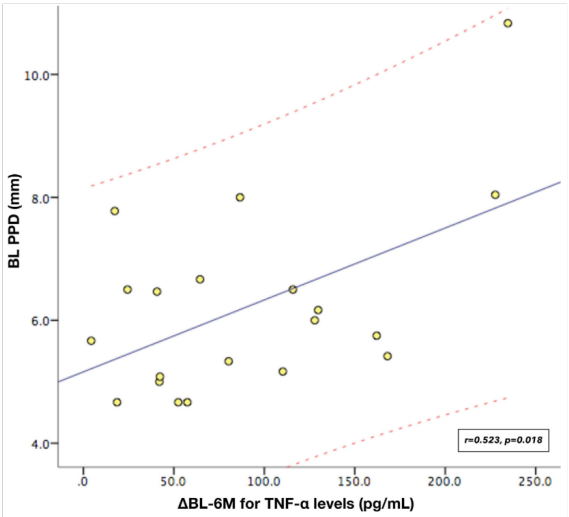


FIGURE 3 Scatter plot showing a positive correlation between baseline probing peri-implant pocket depth (mm) and decrease in serum levels of TNF-α (pg/mL) after 6 months of non-surgical peri-implantitis treatment.

Results from this secondary analysis RCT can shed some light on the systemic impact of peri-implantitis ("Peri-implant Medicine"), which is one of the top research priorities as stated recently by the International Academy of Periodontology at its first research meeting (Bartold et al., 2019). Carcuac and colleagues have demonstrated that the infiltrated connective tissue in sites with peri-implantitis is four to six times larger than in those affected by periodontitis (Carcuac et al., 2013). Based on this, it can be speculated that one implant affected with peri-implantitis equals to four to six teeth with periodontitis in terms of inflamed tissue. Moreover, this inflammatory infiltrate is not only larger but also reaches the surrounding bone, as a deep local infection and inflammation. Therefore, the systemic effect of peri-implantitis could be even greater than periodontitis. In this sense, recent evidence showed that peri-implantitis is associated with a state of low-grade systemic chronic inflammation (Blanco et al., 2021; Ustaoglu & Erdal, 2020). This chronic state of systemic inflammation is often characterized by immune response activation, disruption of physiological cellular functions as well as alteration in tissues and organs which in turn could increase the risk of onset or progression of some of the most disabling and fatal human non-communicable chronic diseases (Furman et al., 2019). For example, it has been shown that increased levels of peripheral CRP and IL-6 are strong predictors of future cardiovascular events (Ridker et al., 1997; Ridker, Hennekens, et al., 2000; Ridker, Rifai, et al., 2000). Moreover, results from a seminal multinational randomized controlled clinical trial including 10,000 participants with established cardiac disease have proved that the use of a monoclonal antibody that blocks the activity of IL-1β significantly reduced recurrent major adverse cardiovascular events by 15%–17% (Ridker et al., 2017) with the benefit directly related to the magnitude of reduction in downstream IL-6 and CRP (Ridker et al., 2018; Ridker, Libby, et al., 2018). Another example of the relationship between anti-inflammatory treatment and improvements in general health is the positive effect of TNF inhibition therapy on insulin resistance in patients with rheumatoid arthritis (Burska et al., 2015). In line with this evidence, in the present clinical trial, we observed a positive, although modest, correlation between reduction in the radiographic intrabony peri-implant defect depth and decrease in the circulating levels of TNF-α. The anti-inflammatory effect of NSPIT that has been observed in our study is confirmed by a modest reduction in neutrophil counts which are key players in the chronic inflammatory response and tissue damage (Rawat & Shrivastava, 2022). Results from our trial also found an increase in platelets after NSPIT. It is believed that platelets might assist in bacterial clearance by presenting bacteria to neutrophils for inducing phagocytic elimination (Margraf & Zarbock, 2019). Therefore, taking all this into account, identifying potential sources of chronic systemic inflammation such as peri-implantitis which is an infectious disease that can be treated with non-pharmacological interventions might be of interest in patients with a hyperinflammatory phenotype that are potentially at high risk of having other comorbidities or systemic complications such as cardiovascular diseases (Wang, Ou, et al., 2021; Wang, Sugai, et al., 2021). On the other hand, it has to be highlighted that in our study, we found that LDL-cholesterol levels were reduced in both groups after 6 months of therapy although only in the control group this decrease reached statistically significance. The effect of NSPIT on LDL reduction as seen in this study is similar in magnitude to that achieved by some of the most commonly used lipid-lowering drugs (Tokgözoğlu & Libby, 2022). Further trials

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with larger samples sizes should explore the potential impact of NSPIT on lipids.

The efficacy of non-surgical treatment of peri-implant lesions has been a matter of debate as in many cases surgical approaches are recommended to control peri-implant infections. In the last years, a number of RCTs have investigated the adjunctive effect of systemic antibiotics in NSPIT with contradictory results (Blanco et al., 2022; De Waal et al., 2021; Polymeri et al., 2022; Shibli et al., 2019; Stein et al., 2017). In this investigation, a clear improvement in both pocket depth and bleeding reduction as well as radiographic bone fill was observed at 6 months after therapy, irrespectively of the use of systemic metronidazole. This results differ with the ones obtained in the original RCT were the test group outperformed the control group (Blanco et al., 2022). Possible explanations to this discrepancy is the lower number of participants in each group as well as the shorter follow-up (6 vs. 12 months) compared to the clinical trial by Blanco et and co-workers (Blanco et al., 2022). In addition, baseline characteristics both at patient level such as gender, smoking habit, presence of systemic conditions and previous history of periodontitis as well as clinical and radiographic parameters, for example, initial PPD or RBL differed between groups and this might have an impact on the outcomes assessed in the present secondary analysis. In fact, initial PPD was correlated with reduction in levels of TNF-α at 6 months. The positive local effect of NSPIT was reflected at a systemic level, as serum concentrations of CRP and TNF-α were reduced over the study period. Furthermore, a correlation was found between radiographic bone gain and reduction in TNF-α levels. On the other hand, the potential adjunctive systemic benefit of systemic antimicrobials to the non-surgical treatment of periodontitis has been investigated in several reports (Cosgarea et al., 2020; Giannopoulou et al., 2016; López et al., 2012). In line with our results, an RCT carried out by López and co-workers observed that in patients with periodontitis and metabolic syndrome, levels of systemic inflammation (as measured by CRP) were reduced irrespective of whether systemic antibiotics were used in conjunction with scaling and root planning (López et al., 2012). Another RCT, did not find differences between the use or not of systemic antibiotics as adjuncts to non-surgical periodontal treatment in aggressive periodontitis patients when host-derived systemic biomarkers were assessed (Giannopoulou et al., 2016). On contrary, a secondary analysis of an RCT showed significant improvements in markers of systemic inflammation when amoxicillin and metronidazole were used together with subgingival debridement to treat periodontitis when compared to non-surgical therapy alone (Cosgarea et al., 2020). However, no differences in systemic outcomes were noted between short and longer antibiotic protocols (3 vs. 7 days) (Cosgarea et al., 2020).

