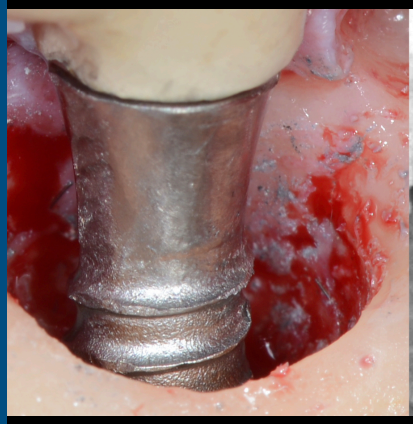
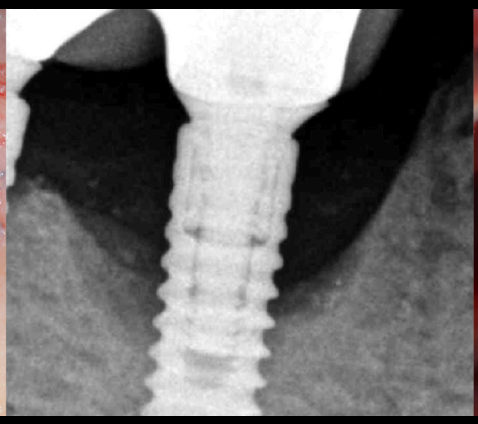
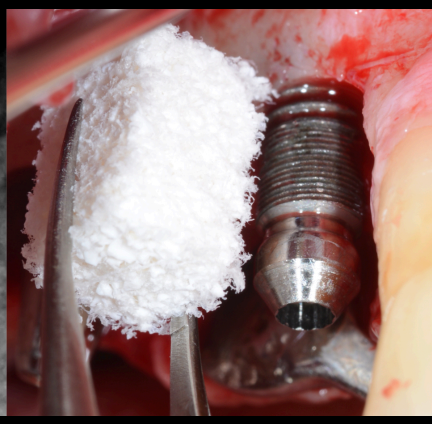
Tratamiento reconstructivo de defectos intra-óseos periimplantarios

Tesis doctoral

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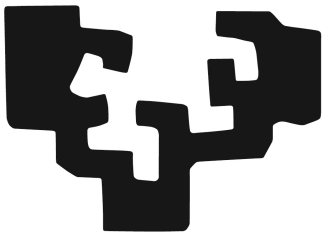

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2023

A Mercedes, a mi hermana Ainhoa y a mis padres por hacerme soñar con los ojos abiertos durante estos 33 años de vida

El valor real de marcarte objetivos NO es alcanzarlos.

El motivo principal de marcarte objetivos es comprometerte a convertirte en una persona que tenga lo necesario para conseguirlos.

Jim Rohn

Sólo aquellos que se arriesgan a ir demasiado lejos pueden descubrir hasta donde se puede llegar

T.S. Eliot

Zaindu maite duzun hori
Ruper Ordorika

Lluita pel que vols i estima el que tens
Pau Capell

Ezina ekinez egina
Proverbio vasco

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2. **Estudio #2.** Derks, J., Ortiz-Vigón, A., Guerrero, A., Donati, M., Bressan, E., Ghensi, P., Schaller, D., Tomasi, C., Karlsson, K., Abrahamsson, I., Ichioka, Y., Dionigi, C., **Regidor, E**., & Berglundh, T. (2022). Reconstructive surgical therapy of peri-implantitis: A multicenter randomized controlled clinical trial. *Clinical Oral Implants Research*, *00*, 1–24. https:// doi. org/10.1111/clr.13972

3. **Estudio #3. Regidor, E**., Ortiz-Vigon, A., Romandini, M., Dionigi, C., Derks, J., & Sanz, M. (2023). The adjunctive effect of a resorbable membrane to a xenogeneic bone replacement graft in the reconstructive surgical therapy of peri-implantitis: A randomized clinical trial. Journal of Clinical Periodontology, 1–19. https://doi.org/ 10.1111/jcpe.13796

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Prefacio

La presente tesis doctoral está basada en los tres siguientes artículos:

Artículo 1.

Tomasi C, **Regidor E,** Ortiz-Vigón A, Derks J. Efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects. A systematic review and meta-analysis. *J Clin Periodontol*. 2019;00:1–17. https:// doi.org/10.1111/jcpe.13070

Artículo 2.

Derks, J., Ortiz-Vigón, A., Guerrero, A., Donati, M., Bressan, E., Ghensi, P., Schaller, D., Tomasi, C., Karlsson, K., Abrahamsson, I., Ichioka, Y., Dionigi, C., **Regidor, E**., & Berglundh, T. (2022). Reconstructive surgical therapy of peri-implantitis: A multicenter randomized controlled clinical trial. *Clinical Oral Implants Research*, *00*, 1–24. https://doi. org/10.1111/clr.13972

Artículo 3.

Regidor, E., Ortiz-Vigon, A., Romandini, M., Dionigi, C., Derks, J., & Sanz, M. (2023). The adjunctive effect of a resorbable membrane to a xenogeneic bone replacement graft in the reconstructive surgical therapy of peri-implantitis: A randomized clinical trial. Journal of Clinical Periodontology, 1–19. https://doi.org/10.1111/jcpe.13796

Introducción

La rehabilitación oral mediante implantes es desde hace décadas un procedimiento seguro y predecible a la hora de reponer dientes ausentes o con pronóstico imposible (Papaspyridakos et al. 2012). No obstante, los implantes dentales no están libres de complicaciones, entre las cuales podemos encontrar las de carácter mecánico o biológico.

Las complicaciones mecánicas pueden ir desde el aflojamiento del tornillo protésico hasta la fractura de la supra-estructura o el propio implante, pasando por complicaciones intermedias como el aflojamiento o fractura del pilar protésico y desgastes o chipping de las coronas implanto-soportadas (Sailer et al. 2022).

Por otra parte, las complicaciones biológicas o enfermedades periimplantarias se agrupan en dos entidades principales, la mucositis periimplantaria y la periimplantitis. Las patologías periimplantarias se definen como aquellas lesiones inflamatorias asociadas a placa bacteriana que afectan a los tejidos que rodean a los implantes dentales (Berglundh et al. 2018; Monje et al. 2019; Karlsson et al. 2020: Cecchinato et al. 2022; Herrera et al. 2023).

Periimplantitis

Definición y conceptos generales

El concepto `periimplantitis´ fue introducido a finales de los años 80 para hacer referencia a aquellas situaciones que incluían procesos inflamatorios y pérdida ósea marginal en implantes osteointegrados. En el consenso del primer Workshop Europeo de Periodoncia el ´termino `periimplantitis´ fue definido como un diagnóstico clínico que requiere la evaluación de la inflamación de los tejidos periimplantarios así como la pérdida de hueso de soporte (Albrektsson e Isidor 1994).

En el informe de consenso del 6º Workshop Europeo de Periodoncia se reportó que el sondaje periimplantario es esencial el diagnóstico de periimplantitis, así como el sangrado al sondaje es indicativo de la presencia de inflamación en la mucosa periimplantaria y puede ser empleado como un factor predictor para la pérdida de soporte alrededor de un implante (Lindhe et al. 2008). En consecuencia, se acordó que los cambios en la profundidad de sondaje deben incluirse en el diagnóstico de la periimplantitis, dado que podrían ser indicativos de pérdida ósea marginal. Por este motivo, la recomendación a partir de entonces fue que las profundidades de sondaje, el sangrado y/o supuración al sondaje son variables clínicas que deben ser evaluadas en cada revisión para un posible diagnóstico precoz de la periimplantitis. Adicionalmente, en este mismo workshop se recomendó la realización de radiografías periapicales a fin de disponer de la posibilidad de evaluar los niveles óseos y la posible presencia de pérdida ósea. Sin embargo, en aquel momento no se llegó a definir un umbral exacto ni preciso para que la pérdida ósea alrededor de un implante se considerase patológica, ni hasta que momento esta posible pérdida ósea podía estar asociada con el remodelado óseo inicial debido al restablecimiento de la anchura biológica periimplantaria (Vandeweghe & De Bruyn, 2012).

Ya en el año 2011, durante el 7º Workshop Europeo de Periodoncia se recalcó la importancia de las mediciones radiográficas iniciales del hueso crestal para poder evaluar en exámenes posteriores la posible pérdida de hueso de soporte tras la remodelación inicial consecuencia del restablecimiento de la anchura biológica (Lang et al., 2011). De hecho, se hizo énfasis en que estos niveles óseos deben ser registrados el día de la colocación de la prótesis definitiva y no el día de la colocación del implante. En aquel momento, la definición de `periimplantitis´ que se acordó fue pérdida de hueso crestal, combinado con sangrado al sondaje, con o sin aumento de las profundidades de sondaje periimplantarias.