This investigation has several limitations to be acknowledged by the authors. Firstly, this is a secondary analysis of a previously published RCT (Blanco et al., 2022) and therefore, no formal sample size was calculated a priori. Hence, future trials with proper sample sizes are needed to replicate our preliminary findings with longer follow-ups and perhaps including patients who also receive surgical treatment. Secondly, the population included in our analysis was heterogeneous since some of the participants were smokers or had concomitant comorbidities such as high blood pressure or hypercholesteremia and even baseline clinical and radiographic characteristics were not comparable between groups. All these factors might have an impact on the systemic inflammatory state. The next trials on this topic should include otherwise healthy subjects to rule out potential confounding effects. Lastly, although a standard assay was used to measure CRP instead of the high sensitivity test that detects mild changes in circulating CRP, we found significant changes from baseline to 6 months after treatment.

5 | CONCLUSION

In this secondary analysis of an RCT, a systemic anti-inflammatory impact with reduction in peripheral levels of CRP, IL-6 and TNF-α was observed after 6 months of non-surgical treatment of peri-implantitis regardless of the use of systemic metronidazole. Large-scale RCTs are needed to confirm these preliminary results. Mechanistic studies are also warranted to elucidate potential biological pathways underlying the systemic effects of peri-implantitis and its treatment.

AUTHOR CONTRIBUTIONS

Antonio Liñares: Conceptualization; funding acquisition; writing – original draft; methodology; writing – review and editing; supervision; resources; project administration. **Jose Dopico:** Investigation; writing – review and editing; methodology. **Carlota Blanco:** Investigation; writing – review and editing; methodology. **Alex Pico:** Investigation; methodology; writing – review and editing. **Tomás Sobrino:** Software; formal analysis; data curation; writing – review and editing; methodology. **Juan Blanco:** Conceptualization; funding acquisition; writing – review and editing; methodology; project administration; supervision; resources. **Yago Leira:** Conceptualization; writing – original draft; writing – review and editing; methodology; software; formal analysis; project administration; data curation; supervision; resources.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethics Committee of Santiago de Compostela/Lugo approved this study (ID: 2017/508).

CONSENT TO PARTICIPATE

Written informed consent to participate in the present study was obtained from all individual participants included in the study.

CONSENT FOR PUBLICATION

Written informed consent for publication was provided by all participants.

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SUPPORTING INFORMATION

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Discusión

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5. DISCUSIÓN

El objetivo principal del presente trabajo fue evaluar la eficacia clínica del tratamiento no quirúrgico de la periimplantitis con metronidazol sistémico como coadyuvante, y la posible repercusión de estas lesiones y su tratamiento en la inflamación sistémica.

La hipótesis general que se planteó fue que el utilizar metronidazol como coadyuvante al tratamiento no quirúrgico de la periimplantitis supondría un beneficio adicional en término clínicos, radiográficos y microbiológicos frente al tratamiento no quirúrgico sólo. Además, también se planteó la relación de estas lesiones con la inflamación sistémica y que su tratamiento podría influir en ella. Los resultados obtenidos de los estudios confirman la hipótesis planteada. En primer lugar, el uso complementario de metronidazol al tratamiento no quirúrgico da como resultado un beneficio clínico, radiológico y mejoría de los parámetros microbiológicos. Además, se ha mostrado la posible asociación de la periimplantitis con la inflamación sistémica. Por último, se informa de cómo el tratamiento de estas lesiones repercute de manera beneficiosa en algunos valores relacionados con la inflamación sistémica, pero sin tener una mejoría adicional en el caso de utilizar metronidazol sistémico.

- Eficacia del tratamiento no quirúrgico de la periimplantitis con metronidazol sistémico en la resolución de las lesiones

Al fin de analizar la eficacia del tratamiento no quirúrgico de la periimplantitis junto con metronidazol, se realizaron una serie de casos (estudio#1) y un ensayo clínico aleatorizado (estudio#2) .

Los estudios de series de casos (estudio#1) son fundamentales para generar nuevas hipótesis de investigación, y se requieren ensayos clínicos controlados aleatorizados para probar la hipótesis nula de que el tratamiento no quirúrgico de la periimplantitis con antibióticos sistémicos, no muestra diferencias significativas en los resultados clínicos (estudio#2).

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El estudio de serie de casos (estudio#1) muestra los resultados clínicos y radiográficos exitosos tras el tratamiento no quirúrgico de periimplantitis con metronidazol sistémico como tratamiento complementario. Se muestra una reducción de la PS de hasta 4,6 mm y una ganancia ósea radiográfica de 2,6 mm después de 54 meses de seguimiento. Estos resultados beneficiosos se han observado en series de casos previos a esta publicación con el uso de antibióticos sistémicos (Estefanía-Fresco et al., 2019; Nart et al., 2020). Mombelli y Lang mostraron una reducción significativa en la profundidad de sondaje y en los parámetros microbianos tras el tratamiento no quirúrgico combinado con 1,000 mg de ornidazol durante 10 días consecutivos y, tras 12 meses de tratamiento, la profundidad de sondaje se redujo de 5,9 mm a 3,4 mm, y los bacilos gramnegativos anaeróbicos se redujeron del 40% al 16%, en algunos casos, se observó incluso ganancia ósea radiográfica (Mombelli & Lang, 1992). Otras series de casos mostraron una reducción de la profundidad de sondaje de 2.5 mm y un relleno óseo radiográfico de 1,6 mm después del tratamiento no quirúrgico de la periimplantitis con diferentes antibióticos sistémicos según la susceptibilidad bacteriana (Khoury & Buchmann, 2001).

Hasta la fecha, este es el primer ensayo clínico (estudio#2) que evalúa la eficacia del tratamiento no quirúrgico de la periimplantitis con el uso complementario de metronidazol. Los resultados muestran que el uso complementario de metronidazol tiene mejoras significativas a nivel clínico, radiográfico y microbiológico tras un seguimiento de un año. A pesar de la escasez de ensayos clínicos aleatorizados que investiguen el efecto de los antibióticos sistémicos como complemento en el tratamiento de la periimplantitis, los resultados de este estudio están en línea con los datos publicados. La reducción de la profundidad de sondaje a los 12 meses fue de 2,53 mm en el grupo test y de 1,02 mm en el grupo control. Shibli y cols. (Shibli et al., 2019) utilizaron metronidazol y amoxicilina como tratamiento complementario y encontraron una reducción de PS de 3,1 mm en el grupo con antibióticos en comparación con 1.8 mm en el grupo control a los 12 meses. En contraste, Stein y cols.(Stein et al., 2017) no encontraron diferencias en la reducción de PS entre los grupos (1,4 mm frente a 1,02 mm), aunque en las bolsas más profunda, el análisis reveló cambios más pronunciados en comparación con las bolsas poco profundas. Tampoco se encontramos diferencias en el estudio de Almohareb y cols. (Almohareb et al., 2020) donde la discrepancia entre el grupo test y control fue de 0,1mm, aunque también añadieron una variable a tener en cuenta que fue la aplicación de terapia fotodinámica, que podría influir en los resultados. Además, esta discrepancia puede ser explicada por el hecho de que la profundidad del sondaje al inicio era menor, pudiendo describirse estas lesiones como periimplantitis iniciales, frente a las de esta investigación que pueden ser consideradas periimplantitis moderadas-avanzadas. Otro factor a tener en cuenta y que puede ser la clave en las diferencias en los resultados es que en el desbridamiento realizamos un curetaje de la bolsa, a diferencia del resto de ensayos

clínicos realizados hasta el momento donde sólo hacen desbridamiento de la superficie del implante. El enfoque de tratamiento de la periimplantitis mediante curetaje se centra en la eliminación del epitelio de la bolsa periimplantaria que está ulcerado, sin necesidad de levantar un colgajo. Tras realizar un legrado exhaustivo de la mucosa inflamada, se procede a descontaminar tanto la superficie del implante como las áreas óseas expuestas. Finalmente, se deja la mucosa intacta en su posición original, permitiendo que se cicatrice de forma natural alrededor del implante. Este concepto de curetaje de la bolsa o cirugía sin colgajo fue el método que realizamos ya en el estudio de serie de casos (estudio#1).

Un estudio publicado recientemente (De Waal et al., 2021) investigó el efecto en los parámetros clínicos y microbiológicos de la clorhexidina o la combinación de amoxicilina/metronidazol con un seguimiento de 3 meses. A diferencia de la presente investigación, aunque encontraron diferencias en los parámetros clínicos a favor del uso de antibióticos, estas diferencias no alcanzaron significancia estadística. La inclusión de casos iniciales de periimplantitis con PS superficiales (5,82 mm en el grupo test y 5,63 mm en el grupo control) y un seguimiento corto pueden explicar las diferencias con el presente estudio. Además, los cálculos del tamaño de la muestra en el estudio de De Waal y colaboradores se realizaron utilizando las diferencias en el índice de sangrado de un estudio anterior sobre el uso complementario de amoxicilina y metronidazol en pacientes con periodontitis (Winkel et al., 2001). Esto puede no ser completamente aplicable a un estudio sobre pacientes con periimplantitis, y pueden existir problemas relacionados con el poder estadístico.

A nivel radiográfico, en el ensayo clínico (estudio#2) se observó un aumento radiográfico promedio de 2,33 mm en el grupo test y de 1,13 mm en el grupo control a los 12 meses. Los resultados en el grupo test son comparables a los resultados obtenidos en la serie de casos (estudio#1), donde se obtuvo una ganancia ósea radiográfica media de 2,6mm. La cantidad de ganancia ósea radiográfica excede lo mostrado en estudios publicados previamente, donde se observó un promedio de 0,5 mm (Shibli et al., 2019; Stein et al., 2017). Esto puede explicarse por el tipo de implantes tratados por Shibli y colaboradores (maquinados) y la severidad moderada de la enfermedad en el estudio de Stein y colaboradores. Ya que se ha demostrado que la terapia quirúrgica de la periimplantitis junto con antibióticos sistémicos es más exitosa en superficies moderadamente rugosas en comparación con superficies maquinadas (Carcuac et al., 2016). Las lesiones de periimplantitis en implantes de superficie rugosa pueden ser más agresivas y extenderse más profundo en el hueso que aquellas presentes en implantes con superficies maquinadas (Carcuac et al., 2013). Esto podría explicar el mayor impacto de los antibióticos sistémicos como coadyuvante al tratar lesiones de periimplantitis en implantes de superficie rugosa.

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Los beneficios adicionales del antibiótico en la ganancia ósea radiográfica pueden ser comparables a los obtenidos con la terapia quirúrgica reconstructiva (1,9 mm) (Tomasi et al., 2019). La justificación de estas mejoras podría estar relacionada con la reducción o eliminación de las bacterias patógenas con metronidazol en la presente investigación y la estabilidad de la formación del coágulo tras el curetaje de la bolsa. Se ha demostrado que la configuración del defecto en el tratamiento quirúrgico de la periimplantitis juega un papel importante en los resultados clínicos y radiográficos (Schwarz et al., 2010). Aunque la configuración del defecto no se evaluó en el estudio, no se puede descartar la influencia potencial de la inclusión de defectos más favorables en comparación con estudios publicados previamente.

La terapia no quirúrgica redujo significativamente el sangrado al sondaje, en una magnitud similar a la observada en un ensayo clínico publicado previamente (Stein et al., 2017). La cantidad de recesión postratamiento estuvo en línea con estudios existentes (0,5 mm) (Faggion et al., 2014).

La razón detrás de por qué se logran mejorías clínicas y radiográficas en estos estudios sigue sin estar clara. Es importante señalar que las lesiones de periimplantitis (particularmente las superficies rugosas) alcanzan el hueso y son mucho más agresivas que la periodontitis (Carcuac et al., 2013). Además, la histología de las lesiones de periimplantitis ha mostrado signos claros de ulceración del epitelio (Berglundh et al., 2004). Se puede plantear la hipótesis de que la invasión bacteriana del tejido conectivo subepitelial puede estar presente en las lesiones de periimplantitis. Este concepto de invasión bacteriana fue descrito por primera vez por Listgarten (Listgarten, 1965) con biopsias humanas de lesiones de periodontitis necrosante aguda. Más tarde, se demostró la invasión bacteriana en lesiones de periodontitis crónica avanzada y agresivas localizadas (Christersson et al., 1985; Saglie et al., 1982). Por lo tanto, el desbridamiento mecánico sólo, puede dejar una colonia importante de bacterias dentro del tejido conectivo. Esta es también la razón de realizar un curetaje del surco periimplantario. Además, se ha demostrado que los antibióticos sistémicos mejoran los resultados clínicos en formas agresivas de periodontitis (Guerrero et al., 2005; Haffajee et al., 2003), y también muestran mejores resultados en la resolución de la periimplantitis en la terapia quirúrgica (56% versus. 29,2%) (Carcuac et al., 2016), (46,7% versus. 25%) (Hallström et al., 2017). La difusión de antibióticos dentro del tejido conectivo subepitelial puede lograrse después de la administración sistémica. En estos estudios, se prescribió 500 mg de metronidazol tres veces al día durante 7 días. La justificación del uso de metronidazol se basa en la alta prevalencia reportada de patógenos anaeróbicos en lesiones de periimplantitis (Charalampakis & Belibasakis, 2015) y las tasas relativamente bajas de resistencia bacteriana (Soares et al., 2012). Es importante señalar que el metronidazol no debe

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emplearse en pacientes anticoagulados con fármacos dicumarínicos como el acenocumarol (Sintrom), ya que pueden aumentar considerablemente el índice INR. Además, por el posible efecto antabus entre el metronidazol y el alcohol se recomienda el no consumo de alcohol mientras el paciente esté tomando metronidazol y hasta las 24 horas de finalizar la última toma. En estos casos se debe valorar el uso de otros antibióticos complementarios a la terapia no quirúrgica.

Una pregunta crítica tras la finalización de la terapia no quirúrgica está relacionada con las bolsas residuales y la necesidad de un tratamiento adicional más allá de la terapia de mantenimiento. La presencia de bolsas residuales ≥5 mm, sangrado al sondaje y pérdida ósea en la reevaluación puede ser útil para predecir una progresión adicional de la enfermedad (Carcuac et al., 2020). El fracaso en lograr este criterio clínico de éxito puede utilizarse como justificación para proporcionar tratamiento adicional. Los estudios publicados previamente y la serie de casos (estudio#1) muestran una tasa de éxito tras la terapia no quirúrgica de alrededor del 50% (Estefanía-Fresco et al., 2019; Nart et al., 2020; Stein et al., 2017). Los resultados del ensayo clínico están en línea con estos datos: se observa que el 57.10% de los implantes del grupo test cumplieron con los criterios de éxito frente al 23.5% en el grupo control después de un año de seguimiento. En contraste, también se han mostrado tasas de éxito similares tras la terapia no quirúrgica sola (55%) en comparación con los antibióticos complementarios (65%) (Shibli et al., 2019). Esto podría explicarse por el hecho de en este estudio de Shibli y cols. los sujetos del grupo control tenían PS menos profundas en comparación con el presente estudio (estudio#2). Estos datos de la presente investigación nos indican que más de la mitad de nuestros pacientes tratados en esta primera fase de terapia no quirúrgica, siguiendo este protocolo, alcanza la resolución de la enfermedad y por lo tanto entran en una fase de mantenimientos. Según la guía de práctica clínica la reevaluación y por tanto la toma de decisión de si es necesario realizar una terapia quirúrgica se debe realizar a las 6-12 semanas tras el tratamiento (Herrera et al., 2023), si tenemos en cuenta los resultados del ensayo clínico (estudio#2) para la toma de decisión de la intervención quirúrgica debería esperarse más tiempo, ya que los resultados de las variables clínicas aunque alcanzan mejoría a los 3 meses sigue habiendo cambios incluso hasta los 6 meses, y por otra parte los cambios en los niveles óseos radiográficos no se observan hasta los 6 meses del tratamiento, teniendo en cuenta esto podrían sobreestimarse la necesidad del tratamiento quirúrgico si solo se esperan a las 6-12 semanas.