En el World Workshop on the Classification of Periodontal and Peri-implant diseases and Conditions celebrado en 2017, fue donde finalmente se abordaron de lleno los criterios diagnósticos de las enfermedades periimplantarias tanto en aquellas situaciones en las que se

tuvieran disponibles datos clínicos y radiográficos basales como en las que no. En aquel momento, los criterios diagnósticos que se establecieron fueron los siguientes (Berglundh et al. 2018; Caton et al. 2018; Schwarz et al. 2018):

- Presencia de signos de inflamación en los tejidos blandos periimplantarios, combinado con sangrado al sondaje y/o supuración.
- Incremento de las profundidades de sondaje comparando con la situación inicial que debe ser el momento de la carga protésica.
- Pérdida ósea progresiva en relación al nivel óseo en la evaluación radiográfica de un año posterior a la carga protésica.
- En ausencia de las profundidades de sondaje y radiografías iniciales, se definirá como periimplantitis aquellas situaciones que presenten en radiografía una pérdida ósea ≥ 3mm, unas profundidades de sondaje ≥ 6mm y sangrado al sondaje.

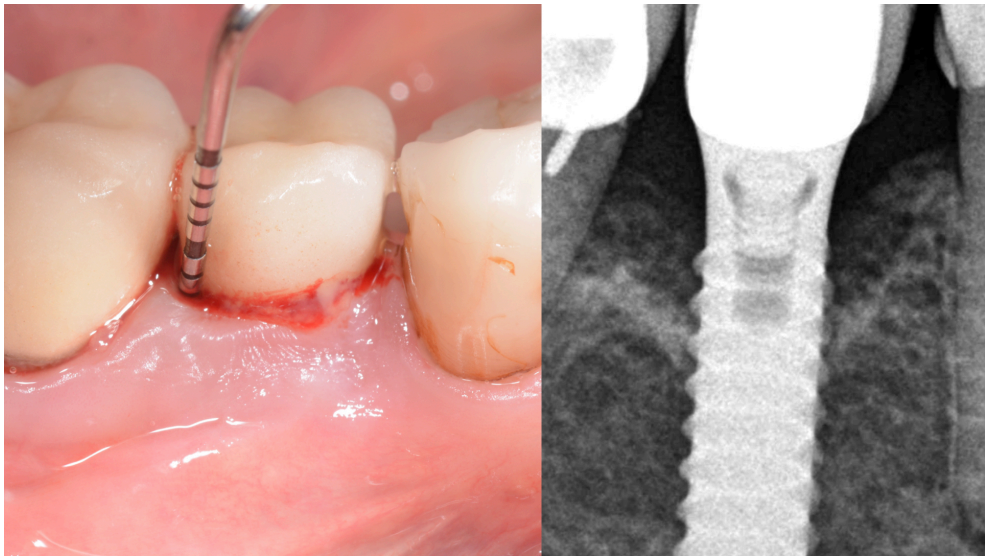

Figura 1: Diagnóstico de periimplantitis. **A)** Sondaje periimplantario profundo incompatible con salud periimplantaria y presencia de sangrado al sondaje. **B)** Radiografía periapical basal donde se puede apreciar la presencia de pérdida ósea.

Prevalencia y factores de riesgo de enfermedades periimplantarias

En relación con su prevalencia, es importante destacar que en función de la población analizada la prevalencia es variable, pudiendo ir en mucositis de 19 a 65% y en periimplantitis de 1 a 47% (Tomasi & Derks 2012; Derks & Tomasi 2015). La literatura existente justifica esta variabilidad en la prevalencia debido a la existencia de diversos factores de confusión como la existencia de diferentes definiciones de mucositis y periimplantitis y el tiempo en función de un implante que puede afectar negativamente, siendo la prevalencia de periimplantitis mayor a medida que un implante lleva más tiempo de función en boca (Derks et al. 2016;, Fransson et al. 2010; Herrera et al. 2023).

Un estudio transversal realizado en la población española en el año 2018, señaló una alta prevalencia de enfermedades periimplantarias, pudiendo alcanzar el 51% de la población portadora de implantes dentales, presentando un 27% mucositis y un 24% periimplantitis (Rodrigo et al. 2018). Este mismo estudio señaló que la terapia periodontal de mantenimiento, la localización del implante, el diámetro y la superficie del mismo, el tipo de prótesis y el acceso a la higiene interproximal como los factores de riesgo con más consistencia (Rodrigo et al. 2018).

Recientemente, se ha desarrollado una herramienta que analiza los parámetros más relacionados con la periimplantitis para acabar formando un diagrama en el que se visualiza de forma gráfica cual es el riesgo individual de desarrollar la patología (Heitz-Mayfield et al. 2020). Entre estos parámetros encontramos los antecedentes de periodontitis, la proporción de localizaciones con sangrado al sondaje, la prevalencia de profundidades de sondaje iguales o superiores a 5mm, la pérdida de hueso alveolar en relación a la edad del paciente, la susceptibilidad a la enfermedad periodontal, la regularidad con la que el paciente acude a terapia periodontal de mantenimiento y factores prostodónticos (distancia de la restauración protésica a la cresta ósea marginal, acceso a

la higiene, ajuste de la prótesis, prótesis atornillada o cementada). Debido al perfil multifactorial de la patología, este tipo de herramientas son de gran utilidad a nivel didáctico y a la hora de establecer la periodicidad con la que cada paciente debe acudir a terapia de soporte periodontal y periimplantaria de manera individualizada (Heitz-Mayfield et al. 2020; Monje et al 2022).

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 marginal periimplantaria e incluso la reconstrucción de la estructura ósea perdida. A fin de lograr estos objetivos, se pueden emplear tratamientos no quirúrgicos y quirúrgicos.

- Tratamiento no quirúrgico de la periimplantitis:

Independientemente del grado de progresión y severidad de la periimplantitis, el tratamiento no quirúrgico es mandatorio en todos los pacientes que presenten patología activa. Existen en la actualidad numerosos estudios de investigación con diferentes protocolos de descontaminación e incluso con antibioterapias como coadyuvantes con resultados realmente satisfactorios y estables en el tiempo (Estefania-Fresco et al. 2019; Blanco et al. 2022; Nart et al. 2020, Suarez-Lopez Del Amo et al. 2016; Verket et al. 2023).

Adicionalmente, los avances de los métodos de descontaminación han supuesto que estos protocolos incrementen sus probabilidades de éxito y su predictibilidad. Sin embargo, cabe

destacar que, en un alto porcentaje de pacientes, el tratamiento no quirúrgico resulta insuficiente para lograr la detención de la progresión de la periimplantitis y por eso es necesario mencionar que el tratamiento quirúrgico, ya sea resectivo, reconstructivo o combinado, es inevitable en muchas ocasiones (Faggion et al. 2014; Karlsson et al. 2019; Romandini et al. 2022).

- Tratamiento quirúrgico de la periimplantitis

En este punto es importante considerar que será la anatomía del defecto óseo periimplantario la que determine el enfoque quirúrgico y el método de descontaminación en gran medida, una vez que el tratamiento no quirúrgico haya resultado insuficiente (Schwarz et al. 2010; Monje et al. 2019; Schwarz et al. 2022; Ramanauskaite et al. 2022).

Anatomía de los defectos óseos periimplantarios:

De idéntica manera a la toma de decisiones en torno a un defecto periodontal en un diente (Papapanou & Tonetti 2000), la decisión de cómo abordar un defecto óseo periimplantario, depende en gran medida de las características anatómicas o de la configuración tridimensional del defecto óseo periimplantario.

En 1994, Jovanovic clasificó los defectos óseos periimplantarios en función del grado de pérdida ósea horizontal e infraósea (Jovanovic et al. 1994):

- Periimplantitis clase 1: presencia de defecto óseo con pérdida ósea horizontal moderada con una componente intraósea mínima.

- Periimplantitis clase 2: presencia de defecto óseo con pérdida ósea horizontal entre moderada y avanzada, con una componente infraósea mínima.

- Periimplantitis clase 3: presencia de defecto óseo con pérdida ósea horizontal entre mínima y moderada, con una componente infraósea en forma circunferencial avanzada.

- Periimplantitis clase 4: presencia de defecto óseo periimplantario con pérdida ósea horizontal moderada, componente infraósea circunferencia avanzada y pérdida del aspecto óseo vestibular y/o lingual.

En el año 2010 se propuso la clasificación más referenciada hasta la fecha de los defectos óseos periimplantarios (Schwarz et al. 2010). En esta clasificación, en primer lugar, se encontraban aquellos defectos horizontales o con una componente intraósea inferior a 3mm que se denominaban como defectos tipo 2. Por otro lado, defectos óseos con alguna pared remanente, defectos verticales o angulares o incluso tipo cráter con una componente intraósea de al menos 3mm de profundidad que se denominaban tipo 1. Además, en función del número de paredes remanentes se sub-clasificaban como 1a, 1b, 1c, 1d o 1e. Acorde a los resultados de este estudio, la prevalencia de los defectos tipo 2 es en un 79% de los pacientes. En cuanto a los defectos intraóseos, la componente intraósea en el 55,3% de los pacientes era de tipo circunferencial (clase 1e).