Teniendo en cuenta los resultados de esta investigación, se podrían implementar modificaciones en los protocolos del tratamiento de la periimplantitis. Recientemente, varias revisiones sistemáticas han actualizado la información sobre el tratamiento no quirúrgico de la periimplantitis, en el marco del desarrollo de la guía de práctica clínica de

la EFP para la prevención y tratamiento de las enfermedades periimplantarias (Herrera et al., 2023). Dichas revisiones evaluaron la eficacia de la instrumentación mecánica (Cosgarea et al., 2023), ya sea combinada o no con métodos de descontaminación química (de Waal et al., 2023), y antimicrobianos (Liñares et al., 2023). En estas revisiones, se observó que, el uso de aeropulidores produjo una reducción media estimada de la profundidad de sondaje inferior a 1,3 mm, y la reducción del sangrado al sondaje varió entre un 0,7% y un 70%, dependiendo del estudio (Cosgarea et al., 2023). De este modo, se concluyó que las terapias coadyuvantes siguen sin aportan una mejoría significativa en los resultados clínicos en comparación con el desbridamiento mecánico convencional (curetas / ultrasonidos). Asimismo, se evaluó el uso de diferentes tipos de láser, como el de erbio (Er), erbio-cromo (Er,Cr) y el láser de diodo. Nuevamente, no se hallaron diferencias estadísticamente significativas en las variables evaluadas, obteniéndose una reducción media en la PS de entre 0,8 y 1,5 mm y una disminución del sangrado al sondaje entre el 11% y el 48% (Cosgarea et al., 2023). Además, evaluaron la eficacia de uso complementario de antibióticos locales (chips de CHX, microesferas de minociclina, gel de metronidazol y amoxicilina), y observaron alguna mejoría clínica en términos de reducción de la PS y sangrado al sondaje, aunque desde un punto de vista clínico son mejorías leves (≈0,5 mm mayor reducción de la PS y ≈10 % mayor reducción del BoP) (Liñares et al., 2023). Por último, en cuanto al uso de los antibióticos sistémicos (Liñares et al., 2023) e incluyendo nuestra investigación en su análisis (estudio#2) concluyen que, a pesar de los beneficios adicionales del uso de antibióticos sistémicos como complemento, debido al aumento de la resistencia a los antibióticos en los últimos años (Soares et al., 2012), y por los posibles daños en la repercusión individual en la disbiosis del paciente no lo recomiendan como tratamiento rutinario y especifican que su uso debe indicarse de manera individualizada. Debe tenerse en cuenta que también se observaron mejorías significativas en los parámetros clínicos y microbiológicos en el grupo control, y aunque una proporción significativamente menor de casos alcanzó el criterio de éxito clínico, los antibióticos complementarios pueden no estar indicados en las etapas iniciales de la enfermedad, ya que se puede lograr el éxito clínico solo con terapia no quirúrgica, o en casos avanzados donde puede estar indicada la terapia quirúrgica adicional independientemente del uso de antibióticos complementarios y también debe evitarse en los cuidados paliativos de implantes perdidos. Por lo que, sólo lo recomiendan a los casos con periimplantitis moderadas-severas (p. ej., bolsas profundas ≥7 mm, supuración extensa) y/o con implantes múltiples y/o estratégicamente afectados que puedan responder bien y mantenerse con el tiempo (el protocolo sugerido en estos casos es el de nuestra investigación: metronidazol 500 mg/8 h/7 días). Aunque en la guía de práctica clínica lo pongan como un protocolo de actuación de primeras no recomendado, debemos tener en cuenta que el antibiótico que utilizamos en este protocolo, el nivel que tiene de resistencias antibióticas como

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mencionamos anteriormente es muy bajo y específico para determinados tratamientos por lo que su uso no es muy recurrente en medicina.

Esta investigación tiene algunas limitaciones, la falta de información detallada sobre las características de la superficie de los implantes y un análisis microbiológico más exhaustivo podría haber ayudado a caracterizar mucho mejor los resultados. Por otro lado un seguimiento más largo nos aportaría saber si estos resultados se mantienen a largo plazo o si hay recidiva de las lesiones.

- Evaluación de la posible relación de la periimplantitis con la inflamación sistémica

Al fin de analizar la posible repercusión de la periimplantitis en la inflamación sistémica se llevó a cabo un estudio transversal (estudio #3).

Hasta la fecha, este es el primer estudio que evalúa el perfil inflamatorio de pacientes con periimplantitis. Los hallazgos de este estudio piloto mostraron un estado inflamatorio sistémico exacerbado, caracterizado por niveles elevados de leucocitos (WBC), así como la presencia de dislipidemia en pacientes con periimplantitis en comparación con individuos con implantes sanos. Se encontraron correlaciones lineales moderadas entre la profundidad de sondaje y el sangrado con marcadores de inflamación (WBC e IL-10) y lípidos sanguíneos (colesterol total y colesterol LDL).

En la periimplantitis, la presencia de patógenos subgingivales provoca una respuesta inflamatoria local, que se caracteriza por mayores proporciones de leucocitos polimorfonucleares y macrófagos. Además, esta respuesta inflamatoria se amplifica debido a la producción de citocinas y prostaglandinas proinflamatorias. La liberación de estas sustancias al torrente sanguíneo estimula un mayor reclutamiento de mediadores proinflamatorios y leucocitos en el sitio. Cabe destacar que se ha demostrado que esta respuesta inflamatoria local es más pronunciada en los tejidos periimplantarios que en los periodontales (Berglundh et al., 2011). El epitelio gingival ulcerado permite que estos mediadores inflamatorios producidos localmente entren al torrente sanguíneo e induzcan una reacción de fase aguda en el hígado, contribuyendo así a la carga inflamatoria sistémica general (Hajishengallis, 2015). Si tenemos en cuenta las similitudes fisiopatológicas de ambas enfermedades, un estado inflamatorio periimplantario persistente también podría tener un impacto en la inflamación sistémica. En el presente estudio, los pacientes con periimplantitis presentaron un aumento de los leucocitos (WBC), lo que refleja un posible estímulo inflamatorio sistémico crónico, que podría haber sido causado por la persistencia de la enfermedad periimplantaria, como se ha demostrado recientemente en la periodontitis (Botelho et al., 2021). También se encontró una correlación lineal entre

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los parámetros clínicos inflamatorios periimplantarios y los niveles de WBC. De manera similar, estudios recientes en animales han mostrado una respuesta inflamatoria sistémica aumentada tras inducir periimplantitis experimental con ligaduras, caracterizada por niveles elevados de proteínas totales, albúmina y WBC, que volvieron a la normalidad tras el tratamiento quirúrgico periimplantario (Chaushu, Tal, Sculean, Fernández-Tomé, et al., 2020). El estado inflamatorio sistémico de los pacientes con periimplantitis se confirmó mediante niveles circulantes más bajos de IL-10, una citoquina con importantes propiedades antiinflamatorias (Moore et al., 2001). Se ha sugerido que los niveles disminuidos de IL-10 pueden favorecer un entorno más inflamatorio, ya que IL-10 tiene potentes propiedades desactivadoras en macrófagos y células T, lo que puede actuar como regulador negativo de las respuestas inmunes mediadas por células, como las que posiblemente se observan en la periimplantitis.