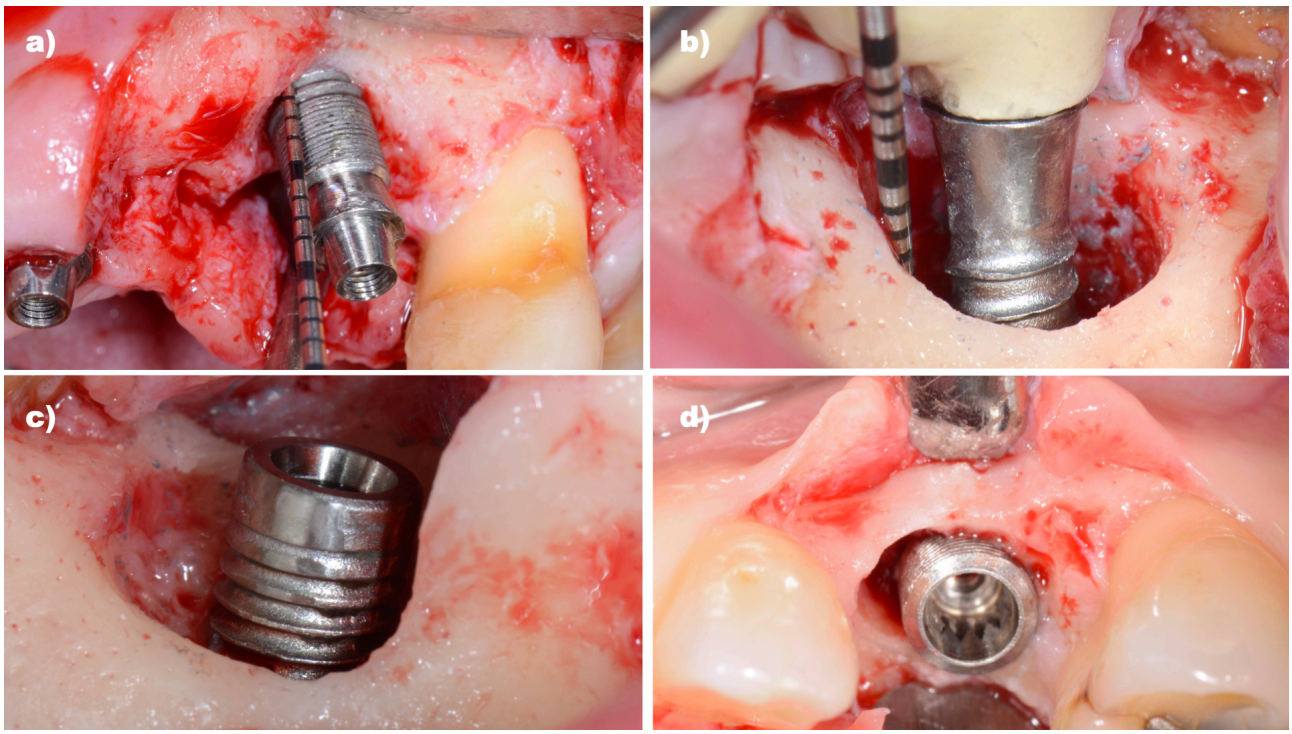

Figura 2: Defectos óseos periimplantarios. **A)** Defecto óseo plano. Tipo II. **B)**Defecto intraóseo. Tipo Ib. **C)** Defecto intraóseo. Tipo Ic. **D)** Defecto intraóseo. Tipo IIIc.

No obstante, en el año 2019, se propuso una modificación o evolución de esta clasificación, dado que en muchas de las ocasiones los pacientes presentan un defecto óseo combinado (tipo 3) (Monje et al. 2019). Además, se clasificaron en base a las características (dehiscencia, 2-3 paredes o circunferencial) y a la severidad (leve, moderada, avanzada). Este estudio fue realizado mediante la obtención de radiografías 3D o CBCTs y es que la literatura científica describe que es el método diagnóstico más preciso para conocer las características de los defectos óseos periimplantarios de manera pre-quirúrgica (Garcia-Garcia et al. 2016; Ramanauskaite & Juodzbalys 2016; Bender et al. 2017; Pelekos et al. 2019; Insua et al. 2021; Almohandes et al. 2022).

Un estudio reciente describe que, en la actualidad, el defecto más prevalente es una combinación de una componente intraósea con una dehiscencia bucal o vestibular, mientras que rara vez se encuentra un defecto puramente circunferencial. Además, menciona que los implantes con dehiscencia bucales o vestibulares presentaban con mayor frecuencia una posición demasiado vestibular (Wehner et al. 2021).

En definitiva, la anatomía del defecto óseo periimplantario es crucial a la hora de seleccionar el enfoque y el tipo de tratamiento quirúrgico (Schwarz et al. 2010; Aljateeli et al. 2012; Aghazadeh et al. 2020). Adicionalmente, es necesario tener en cuenta el grado de pérdida ósea (Okayasu & Wang 2011) y la localización del implante (Schwarz et al. 2008).

- Tratamiento quirúrgico resectivo

En pacientes en los que la periimplantitis haya provocado un defecto horizontal, supraóseo o con una componente intraósea inferior a 3mm, el tratamiento quirúrgico ha de ser resectivo, eliminado

el tejido de granulación provocado por la progresión de la periimplantitis, descontaminando la superficie expuesta del implante y proporcionando una reposición apical de los tejidos blandos periimplantarios (Carcuac et al. 2016; Carcuac et al. 2017). En ocasiones, al igual que en cirugía periodontal resectiva, es necesario realizar un recontorneado óseo para dejar una anatomía más favorable que impida la reproducción de la bolsa periimplantaria (Berglundh et al. 2018). Además, la literatura científica reporta la posibilidad de utilizar como coadyuvante protocolos de implantoplastia o al menos reducir la rugosidad de superficie del implante con el fin de poder higienizar mejor la superficie expuesta por parte del clínico durante el tratamiento y mantenimientos periimplantarios posteriores y por parte del paciente en el día a día (Romeo et al. 2005; Romeo et al. 2007). Además, existen estudios de investigación que analizan la eficacia clínica de realizar este tipo de procedimientos quirúrgicos resectivos de manera simultánea a un aumento de tejidos blandos alrededor de implantes cuando la banda de mucosa queratinizada sea insuficiente (<2mm) (Solonko et al. 2021).

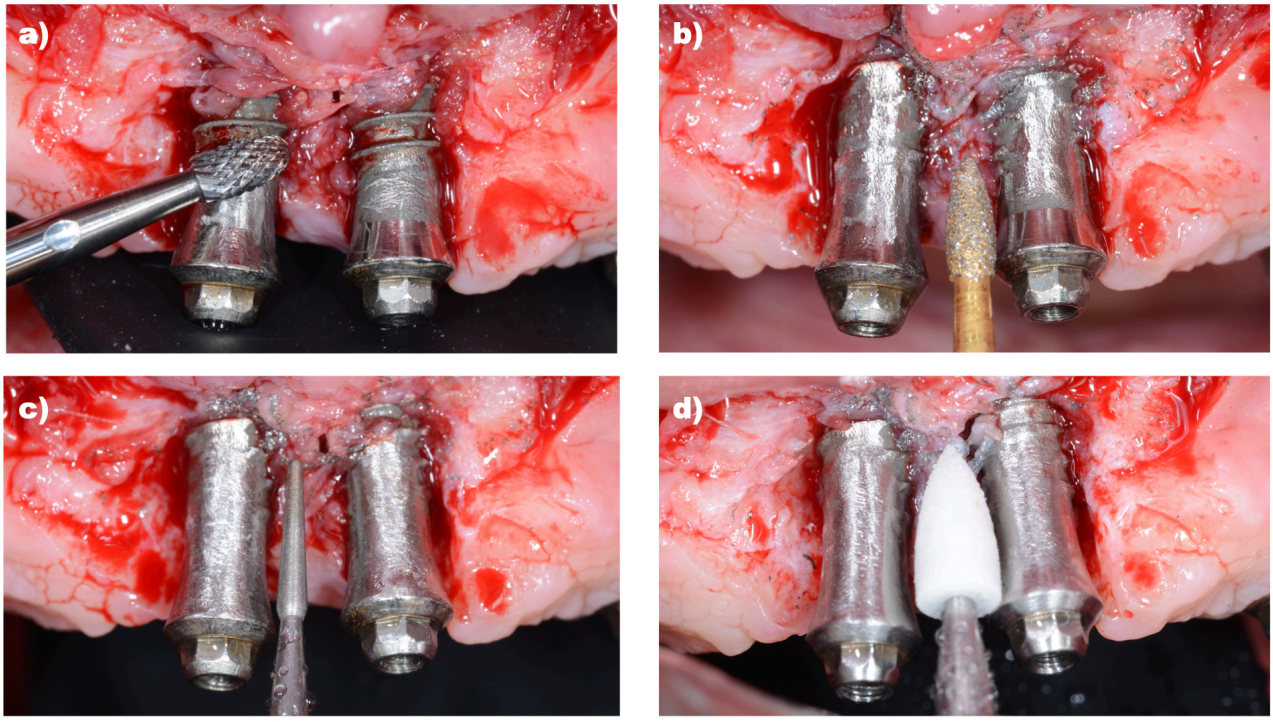

Figura 3: Protocolo de implantoplastia como coadyuvante al tratamiento quirúrgico resectivo de la periimplantitis. **A)** Utilización de fresa de carburo de tungsteno. **B)** Utilización de fresa de PerioSet® de balón de rugby. **C)** Utilización de fresa de PerioSet® lanceolada. **D)** Utilización de fresa de piedra de Arkansas blanca.

En cualquiera de los casos, los objetivos de este enfoque quirúrgico son conseguir la reducción de la bolsa periimplantaria y mejorar la anatomía de los tejidos para así lograr un mejor acceso a la higiene oral y por ende un re-establecimiento y mantenimiento de la salud periimplantaria.

- Tratamiento quirúrgico reconstructivo:

Aquellos pacientes en los que se realiza un procedimiento quirúrgico y tras la eliminación y remoción del tejido de granulación, presentan una componente intraósea de al menos 3mm de profundidad e idealmente no más de 3mm de anchura, el tratamiento que estaría indicado sería el reconstructivo. La presencia de defectos de al menos 2-3 paredes o incluso cráteres circunferenciales debe hacer al clínico plantearse un enfoque reconstructivo (Renvert et al. 2018; Roccuzzo et al. 2021).

Cabe destacar en este punto la importancia de hacer la distinción entre los términos regenerativo y reconstructivo. En terapia periodontal regenerativa de defectos periodontales, la literatura científica que demuestra la creación o la formación de una nueva inserción alrededor del diente es amplia y en consecuencia estaríamos hablando de un proceso regenerativo per se (Reynolds et al. 2015). Por el contrario, el término adecuado en el mismo tratamiento sobre implantes sería reconstructivo dado que para poder hablar de regeneración debería haberse demostrado una re-oseointegración o al menos un incremento del contacto hueso-implante y hasta la fecha todos los intentos han sido fallidos (Almohandes et al. 2019; Sanz-Esporrin et al. 2019).

Injertos óseos:

A pesar de la alta heterogeneidad entre los resultados de los diferentes estudios publicados hasta el momento (Donos et al. 2023; Ramanauskaite et al. 2023), la literatura científica coincide en la posibilidad de emplear diferentes biomateriales para reconstruir la componente intraósea y las

paredes ausentes como puede ser una dehiscencia vestibular de los defectos óseos provocados por la periimplantitis. Habitualmente, la clasificación de los diferentes injertos óseos está caracterizada por su origen. De esta manera se pueden distinguir injertos óseos autólogos, xenogénicos, alogénicos o aloplásticos.

- Injertos óseos autólogos:

Los injertos óseos autólogos se han considerado hasta la fecha como el gold standard para la regeneración ósea guiada para la colocación de implantes (Cordaro et al. 2002). En este sentido, numerosos estudios describen resultados favorables en pacientes sometidos a procedimientos de reconstrucción ósea mediante injertos autólogos para la posterior colocación de implantes, en términos de ganancia ósea y mantenimiento del volumen (Sanz-Sanchez et al. 2015). Estos resultados están asociados a las propiedades biológicas de este tipo de injertos óseos (Osteoconductividad, osteoinducción y osteogénesis). Por ende, no es de extrañar que exista literatura científica que haya analizado su uso en terapia reconstructiva de defectos periimplantarios ya sea solo (Behneke et al. 2000) o en combinación con otros injertos (Wiltfang et al. 2012) y membranas (Khoury & Buchmann 2001; Monje et al. 2020).

Sin embargo, la utilización de injertos autólogos también se asocia a inconvenientes tales como la limitada disponibilidad intraoral (Cremonini et al. 2010), un incremento de la morbilidad (Cordaro et al. 2002; Cordaro et al. 2011) e incluso el riesgo de alteraciones sensoriales (Von Arx et al. 2005). Con el objetivo de reducir estos inconvenientes, se están llevando a cabo estudios de investigación con injertos de otro origen, como son los injertos xenogénico o alogénicos tanto en regeneración ósea guiada (Di Raimondo et al. 2020) como en terapia reconstructiva periimplantaria (Renvert et al. 2018).

- Injertos óseos xenogénicos:

En las últimas décadas los injertos óseos xenogénicos han sido los injertos óseos más investigados. A pesar de que se trata de un tipo de injerto que carece de capacidad osteogénica, son muchos los estudios de investigación que han analizado su uso ya sea solo o en combinación con otros y/o membranas barrera. Existe un estudio de investigación que analiza su uso en comparación con el de injertos óseos autólogos en terapia reconstructiva de defectos óseos alrededor de implantes provocados por periimplantitis (Aghzadeh et al. 2012). Los resultados de este estudio reportan que el tratamiento con cualquiera de los dos injertos óseos tiene una eficacia limitada. No obstante, si se observa una mejoría significativa en las variables clínicas periimplantarias mediante cualquiera de los dos injertos óseos, obteniendo mayor relleno óseo radiográfico con el injerto óseo xenogénico (Aghzadeh et al. 2012). Hasta la fecha, existe evidencia científica que demuestra resultados más favorables colocando un injerto óseo xenogénico en defectos óseos periimplantarios de 3 o 4 paredes (Renvert et al. 2018).

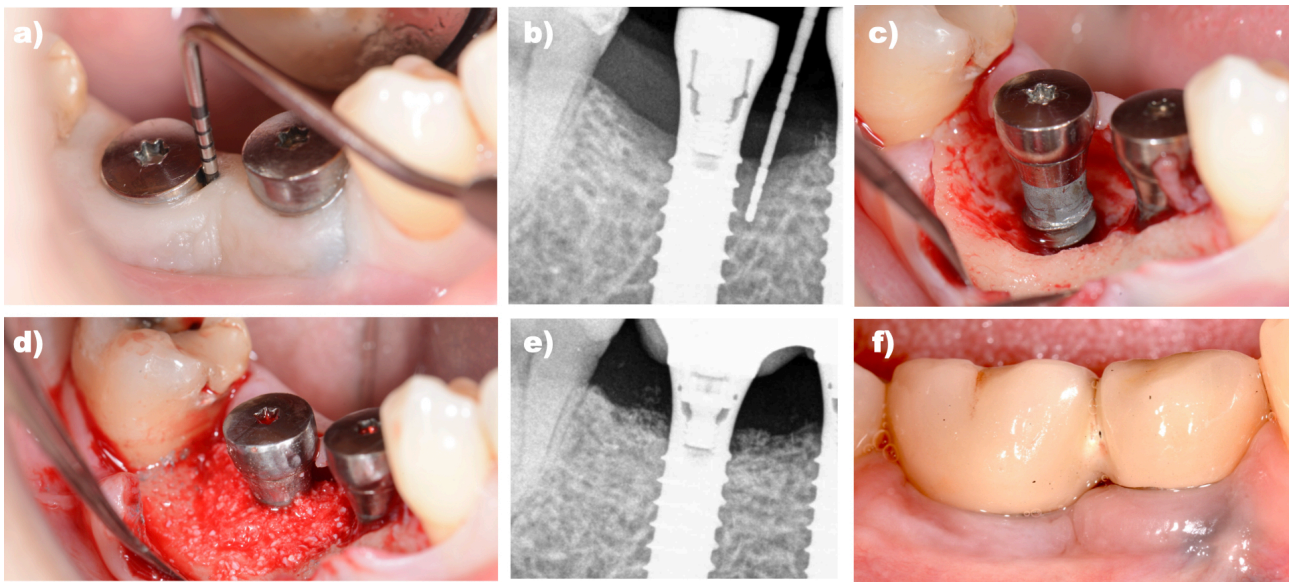

Figura 4: Tratamiento quirúrgico reconstructivo de la periimplantitis. **A)** Situación clínica basal. **B)** Situación radiográfica basal. **C)** Situación clínica tras elevar un colgajo a espesor total y eliminar el tejido de granulación. **D)** Utilización de un xenoinjerto colágeno (BioOss Collagen®) para reconstruir la componente intraósea del defecto. **E)** Situación radiográfica a 12 meses de seguimiento. **F)** Situación clínica a 12 meses de seguimiento.

Además, existen estudios de investigación que demuestran el mantenimiento de los resultados obtenidos incluso a 10 años de seguimiento (Rocuzzo et al. 2011; Rocuzzo et al. 2017; Rocuzzo et al. 2020). Sin embargo, cabe la necesidad de destacar las características de superficie de los implantes tratados parece tener una influencia enorme en los resultados (Roccuzzo et al. 2020).