Otro hallazgo relevante de este estudio es que los pacientes con periimplantitis exhibieron dislipidemia, caracterizada por niveles más altos de colesterol LDL en sangre. Esta observación confirma resultados previos que informan de niveles más altos de colesterol LDL y colesterol total entre pacientes con periodontitis en comparación con controles sanos (Cutler et al., 1999; Nibali et al., 2007). En las últimas décadas, se ha documentado ampliamente una relación entre las infecciones y el metabolismo lipídico. Ahora se cree que las enfermedades infecciosas crónicas tienen un impacto en los niveles de lípidos plasmáticos (Alvarez & Ramos, 1986; Iacopino & Cutler, 2000). Se piensa que esta dislipidemia es parte de la respuesta del huésped para disminuir la toxicidad de los agentes microbiológicos dañinos (Khovidhunkit et al., 2004). En la presente investigación se encontró una asociación entre la periimplantitis y niveles anormales de lípidos, que pueden estar mediada por la activación constante del proceso inflamatorio determinado por la presencia de patógenos periodontales en la bolsa periodontal.

Según los resultados actuales, podría especularse que la periimplantitis podría estar asociada con la enfermedad aterosclerótica. La respuesta de fase aguda durante la infección/inflamación periimplantaria protege al huésped de infecciones adicionales. Los cambios en las proteínas de fase aguda (por ejemplo, la proteína C reactiva [PCR]) neutralizan a los microorganismos invasores como las bacterias periodontales, minimizan la extensión del daño tisular, participan en la respuesta inmune local y la regeneración tisular, y reponen las proteínas utilizadas en el proceso inflamatorio (Khovidhunkit et al., 2004; Shapiro & Fazio, 2016). Estos cambios, si se mantienen durante un período prolongado, pueden tener consecuencias perjudiciales para el huésped, como el desarrollo de una inflamación sistémica crónica de grado bajo. En este sentido, los cambios en la síntesis de reactantes de fase aguda están mediados por citoquinas producidas en respuesta a una variedad de estímulos en múltiples tipos celulares, incluidos macrófagos, monocitos,

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linfocitos y células endoteliales (Libby et al., 2019; Raggi et al., 2018). Las citoquinas responsables de coordinar las respuestas inmunes e inflamatorias, como las interleucinas (IL) o el factor de necrosis tumoral alfa (TNF-α), pueden inducir alteraciones en el metabolismo de lípidos y lipoproteínas que contribuyen a la aterogénesis (Khovidhunkit et al., 2004).

Se trata de un estudio piloto, por lo que los resultados son preliminares y generadores de hipótesis. Sin embargo, se realizó un cálculo de potencia post-hoc, que mostró que nuestro estudio tenía una potencia del 90% para detectar diferencias clínicamente significativas en las concentraciones de WBC entre los pacientes con periimplantitis y los controles.

Un factor importante que podría haber influido en los resultados fue la historia previa de periodontitis, ya que la mayoría de los casos de periimplantitis presentaban enfermedad periodontal tratada con éxito. Incluso después de ajustar este factor de confusión, la significancia se mantuvo para los niveles de WBC, IL-10, colesterol y LDL. Además, cuando se realizó la evaluación clínica periimplantaria y se recogieron las muestras de sangre, ninguno de los pacientes presentaba signos activos de periodontitis, lo que podría no haber tenido un impacto fuerte a nivel sistémico. Otra limitación importante es que los biomarcadores séricos comúnmente utilizados que reflejan procesos proinflamatorios sistémicos, como la hs-PCR o la IL-6 no se midieron en esta investigación. Aunque, los leucocitos (WBC) se han utilizado ampliamente en la literatura como indicación de inflamación sistémica (Libby et al., 2016). También incluimos una citoquina bien conocida con acción antiinflamatoria (IL-10) (Moore et al., 2001). Nuestros resultados mostraron no sólo que las concentraciones de glóbulos blancos estaban elevadas en pacientes con periimplantitis, sino también que los niveles séricos de IL-10 se redujeron en comparación con los sujetos con implantes sanos, apoyando así nuestra hipótesis inicial.

Se necesitan más estudios para confirmar estos resultados preliminares utilizando grandes cohortes poblacionales. También se necesitan estudios experimentales para investigar los posibles mecanismos biológicos detrás de este vínculo.

Esta investigación tiene varias limitaciones, la presencia de historia de periodontitis puede influir en los resultados obtenidos, y la falta de análisis de biomarcadores séricos que se utilizan como referencia para la inflamación sistémica lo que limite no sólo nuestro resultados sino su posible comparación con los resultados de otros estudios.

- Eficacia del tratamiento no quirúrgico de la periimplantitis con metronidazol sistémico en la inflamación sistémica

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Se llevó a cabo un subanálisis del ensayo clínico (estudio #4) para analizar la posible repercusión del tratamiento no quirúrgico de la periimplantitis en la inflamación sistémica.

Este estudio representa la primera investigación en humanos que evalúa los efectos sistémicos del tratamiento no quirúrgico de la periimplantitis (NSPIT). Este análisis secundario del ensayo clínico controlado aleatorizado (estudio #2) sugiere que el NSPIT reduce significativamente la inflamación sistémica, evidenciada por la disminución de los niveles circulantes de proteína C reactiva (CRP), interleucina-6 (IL-6) y factor de necrosis tumoral alfa (TNF-α) en un seguimiento de 6 meses. Estos hallazgos concuerdan con los resultados del estudio transversal (estudio#3) y otra investigación previa que indican que la periimplantitis podría estar relacionada con un estado inflamatorio sistémico (Ustaoğlu & Erdal, 2020). En estos estudios en humanos, los pacientes con periimplantitis mostraron mayores concentraciones de glóbulos blancos (WBCs) y TNF-α en comparación con aquellos sujetos con implantes sanos. Estos hallazgos concuerdan con los experimentos en animales, donde tras la inducción de la periimplantitis mediante la colocación de ligaduras, se observó un aumento en algunos parámetros inflamatorios, como proteína total, albúmina y WBC (Chaushu, Tal, et al., 2020a; Chaushu, Tal, Sculean, Fernández-Tomé, et al., 2020). En el presente estudio, se observa que, después de 6 meses de NSPIT, los niveles de mediadores inflamatorios bien caracterizados (CRP, IL-6, TNF-α) se redujeron de manera estadísticamente significativa en comparación con los valores iniciales. En línea con estos resultados, estudios previos en animales demostraron que el tratamiento de la periimplantitis mediante un enfoque quirúrgico que consistía en desbridamiento a colgajo abierto fue capaz de revertir las concentraciones de biomarcadores inflamatorios a niveles iniciales (Chaushu, Tal, et al., 2020a; Chaushu, Tal, Sculean, Fernández-Tomé, et al., 2020). Al igual que los hallazgos observados en el presente ensayo clínico, muchas investigaciones apoyan una reducción a medio plazo de la inflamación sistémica (medida por CRP, IL-6, TNF-α y otros marcadores inflamatorios) tras la terapia periodontal no quirúrgica en pacientes con y sin comorbilidades (D'Aiuto et al., 2018; Iwamoto et al., 2003; Kamil et al., 2011; Marcaccini et al., 2009).

Los resultados de este análisis secundario del ensayo clínico aleatorizado (RCT) pueden arrojar luz sobre el impacto sistémico de la periimplantitis, que es una de las principales prioridades de investigación, según lo declarado recientemente por la Academia Internacional de Periodoncia en su primera reunión de investigación (Bartold et al., 2019). Carcuac y cols. (Carcuac et al., 2013) han demostrado que el tejido conectivo infiltrado en las periimplantitis es de cuatro a seis veces mayor que en los afectados por periodontitis. Basándonos en esto, se puede especular que un implante afectado por periimplantitis equivale a cuatro o seis dientes con periodontitis en términos de tejido inflamado. Además, este infiltrado inflamatorio no solo es mayor, sino que también

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alcanza el hueso circundante, lo que constituye una infección e inflamación local profunda. Por lo tanto, el efecto sistémico de la periimplantitis podría ser incluso mayor que el de la periodontitis. En este sentido, la evidencia reciente del estudio transversal (estudio #3) muestra que la periimplantitis está asociada con un estado de inflamación crónica sistémica de grado bajo, como también lo mostraron en otro estudio (Ustaoğlu & Erdal, 2020).

Este estado crónico de inflamación sistémica suele caracterizarse por la activación de la respuesta inmunitaria, la alteración de las funciones celulares fisiológicas, así como la modificación de tejidos y órganos, lo que a su vez podría aumentar el riesgo de aparición o progresión de algunas de las enfermedades crónicas no transmisibles más discapacitantes y mortales en humanos (Furman et al., 2019). Por ejemplo, se ha demostrado que niveles elevados de CRP periférica e IL-6 son predictores fuertes de futuros eventos cardiovasculares (Ridker et al., 1997; Ridker et al., 2000). Además, los resultados de un ensayo clínico multicéntrico aleatorizado, que incluyó a 10,000 participantes con enfermedad cardíaca establecida, mostró que el uso de un anticuerpo monoclonal que bloquea la actividad de IL-1β redujo significativamente los eventos cardiovasculares adversos recurrentes en un 15% - 17% (Ridker et al., 2017), con un beneficio directamente relacionado con la magnitud de la reducción de IL-6 y CRP (Ridker, Libby, et al., 2018; Ridker, MacFadyen, et al., 2018). Otro ejemplo de la relación entre el tratamiento antiinflamatorio y las mejoras en la salud general es el efecto positivo de la terapia de inhibición de TNF en la resistencia a la insulina en pacientes con artritis reumatoide (Burska et al., 2015).

En línea con esta evidencia, en el presente ensayo clínico, observamos una correlación positiva, aunque modesta, entre la reducción de la profundidad del defecto óseo radiográfico y la disminución en los niveles circulantes de TNF-α. El efecto antiinflamatorio del NSPIT que se ha observado en este estudio se confirma por una modesta reducción en el recuento de neutrófilos, que son clave en la respuesta inflamatoria crónica y el daño tisular (Rawat & Shrivastava, 2022). También se encontró un aumento en las plaquetas después del NSPIT. Se cree que las plaquetas pueden ayudar en la eliminación de bacterias presentándolas a los neutrófilos para inducir su eliminación fagocítica (Margraf & Zarbock, 2019).

Por lo tanto, teniendo todo esto en cuenta, identificar fuentes potenciales de inflamación sistémica crónica, como la periimplantitis, que es una enfermedad infecciosa que puede tratarse con intervenciones no farmacológicas, podría ser de interés en pacientes con un fenotipo hiperinflamatorio que potencialmente están en alto riesgo de tener otras comorbilidades o complicaciones sistémicas como enfermedades cardiovasculares (Wang, Ou, et al., 2022; Wang, Sugai, et al., 2022).

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Por otro lado, es importante destacar que se encontró que los niveles de colesterol LDL se redujeron en ambos grupos después de 6 meses del tratamiento, aunque solo en el grupo control esta disminución fue estadísticamente significativa. El efecto del NSPIT sobre la reducción del LDL, como se observó en este estudio, es similar en magnitud al logrado por algunos de los fármacos reductores de lípidos más utilizados (Tokgözoğlu & Libby, 2022).

Las características basales tanto a nivel del paciente (género, tabaco, enfermedades sistémicas, historia de periodontitis), así como los parámetros clínicos y radiográficos difirieron entre los grupos y esto podría tener un impacto en los resultados evaluados. De hecho, la PS inicial se correlacionó con la reducción de los niveles de TNF-α a los 6 meses. El efecto local positivo de NSPIT se reflejó a nivel sistémico, ya que las concentraciones séricas de PCR y TNF-α se redujeron durante el período de estudio. Además, se encontró una correlación entre la ganancia ósea radiográfica y la reducción de los niveles de TNF-α. Por otra parte, el potencial beneficio sistémico complementario de los antimicrobianos sistémicos al tratamiento no quirúrgico de la periodontitis ha sido investigado en varios informes (Cosgarea et al., 2020; Giannopoulou et al., 2016; López et al., 2012). En consonancia con estos resultados, López y cols.(López et al., 2012) mostraron que, en pacientes con periodontitis y síndrome metabólico, los niveles de inflamación sistémica (medidos por PCR) se redujeron independientemente de si se utilizaron antibióticos sistémicos junto con el raspado y alisado radicular. Otro estudio no encontró diferencias entre el uso o no de antibióticos sistémicos como complemento del tratamiento periodontal no quirúrgico en pacientes con periodontitis agresiva cuando se evaluaron biomarcadores sistémicos derivados del huésped (Giannopoulou et al., 2016). Por el contrario, un análisis secundario mostró mejoras significativas en los marcadores de inflamación sistémica cuando se utilizaron amoxicilina y metronidazol junto con desbridamiento subgingival para tratar la periodontitis en comparación con la terapia no quirúrgica sola (Cosgarea et al., 2020). Sin embargo, no se observaron diferencias en los resultados sistémicos entre protocolos de antibióticos cortos y más largos (3 frente a 7 días).

Esta investigación tiene varias limitaciones. En primer lugar, se trata de un análisis secundario del ensayo clínico (estudio#2) y, por lo tanto, no se calculó a priori un tamaño muestral. Por lo tanto, se necesitan ensayos futuros con tamaños de muestra adecuados para replicar estos hallazgos preliminares con seguimientos más prolongados y quizás incluyendo pacientes que también reciben tratamiento quirúrgico. En segundo lugar, la población incluida en el análisis fue heterogénea, ya que algunos de los participantes eran fumadores o tenían comorbilidades concomitantes como presión arterial alta o hipercolesterolemia e incluso las características clínicas y radiográficas basales no eran

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comparables entre los grupos. Todos estos factores podrían tener un impacto en el estado inflamatorio sistémico. Los próximos ensayos sobre este tema deberían incluir sujetos por lo demás sanos para descartar posibles efectos de confusión. Por último, se utilizó una medida estándar para medir la PCR, en lugar de la prueba de alta sensibilidad que detecta cambios leves en la PCR circulante, aunque igualmente encontramos cambios significativos desde el inicio hasta 6 meses después del tratamiento.