Estos injertos óseos xenogénicos se pueden encontrar en forma de partícula o en forma de bloque e incluso pueden contener cierto porcentaje de colágeno (Roccuzzo et al. 2020). La literatura científica que existe al respecto sugiere que la utilización de injertos óseos xenogénicos en forma de bloque es más favorable que la del injerto óseo particulado en términos de ganancia ósea y estabilidad volumétrica (Mir Mari et al. 2016; Benic et al. 2019).

- Injertos óseos alogénicos:

Si bien es cierto que el respaldo científico que tienen hoy en día los injertos óseos de origen alogénico es inferior a la evidencia que tienen los xenoinjertos, es necesario destacar a su favor que tienen propiedades como la osteoinducción y la osteoconducción. No obstante, el uso de aloinjertos tiene como desventaja la necesidad de un tiempo mayor y además resulta en una menor cantidad de hueso neoformado que los injertos óseos autólogos.
En relación con la terapia reconstructiva de defectos óseos periimplantarios la literatura científica que existe es escasa. Una serie de casos que analizó la reconstrucción del defecto óseo mediante un alonjerto mezclado con antibiótico (Vancomicina and Tobramicina) y además utilizaba una membrana de colágeno para cubrir el injerto óseo, reportó resultados favorables a 12 meses de seguimiento (Nart et al. 2017).

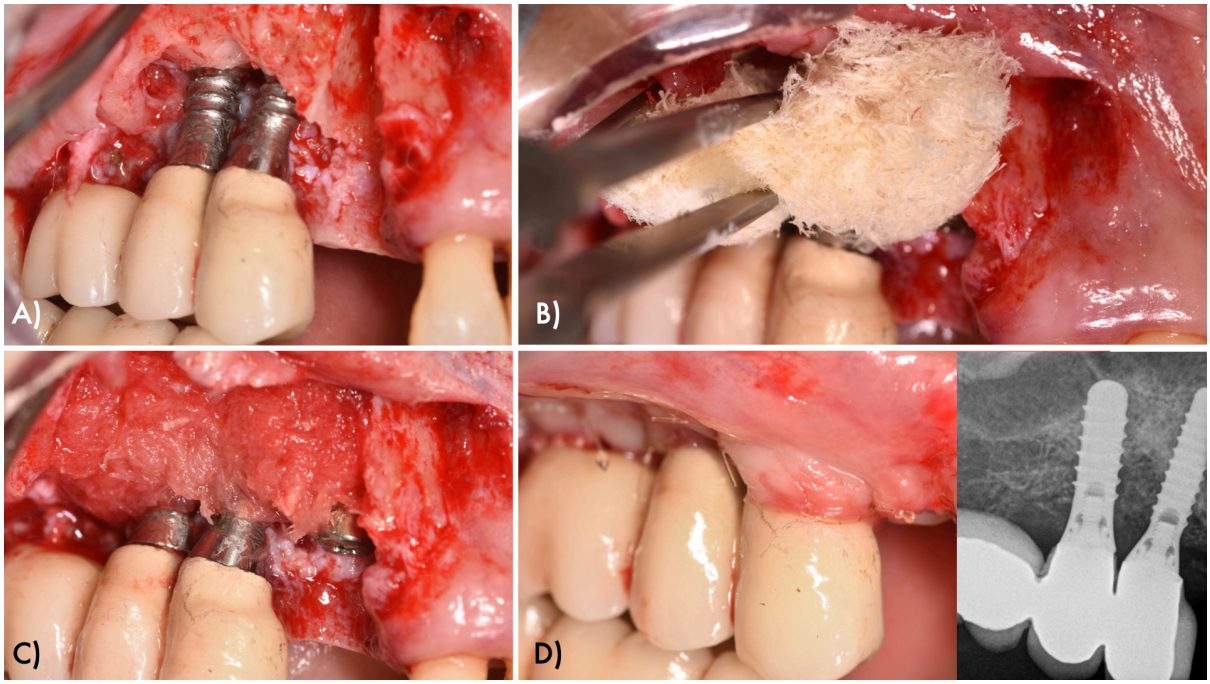

Figura 5: Tratamiento quirúrgico reconstructivo de la periimplantitis. **A)** Situación clínica tras elevación de un colgajo a espesor completo, eliminación del tejido de granulación periimplantario y extracción del canino (13) por caries **B)** Manejo clínico del aloinjerto en fibras (Oragraft Prime® Salugraft Dental). **C)** Utilización del aloinjerto para reconstruir la componente ósea perdida por la progresión de la periimplantitis y la pared vestibular del nuevo implante en posición de canino (Oragraft Prime® Salugraft Dental). **D)** Situación clínica y radiográfica inmediata postoperatoria.

- Injertos óseos aloplásticos:

Los injertos óseos aloplásticos son los que están realizados a partir de materiales inertes y se describen como materiales de injerto de hueso sintético. Un tipo de injerto óseo aloplástico que se ha utilizado en algunas líneas de investigación del tratamiento quirúrgico de la periimplantitis son los gránulos de titanio poroso. Se trata de un tipo de partículas que se introdujeron como un injerto óseo osteoconductivo para el tratamiento reconstructivo de defectos óseos periimplantarios. No obstante, no ha sido una línea de investigación en la que se haya profundizado, probablemente debido a que en los estudios realizados solamente se observó un beneficio a nivel radiográfico sin poder llegar a discernir si se trataba de nuevo hueso formado o restos del biomaterial (Jepsen et al. 2016; Wohlfahrt et al. 2012; Andersen et al. 2017).

Membranas barrera

El uso de membranas barrera durante un procedimiento regenerativo o reconstructivo de manera previa o simultáneo a la colocación de implantes ha sido ampliamente evaluado por la literatura científica y se ha llegado a reportar un beneficio claro a favor de su uso recubriendo un injerto óseo (Sanz-Sanchez et al. 2015; Thoma et al. 2019; Naenni et al. 2019). Además, existen estudios de investigación que defienden la fijación de la membrana para evitar un desplazamiento de esta al avanzar el colgajo para conseguir un cierre primario (Mir-Mari et al. 2016) y para lograr mejorar la expresión de factores osteogénicos y por ende una mayor formación de hueso nuevo (An et al. 2022).

En consecuencia, en los últimos años también se ha analizado si uso en terapia reconstructiva de defectos periimplantarios ofrece algún beneficio adicional frente a la sola utilización de algún injerto óseo.

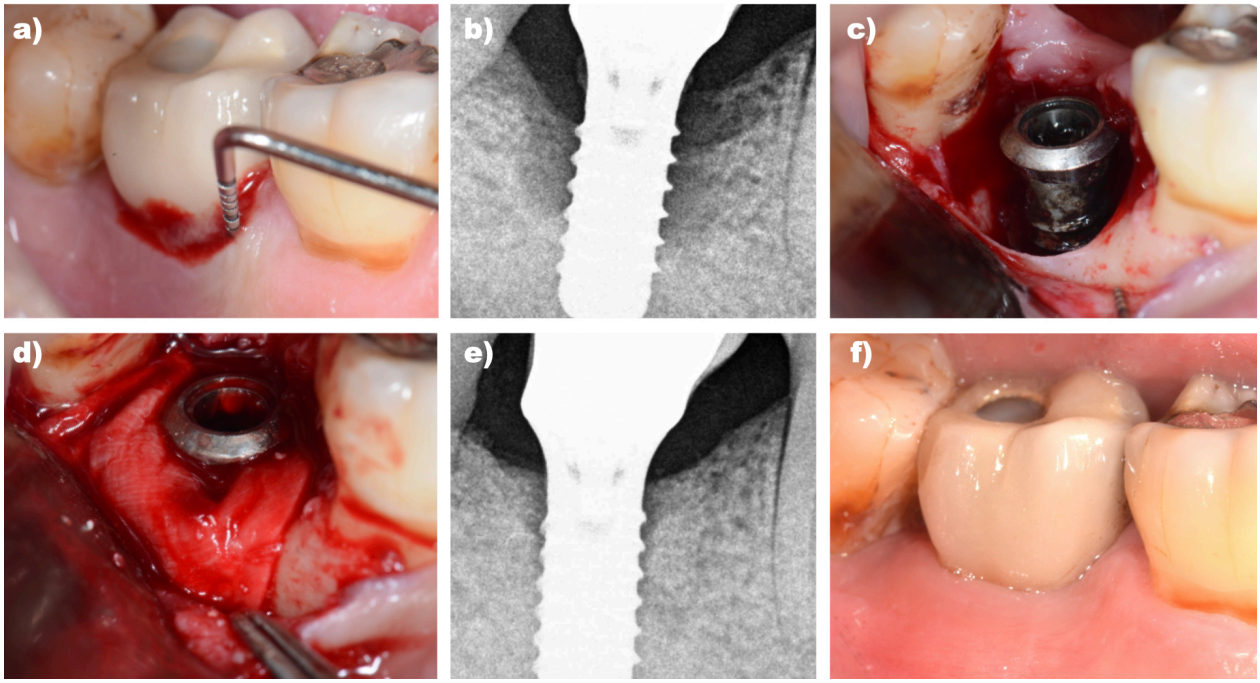

Figura 6: Tratamiento quirúrgico reconstructivo de la periimplantitis. **A)** Situación clínica basal. **B)** Situación radiográfica basal. **C)** Situación clínica tras elevar un colgajo a espesor total y eliminar el tejido de granulación. **D)** Utilización de un xenoinjerto colágeno (BioOss Collagen®) para reconstruir la componente intraósea del defecto y una membrana de colágeno reabsorbible (BioGuide®) para cubrir el injerto óseo. **E)** Situación radiográfica a 12 meses de seguimiento. **F)** Situación clínica a 12 meses de seguimiento.

Existen varias series de casos que incluyen el uso de membranas barrera en sus protocolos reconstructivos, pero no analizan el beneficio concreto de la utilización de la membrana (Matarasso et al. 2014; Nart et al. 2017).

Varios estudios de un mismo grupo de investigación con resultados de hasta 5 años de seguimiento, sugieren que su uso no ofrece ningún beneficio adicional frente al uso de un injerto óseo xenogénico y que por tanto su utilidad quedaría en entredicho (Roos-Jansaker et al. 2007a; Ross-Jansaker et al. 2007b; Roos-Jansaker et al. 2011; Roos-Jansaker et al. 2014). Estos resultados concuerdan con los de un ensayo clínico aleatorizado reciente que analiza el beneficio adicional de utilizar una membrana reabsorbible de colágeno recubriendo un aloinjerto (Monje et al. 2022).

Otros biomateriales:

- Proteínas derivadas de la matriz del esmalte:

Las proteínas derivadas de la matriz del esmalte son el gold standard en la regeneración de defectos periodontales alrededor de dientes. El uso de proteínas derivadas de la matriz del esmalte solas o en combinación con injertos óseos ha sido motivo de investigación en las últimas décadas, mostrando resultados verdaderamente eficaces y estables a largo plazo en el tiempo. Por eso y teniendo en cuenta sus propiedades biológicas, no es de extrañar que se haya especulado con extrapolar su uso a la cirugía reconstructiva de defectos periimplantarios. La hipótesis es que su uso promovería la regeneración ósea en combinación con un injerto óseo. Hasta la fecha, la literatura científica que ha analizado su uso es escasa y se necesitan ensayos clínicos que analicen el beneficio adicional de su uso (Isehed et al. 2016; Mercado et al. 2018).

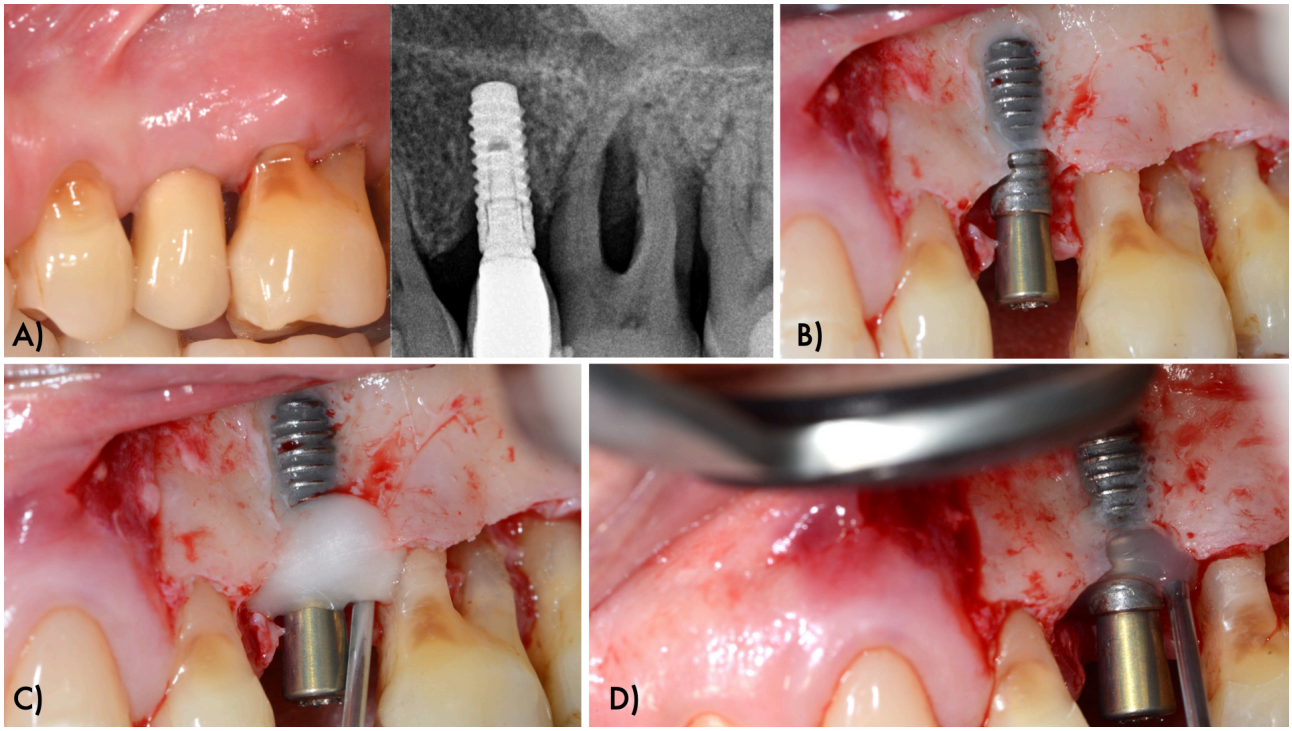

Figura 7: Tratamiento quirúrgico reconstructivo de la periimplantitis. **A)** Situación clínica y radiográfica basal. Diagnóstico de periimplantitis. **B)** Colgajo a espesor total, eliminación del tejido de granulación y descontaminación de las superficies periodontales en los defectos de furcación y de la superficie periimplantaria afectada por la periimplantitis. **C)** Utilización de PrefGel / EDTA (ácido etilendiaminotetraacético) como método químico para descontaminación de la superficie periimplantaria y para eliminar el barrillo dentinario en los dientes. **D)** Utilización de amelogeninas (Straumann Emdogain®) para la regeneración periodontal y para estimular el crecimiento óseo.

- Plasma rico en factores de crecimiento:

El uso de plasma rico en factores de crecimiento se ha propuesto en procedimientos quirúrgicos tanto periodontales como periimplantarios. Alrededor de implantes, se han propuesta para mejorar la cicatrización de tejidos blandos periimplantarios y para favorecer los procedimientos reconstructivos o regenerativos (Temmerman et al. 2018). Por eso, no es de extrañar que la literatura científica haya querido indagar acerca del efecto que podría llegar a tener su uso en el tratamiento reconstructivo de defectos óseos periimplantarios (Hamzacebi et al. 2015; Isler et al.

2018). La escasa literatura científica reporta que el uso adicional de plasma rico en factores de crecimiento mejora los resultados de la cirugía de acceso (Hamzacebi et al. 2015). Sin embargo, la comparación del plasma rico en factores de crecimiento con la utilización de una membrana de colágeno arroja mejores resultados a favor de la membrana (Isler et al. 2018). Por tanto, sería necesario analizar el beneficio adicional que puede llegar a tener en combinación con diferentes biomateriales para poder evaluar el mejor ratio coste-beneficio de su utilización y sus ventajas.

JUSTIFICACIÓN

En la actualidad, la predictibilidad del tratamiento quirúrgico reconstructivo de la periimplantitis es incierta. Por el momento, se desconoce si la aplicación del tratamiento quirúrgico reconstructivo ofrece resultados superiores frente al tratamiento quirúrgico resectivo o desbridamiento con colgajo de la patología. Si bien es cierto que la terapia regenerativa de defectos periodontales alrededor de dientes ha sido ampliamente investigada por la literatura científica, hasta la fecha, la literatura existente para estos mismos procedimientos alrededor de implantes es limitada y controvertida.

La falta de predictibilidad del tratamiento quirúrgico reconstructivo se debe en gran medida a la escasez de estudios y a la falta de homogeneidad entre ellos. Esta falta de homogeneidad en los estudios está caracterizada por la utilización de numerosas tecnologías regenerativas que incluyen diferentes biomateriales e incluso la utilización de membranas barrera. Cabe destacar que, hasta el momento, ningún biomaterial ha demostrado resultados superiores frente a otros y la utilización de membranas barrera que aíslen los biomateriales está en entredicho.

Adicionalmente, la tendencia habitual en los estudios existentes hasta la fecha, es la inclusión de variables clínicas y radiográficas. No obstante, la mayoría de los estudios no reportan variables relacionadas con la morbilidad, percepción y satisfacción de los pacientes con el tratamiento recibido.