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Conclusiones

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6. CONCLUSIONES

- El uso coadyuvante de metronidazol sistémico en el tratamiento no quirúrgico de la periimplantitis ha dado como resultado mejoras adicionales significativas en los parámetros clínicos, radiográficos y microbiológicos después de 12 meses de seguimiento en comparación con el grupo control con placebo.

- En los pacientes diagnosticados con periimplantitis se observa la presencia de una inflamación sistémica de bajo grado (niveles elevados de glóbulos blancos circulantes) acompañado de dislipidemia (niveles elevados de colesterol y LDL en sangre).

- El tratamiento no quirúrgico de la periimplantitis independientemente del uso de metronidazol sistémico tiene un impacto antiinflamatorio sistémico con reducción de los niveles periféricos de PCR, IL-6 y TNF-α después de 6 meses de seguimiento.

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7

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8

Anexos

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8. ANEXOS

8.1. ÍNDICES DE CALIDAD DE LAS PUBLICACIONES.

8.1.1. Adjunctive systemic metronidazole to nonsurgical therapy of peri-implantitis with intrabony defects: a retrospective case series study.

Liñares A (1), Pico A (1), Blanco C (1), Blanco J (1).

1 Unidad de Periodoncia, Facultad de Odontología, Universidad de Santiago de Compostela y Grupo de Investigación en Odontología Médico-Quirúrgica, Instituto de Investigaciones Sanitarias de Santiago de Compostela, Santiago de Compostela, España.

Int J Oral Maxillofac Implants. 2019 sep/oct;34(5):1237-1245.

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8.1.2. Adjunctive benefits of systemic metronidazole on non-surgical treatment of peri-implantitis. A randomized placebo-controlled clinical trial.

Blanco C (1,2), Pico A (1,2), Dopico J (1,2), Gándara P (2,3), Blanco J (1,2), Liñares A (1,2).

1 Unidad de Periodoncia, Facultad de Odontología, Universidad de Santiago de Compostela y Grupo de Investigación en Odontología Médico-Quirúrgica, Instituto de Investigaciones Sanitarias de Santiago de Compostela, Santiago de Compostela, España.

2 Grupo de Investigación en Odontología Médico-Quirúrgica, Instituto de Investigaciones en Salud de Santiago de Compostela, Santiago de Compostela, España.

3 Unidad de Cirugía Bucal, Facultad de Odontología, Universidad de Santiago de Compostela,Santiago de Compostela, España.

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8.1.3. Peri-implantitis, systemic inflammation, and dyslipidemia: a cross-sectional biochemical study.

Blanco C (1), Liñares A, (1), Dopico J(1), Pico A(1), Sobrino T(2), Leira Y(1,2,3), Blanco J(1).

1 Unidad de Periodoncia, Facultad de Odontología, Universidad de Santiago de Compostela y Grupo de Investigación en Odontología Médico-Quirúrgica, Instituto de Investigaciones Sanitarias de Santiago de Compostela, Santiago de Compostela, España.

2 Laboratorio de Investigación en Neurociencias Clínicas, Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago de Compostela, España.

3 Unidad de Periodoncia, UCL Eastman Dental Institute y NIHR UCLH Biomedical Research Centre, University College London, Londres, Reino Unido.

J Periodontal Implant Sci. 2021 Oct;51(5):342-351.

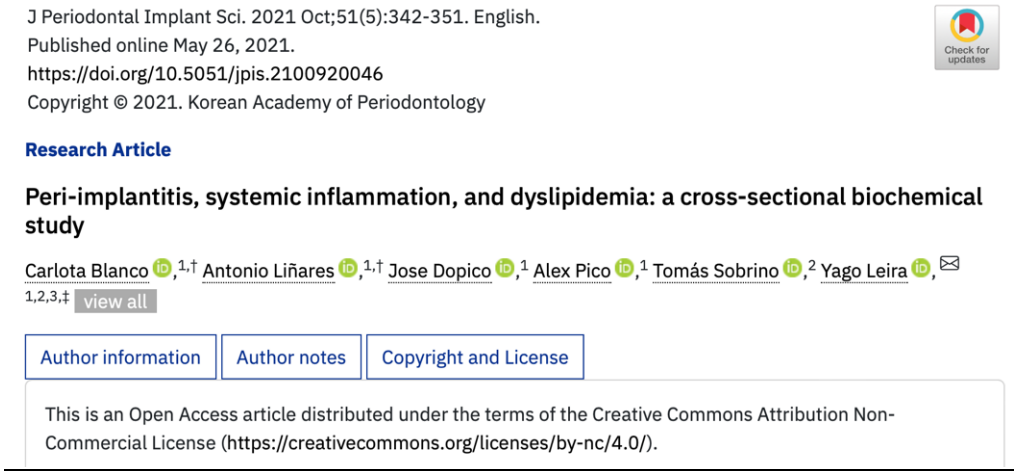
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Research Article

Peri-implantitis, systemic inflammation, and dyslipidemia: a cross-sectional biochemical study

Carlota Blanco [1,†] Antonio Liñares [1,†] Jose Dopico [1] Alex Pico [1] Tomás Sobrino [2] Yago Leira [1,2,3,‡] view all

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8.1.4. The systemic impact of non-surgical treatment of peri-implantitis with or without adjunctive systemic metronidazole: Secondary analysis of a randomized clinical trial.

Liñares A (1), Dopico J (1), Blanco C (1), Pico A (1), Sobrino T (2), Blanco J (1), Leira Y (1,2).

1 Unidad de Periodoncia, Facultad de Odontología, Universidad de Santiago de Compostela y Grupo de Investigación en Odontología Médico-Quirúrgica, Instituto de Investigaciones Sanitarias de Santiago de Compostela, Santiago de Compostela, España.

2 Laboratorio de Investigación en Neurociencias Clínicas, Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago de Compostela, España.

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Factor de impacto: 4,8 (2023), cuartil 1 (Q1) en Cirugía Oral (SJR 2023 1,87).

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8.2. ÍNDICES DE TABLAS Y FIGURAS

8.2.1. Tablas

Tabla 1. Diagnóstico condiciones periimplantarias 28

Tabla 2. Estudios tratamiento no quirúrgico sólo de la periimplantitis (RCTs) 46

Tabla 3. Estudios tratamiento no quirúrgico de la periimplantitis con aeropulidores (RCTs) 47

Tabla 4. Estudios tratamiento no quirúrgico de la periimplantitis con láser (RCTs) 48

Tabla 5. Estudios tratamiento no quirúrgico de la periimplantitis con terapia fotodinámica (RCTs) 49

Tabla 6. Estudios tratamiento no quirúrgico de la periimplantitis con antisépticos (RCTs) 50

Tabla 7. Estudios tratamiento no quirúrgico de la periimplantitis con antibióticos locales (RCTs) 51

Tabla 8. Estudios tratamiento no quirúrgico de la periimplantitis con probióticos (RCTs) 52

Tabla 9. Estudios tratamiento no quirúrgico de la periimplantitis con antibióticos sistémicos (series de casos) 53

Tabla 10. Estudios tratamiento no quirúrgico de la periimplantitis con antibióticos sistémicos (RCTs) 53

8.2.2. Figuras

Figura 1. Esquema patogénesis periimplantitis. 29

Figura 2. Lesiones periodontitis versus periimplantitis. 32

Figura 3. Microbioma y perfiles de las biopelículas de la periimplantitis 34

Figura 4. Medios de conexión entre la periodontitis y la inflamación sistémica. 43

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8.3. DICTAMEN COMITÉ ÉTICO DE GALICIA

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DICTAMEN DEL COMITÉ AUTONÓMICO DE ÉTICA DE LA INVESTIGACIÓN DE GALICIA

Paula M. López Vázquez, Secretaria del Comité Autonómico de Ética de la Investigación de Galicia,

CERTIFICA:

Que este Comité evaluó la propuesta del ensayo clínico:

Nº **EudraCT**: 2017-001848-35
Título: Tratamiento no quirúrgico de peri-implantitis con o sin metronidazol sistémico: ensayo clínico aleatorizado en humanos
Código del promotor: APB-MET-2017-01
Código de Registro: 2017/508
Promotor: Juan Blanco Carrión
Versión/fecha del protocolo y Hoja de Información al Paciente: Protocolo V2 de 19.11.17 - HIP/CI V2 de 15 de noviembre de 2017

Que este Comité ha realizado la evaluación de la parte I de la solicitud de autorización del ensayo, ha valorado las respuestas del promotor a las aclaraciones solicitadas (si las hubiera) y ha transmitido a la Agencia Española de medicamentos su opinión final sobre la parte I.

Que este Comité ha realizado la evaluación de la parte II de la solicitud de autorización del ensayo, de acuerdo con lo previsto en el Real Decreto 1090/2015 y en el art 7 del reglamento (UE) 536/2014 y considera que:

1. El procedimiento para obtener el consentimiento informado (incluyendo las hojas de información al sujeto de ensayo y consentimientos informados mencionados en el encabezamiento), y el plan de reclutamiento de sujetos previsto son adecuados y cumplen con los requisitos para la obtención del consentimiento informado previstos en el capítulo II del Real Decreto 1090/2015. Podrán realizarse versiones lingüísticas de los documentos aprobados mencionados, siendo responsabilidad del promotor garantizar al CEIm que se trata de una traducción fiel de los documentos aprobados por el CEIm.
2. Las compensaciones previstas a los participantes son adecuadas, así como las previsiones de indemnización por daños y perjuicios que pueda sufrir el participante.
3. El procedimiento previsto para el manejo de datos personales es adecuado.
4. El uso futuro de las muestras biológicas obtenidas durante el ensayo se adecua a lo previsto en el Real Decreto 1716/2011.
5. Para la realización del ensayo se consideran adecuados los centros e investigadores previstos en el anexo II a este dictamen, teniendo en cuenta las declaraciones de idoneidad emitidas por el promotor y por los responsables de las instituciones correspondientes.

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Que este Comité decidió emitir **DICTAMEN FAVORABLE** en la reunión celebrada el día 30/11/2017 (acta n.º 255)

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Que en dicha reunión se cumplieron los requisitos establecidos en la legislación vigente - Real Decreto 1090/2015 - para que la decisión del citado CEIm sea válida.

Que el Comité tanto en su composición como en sus procedimientos, cumple con las normas de BPC (CPMP/ICH/135/95) y con la legislación vigente que regula su funcionamiento, y que la composición del mismo es la indicada en el anexo I, teniendo en cuenta que en el caso de que algún miembro participe en el ensayo o declare algún conflicto de interés, se ausentará durante la evaluación.

En Santiago de Compostela, a 04 de noviembre de 2017



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Anexo I : Composición del Comité Autonómico de Ética de la Investigación de Galicia (CAEIG)

Manuel Portela Romero. (Presidente). Médico Especialista en Medicina Familiar y Comunitaria.
Irene Zarra Ferro. (Vicepresidenta). Farmacéutica de Atención Especializada.
Paula Mª López Vázquez, (Secretaria). Médico Especialista en Farmacología Clínica.
Juan Vázquez Lago (Secretario Suplente). Médico Especialista en Medicina Preventiva y Salud Pública.
Jesús Alberdi Sudupe. Médico especialista en Psiquiatría.
Rosendo Bugarín González. Médico Especialista en Medicina Familiar y Comunitaria.
Juan Casariego Rosón. Médico Especialista en Cardiología.
Xoán X. Casas Rodríguez. Médico Especialista en Medicina Familiar y Comunitaria.
Juana Mª Cruz del Río. Trabajadora Social.
Juan Fernando Cueva Bañuelos. Médico Especialista en Oncología Médica.
José Álvaro Fernández Rial. Médico Especialista en Medicina Interna.
José Luis Fernández Trisac. Médico Especialista en Pediatría.
Mª José Ferreira Díaz. Diplomada Universitaria de Enfermería.
Pablo Nimo Ríos. Licenciado en Derecho.
Pilar Gayoso Diz. Médico Especialista en Medicina Familiar y Comunitaria.
Agustín Pía Morandeira. Farmacéutico de Atención Primaria
Salvador Pita Fernández. Médico Especialista en Medicina Familiar y Comunitaria.
Carmen Rodríguez-Tenreiro Sánchez. Licenciada en Farmacia.
Susana María Romero Yuste. Médico Especialista en Reumatología.
Mª Asunción Verdejo González. Médico Especialista en Farmacología Clínica.

Anexo II: Centros e investigadores principales participantes en España

CÓDIGO: APB-MET-2017-01 NÚMERO EUDRACT: 2017-001848-35
TÍTULO: Tratamiento no quirúrgico de peri-implantitis con o sin metronidazol sistémico: ensayo clínico aleatorizado en humanos
PROMOTOR: Juan Blanco Carrión

FECHA ACTUALIZACIÓN ANEXO II: 30/11/2017

Centros	Investigadores Principales
Universidad de Santiago de Compostela	Juan Blanco Carrión

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Hasta el momento el tratamiento no quirúrgico de la periimplantitis había demostrado ser ineficaz para el control de la enfermedad. Pero, una serie de publicaciones de casos han mostrado el posible beneficio adicional del tratamiento no quirúrgico en combinación con antibiótico sistémico. Teniendo en cuenta estos resultados clínicos prometedores, llevamos a cabo esta investigación en la cual el objetivo fue evaluar la eficacia del tratamiento no quirúrgico de la periimplantitis junto con metronidazol y su posible asociación con la inflamación sistémica. Para ello se llevaron a cabo cuatro investigaciones, en los cuales incluimos una serie de casos donde mostramos el efecto de esta terapia de tratamiento sobre las lesiones de periimplantitis, un estudio transversal para estudiar la implicación de la periimplantitis en los biomarcadores sistémicos, y un ensayo clínico aleatorizado a triple ciego que dividimos en dos partes para evaluar la eficacia de este tratamiento a nivel clínico, radiográfico y microbiológico y por otro lado su implicación en los biomarcadores sistémicos. Tras llevar a cabo estas investigaciones observamos que el tratamiento no quirúrgico junto con el uso coadyuvante de metronidazol es efectivo en la reducción de la inflamación, ganancia ósea radiográfica y reducción de la carga bacteriana en las lesiones de periimplantitis, y se consigue la resolución de la periimplantitis es más de la mitad de los casos tratados y por otro lado abrimos una vía de investigación donde se observa una posible relación entre la periimplantitis y la inflamación sistémica de bajo grado, ya que observamos un aumento de biomarcadores inflamatorios en pacientes con periimplantitis y mostramos cómo su tratamiento puede repercutir a nivel sistémico en la reducción de la inflamación.