Por ende, teniendo en cuenta la falta de superioridad del tratamiento quirúrgico reconstructivo de la periimplantitis frente al tratamiento quirúrgico resectivo o desbridamiento con colgajo, así como la incógnita de si la utilización de una membrana barrera podría llegar a ofrecer un beneficio adicional en el tratamiento quirúrgico reconstructivo, se ha diseñado un conjunto de estudios que

evalúen estas áreas incluyendo el análisis de variables clínicas, radiografías y resultados reportados por los pacientes.

HIPÓTESIS

La hipótesis general del presente trabajo es que ante la existencia de un defecto intra-óseo asociado a la progresión de la periimplantitis, los protocolos de tratamiento quirúrgicos reconstructivo que se basan en la utilización de sustitutos óseos y membranas barrera ofrecen un beneficio adicional en comparación a la cirugía resectiva o cirugía de acceso y descontaminación de la superficie periimplantaria en términos de variables clínicas y radiográficas.

OBJETIVOS

Objetivo general:

El fin último de este trabajo es evaluar la eficacia clínica de los procedimientos quirúrgicos reconstructivos de los defectos óseos periimplantarios provocados por la progresión de la periimplantitis.

Objetivos específicos:

(Estudio #1)

Realizar una revisión sistemática de la evidencia científica, basada en publicaciones hasta febrero del 2018, de ensayos clínicos controlados y series de casos prospectivas de al menos 10 pacientes (5 por grupo en estudios controlados) y 12 meses de seguimiento, que realizasen procedimientos quirúrgicos de reconstrucción ósea de los defectos periimplantarios asociados a la progresión de la periimplantitis.

(Estudio #2)

Evaluar los cambios, en las variables clínicas, radiográficas y satisfacción de los pacientes tras la aplicación de un protocolo de manejo de defectos óseos alrededor de implantes provocados por la periimplantitis, que incluye la utilización de un xenoinjerto óseo (o no) tras acceder quirúrgicamente, haber eliminado el tejido de granulación y haber descontaminado la superficie del implante afectada por la patología.

(Estudio #3)

Analizar la seguridad (aparición de complicaciones) y eficacia en términos resultados clínicos, radiográficos y de satisfacción de los pacientes de la utilización de una membrana de colágeno

reabsorbible cubriendo un injerto óseo para el tratamiento quirúrgico reconstructivo de los defectos intra-óseos periimplantarios.

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 tres publicaciones independientes con las siguientes referencias:

Estudio #1. Tomasi C, **Regidor E,** Ortiz-Vigón A, Derks J. Efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects. A systematic review and meta-analysis. *J Clin Periodontol*. 2019;00:1–17. https:// doi.org/10.1111/jcpe.13070

Estudio #2. Derks, J., Ortiz-Vigón, A., Guerrero, A., Donati, M., Bressan, E., Ghensi, P., Schaller, D., Tomasi, C., Karlsson, K., Abrahamsson, I., Ichioka, Y., Dionigi, C., **Regidor, E**., & Berglundh, T. (2022). Reconstructive surgical therapy of peri-implantitis: A multicenter randomized controlled clinical trial. *Clinical Oral Implants Research*, *00*, 1–24. https://doi. org/10.1111/clr.13972

Estudio #3. Regidor, E., Ortiz-Vigon, A., Romandini, M., Dionigi, C., Derks, J., & Sanz, M. (2023). The adjunctive effect of a resorbable membrane to a xenogeneic bone replacement graft in the reconstructive surgical therapy of peri-implantitis: A randomized clinical trial. Journal of Clinical Periodontology, 1–19. https://doi.org/10.1111/jcpe.13796

I

Artículo 1:

Tomasi C, Regidor E, Ortiz-Vigón A, Derks J. Efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects. A systematic review and meta-analysis. *J Clin Periodontol*. 2019;00:1–17. https:// doi.org/10.1111/jcpe.13070

Objetivo:

La presente revision sistemática tiene como objetivo evaluar la eficacia del tratamiento quirúrgico reconstructivo de los defectos óseos asociados a la periimplantitis.

Material y métodos:

Mediante una búsqueda electrónica se identificaron estudios que reportasen resultados de tratamiento quirúrgico reconstructivo de la periimplantitis a 12 meses. Tras la extracción de datos, se realizaron dos conjuntos diferentes de metaanálisis. En primer lugar, se utilizaron estudios controlados para evaluar el beneficio potencial de la terapia quirúrgica reconstructiva frente a tratamientos control. En segundo lugar, se evaluó en resultado general de la terapia quirúrgica reconstructiva comparando los valores basales con los resultados a 12 meses.

Resultados:

El beneficio potencial de las técnicas reconstructivas sobre los procedimientos control se evaluó en 3 estudios, lo que presentaba un total de 116 implantes. En total, 16 estudios reportaron información sobre el resultado de la terapia reconstructiva 12 meses después del procedimiento quirúrgico. Los metaanálisis identificaron una mayor mejoría en los niveles óseos marginal (MBL, WMD = 1.7mm) y en relleno del defecto óseo (WMD = 57%) para los procedimientos test, pero no se encontraron diferencias para las medidas clínicas (reducción de las profundidades de sondaje (PD) y sangrado al sondaje (BOP). No se analizaron los cambios en la inserción clínica y en los niveles de tejidos blandos. En cuanto a resultados generales, la terapia resultó en una mejoría de

los niveles óseos marginales (WMD=2.0mm) y niveles de inserción clínica (WMD=1.8mm), en recesión (WMD= 0.7mm) en la reducción de la profundidad de sondaje (WMD=2.8mm) y en la reducción de sangrado al sondaje (Implantes: RR=0.4/ Localizaciones: RR=0.2). Ninguno de los estudios incluidos reportó resultados en relación con la satisfacción de los pacientes.

Conclusiones:

La evidencia disponible acerca de la terapia reconstructiva de los defectos óseos asociados a periimplantitis es limitada por (a) número reducido de estudios controlados, (b) falta de estudios controlados para los procedimientos utilizados comúnmente, (c) heterogeneidad entre los estudios y (d) la elección de las medidas de resultados. Se observó una alta variabilidad en los resultados a 12 meses. La interpretación de una mayor ganancia ósea marginal para los procedimientos test es complicada debido a que el injerto óseo podría no distinguirse del nuevo hueso formado. El potencial estético y las ventajas reportadas por los pacientes permanecen aún sin demostrar.

Palabras clave:

Regeneración ósea, implante dental, periimplantitis, terapia reconstructiva.

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SUPPLEMENT ARTICLE

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Efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects. A systematic review and meta-analysis

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Abstract

Objectives: The present systematic review aimed at evaluating the efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects.

Methods: Studies reporting on outcomes of reconstructive surgery at peri-implantitis-related bone defects at 12 months were identified through an electronic search. Following data extraction, two different sets of meta-analyses were performed. Primarily, controlled studies were used to evaluate the potential benefit of reconstructive surgical therapy over controls. Secondly, overall outcome of reconstructive surgical therapy was assessed by comparing baseline values with outcomes at 12 months. Results were expressed as weighted mean differences (WMD) or risk ratios (RR). Heterogeneity was described by I^2 and prediction intervals.

Results: The potential benefit of reconstructive techniques over control procedures was evaluated in three studies, representing a total of 116 implants. Altogether, 16 studies reported on the outcome of reconstructive measures at 12 months after surgery. The meta-analyses identified a larger improvement in marginal bone levels (MBL, WMD = 1.7 mm) and in defect fill (WMD = 57%) for test procedures, but found no differences for clinical measures (reduction of probing depth (PD) and bleeding on probing (BOP). Changes of clinical attachment and soft tissue levels were not considered. In terms of overall outcome, therapy resulted in improved MBL (WMD = 2.0 mm) and CAL (WMD = 1.8 mm), in recession (WMD = 0.7 mm), in reduced PD (WMD = 2.8 mm) and in reduced BOP (Implants: RR = 0.4/Sites: RR = 0.2). None of the included studies addressed patient-reported outcome measures.

Conclusions: The available evidence on reconstructive therapy at peri-implantitis-related defects is limited by (a) the low number of controlled studies, (b) the lack of controlled studies for commonly used procedures, (c) the heterogeneity between studies and (d) the choice of outcome measures. A high variability for predicted outcomes at 12 months was noted. The interpretation of the demonstrated larger MBL gain for test procedures is difficult as graft material may not be distinguishable from newly formed bone. Potential aesthetic and patient-reported advantages remain to be demonstrated.

KEYWORDS

bone regeneration, dental implant, peri-implantitis, reconstructive therapy

1 | INTRODUCTION

Peri-implantitis is a pathological condition occurring in tissues around dental implants. It is characterized by inflammation in the peri-implant connective tissue and progressive loss of supporting bone (Schwarz, Derks, Monje, & Wang, 2018). In a systematic review, a weighted mean patient prevalence of peri-implantitis of 22% was reported (Derks & Tomasi, 2015). The prevalence ranged from 1% to 47% in different reports, mainly due to the variation of case definitions among studies (Tomasi & Derks, 2012). It was suggested that peri-implantitis-associated bone loss was time-dependent and accelerated over time (Derks et al., 2016; Fransson et al., 2010).

The goal of peri-implantitis treatment is resolution of soft tissue inflammation and, subsequently, the prevention of further marginal bone loss. Non-surgical treatment modalities are frequently insufficient to achieve this objective (Faggion, Listl, Frühauf, Chang, & Tu, 2014; John, Becker, Schmucker, & Schwarz, 2017), while surgical procedures are considered more efficacious in the treatment of peri-implantitis (Faggion, Chambrone, Listl, & Tu, 2013; Lindhe & Meyle, 2008). The feasibility of a surgical approach has been extensively demonstrated in pre-clinical research (Albouy, Abrahamsson, Persson, & Berglundh, 2011; Carcuac, Abrahamsson, Charalampakis, & Berglundh, 2015; Persson, Araújo, Berglundh, Gröndahl, & Lindhe, 1999), and clinical efficacy has been documented in studies with substantial periods of follow-up (Berglundh, Wennström, & Lindhe, 2018; Roccuzzo, Pittoni, Roccuzzo, Charrier, & Dalmasso, 2017; Schwarz, John, Schmucker, Sahm, & Becker, 2017).

Outcomes of surgical therapy of peri-implantitis are reported to be influenced by implant surface characteristics (Carcuac et al., 2017; Roccuzzo et al., 2017) and by the configuration of the peri-implant bone defect (Schwarz, Sahm, Schwarz, & Becker, 2010). Bone defects associated with peri-implantitis commonly involve the whole circumference of the affected implant and have an angular outline on the mesial and distal aspects (Schwarz et al., 2007). Angular bone defects at teeth may have an overall different morphology, and studies have indicated that reconstructive techniques are successful in terms of clinical attachment gain and prevention of soft tissue recession (Reynolds et al., 2015). While the documentation of reconstructive surgery in the periodontal literature is extensive, evidence on its use at peri-implantitis sites is only emerging. The aim of the present systematic review was to evaluate the efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects.

Clinical Relevance

Scientific rationale for review: Peri-implantitis is a common complication in patients provided with implant-supported restorative therapy, and treatment commonly requires surgical access. *Principal findings*: Evidence on reconstructive therapy at peri-implantitis-related bone defects is limited. A benefit for reconstructive techniques over control procedures was observed for radiographic outcomes only. *Practical implications*: Clinicians should be aware of the lack of evidence suggesting improved aesthetic or patient-reported outcomes following reconstructive therapy at peri-implantitis-related bone defects.

2 | MATERIALS AND METHODS

2.1 | Protocol and eligibility

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were considered (Moher, Liberati, Tetzlaff, & Altman, 2009), and the protocol was registered at Prospero (CRD42018089236). The focused question of this systematic review was: What is the benefit of using a reconstructive technique as adjunct to surgical therapy of peri-implantitis?

2.2 | Inclusion criteria (PICOS)

2.2.1 | Population

Patients in good general health requiring treatment of peri-implantitis.

2.2.2 | Intervention

Reconstructive technique as adjunction to surgical therapy of peri-implantitis.

2.2.3 | Comparison

Surgical therapy of peri-implantitis alone (open-flap debridement).

2.2.4 | Outcomes

Changes of radiographic marginal bone level, clinical attachment level and soft tissue level. Reduction of probing depth and peri-implant bleeding on probing. Implant survival (in studies with a follow-up of ≥5 years).

2.2.5 | Study design

Randomized clinical trials (RCT), controlled clinical trials or prospective case series with at least 12 months of follow-up with a minimum of 10 patients (5 per group in controlled studies).

2.3 | Exclusion criteria

- Pre-clinical studies.
- Surgical therapy of peri-implantitis applying pocket elimination.
- Articles published in languages other than English.

2.4 | Interventions and comparisons

Studies on reconstructive techniques in the surgical therapy of peri-implantitis were considered. The following procedures and possible combinations were accepted: (a) bone grafting (autologous, allogeneic or xenogeneic); (b) guided bone regeneration; and (c) use of biological agents/growth factors.

Primarily, the outcomes of reconstructive therapy were compared to results after identical surgical interventions omitting the reconstructive technique (control: open-flap debridement). In a second step, the overall outcome of reconstructive therapy was evaluated by comparing pre-surgical findings with outcomes at 12 months.

2.5 | Outcome measures

Outcomes at 12 months following surgical therapy of peri-implantitis were extracted. The primary outcome was change of radiographic marginal bone level (MBL) expressed in mm. We further considered fill of the bone defect expressed as a percentage. Additional secondary outcomes were changes of clinical attachment level (CAL), changes of soft tissue level (REC), changes of bleeding on probing (BOP), changes of suppuration on probing (SUP) and changes of probing depth (PD). Combinations of outcomes, that is composite outcomes (absence of additional bone loss, absence of inflammation and shallow probing), and patient-reported outcome measures (PROMs) were also considered. Implant survival was assessed in studies with a follow-up of ≥5 years.

2.6 | Search strategy

Three electronic databases were searched for relevant articles in February 2018 using the following search algorithms.

2.6.1 | MEDLINE via PubMed (2018-02-20)

(peri-implantitis OR periimplantitis OR peri implantitis) AND (surgical treatment OR surgery OR surgical OR reconstructive OR regenerative OR regeneration) NOT (retrospective OR review OR in vitro OR case report OR orthopedic OR animal OR experimental)

Filter: English

2.6.2 | Web of science (2018-02-20)

((peri-implantitis OR periimplantitis OR peri implantitis) AND (surgical treatment OR surgery OR surgical OR reconstructive OR regenerative OR regeneration))

Refined by: WEB OF SCIENCE CATEGORIES: (DENTISTRY ORAL SURGERY MEDICINE) AND DOCUMENT TYPES: (ARTICLE) AND LANGUAGES: (ENGLISH)

2.6.3 | Cochrane central register of controlled trials (2018-02-20)

(peri-implantitis OR periimplantitis OR peri implantitis) AND (surgical treatment OR surgery OR surgical OR reconstructive OR regenerative OR regeneration)

In addition, a hand search was performed including reference lists and previous systematic reviews. Titles of all identified articles were screened for eligibility. Abstracts were then studied and selected independently by two reviewers (CT & JD). Relevant articles were analysed in full text and, again, independently selected for inclusion. The level of agreement for the two selections was expressed by *k*-scores. Disagreement was resolved by discussion.

2.7 | Data extraction

Two reviewers (ER & JD) extracted data from included articles and entered relevant information into pre-defined evidence tables. Studies were sorted according to design (controlled studies vs. studies without controls), and outcomes at 12 months were illustrated for all study arms. For controlled studies, potential benefits of test procedures were highlighted. We specifically focused on inclusion and exclusion criteria for each of the study samples in order to evaluate potential heterogeneity among the sampled populations. In case of missing data/information, authors were contacted.

2.8 | Quality assessment

One reviewer (AOV) assessed the risk of bias for included studies. For randomized trials, criteria described in the Cochrane Handbook (Higgins et al., 2011) were used. In six categories (sequence generation, allocation concealment, detection bias, attrition bias, selective reporting bias and other potential risk of bias), a rating of low, unclear or high risk of bias was performed.

For studies lacking controls, that is observational studies, risk of bias was assessed using a modified version of the Newcastle-Ottawa Scale for cohort studies (Wells et al., 2014). Thus, five items (representativeness of cohort, ascertainment of exposure, outcome at start of study, comparability of cohorts and assessment of outcome) were scored as present, not present or not applicable.

2.9 | Risk of bias across studies

The publication bias was evaluated using funnel plots for the outcomes: (a) changes of MBL and (b) PD reduction. A sensitivity analysis of the meta-analysis results was also performed, if plausible, by selectively excluding studies from the different analyses.

2.10 | Data analysis

For continuous outcomes at 12 months (changes of MBL, defect fill, CAL, REC and PD), mean values and standard deviations were pooled

and analysed with weighted mean differences (WMD) and 95% confidence intervals (CIs). For dichotomous data (BOP), the estimates of the effect were expressed as risk ratios (RR) and 95% CIs. Study-specific estimates were pooled with both the fixed- and random-effects models (DerSimonian & Laird, 1986), and the random-effects model results were presented.

We performed two different sets of analyses. Primarily, controlled studies were used to evaluate the potential benefit of reconstructive surgical therapy. For this analysis, no distinction was made between the different surgical techniques. Open-flap debridement was considered as control. Secondly, the outcome of reconstructive surgical therapy was assessed by comparing baseline values with outcomes at 12 months. In this analysis, controlled studies and studies without controls were included. For studies with multiple arms, each reconstructive intervention was considered separately. Further, sensitivity analysis was performed by considering studies with and without controls separately.

Statistical heterogeneity among studies was explored by the I^2 index (Higgins, Thompson, Deeks, & Altman, 2003) and Cochrane's Q statistic ($p < 0.1$). Forest plots were used to illustrate the outcomes of the analyses. Results were combined with random-effects meta-analysis, reporting tau-squared (between studies variance

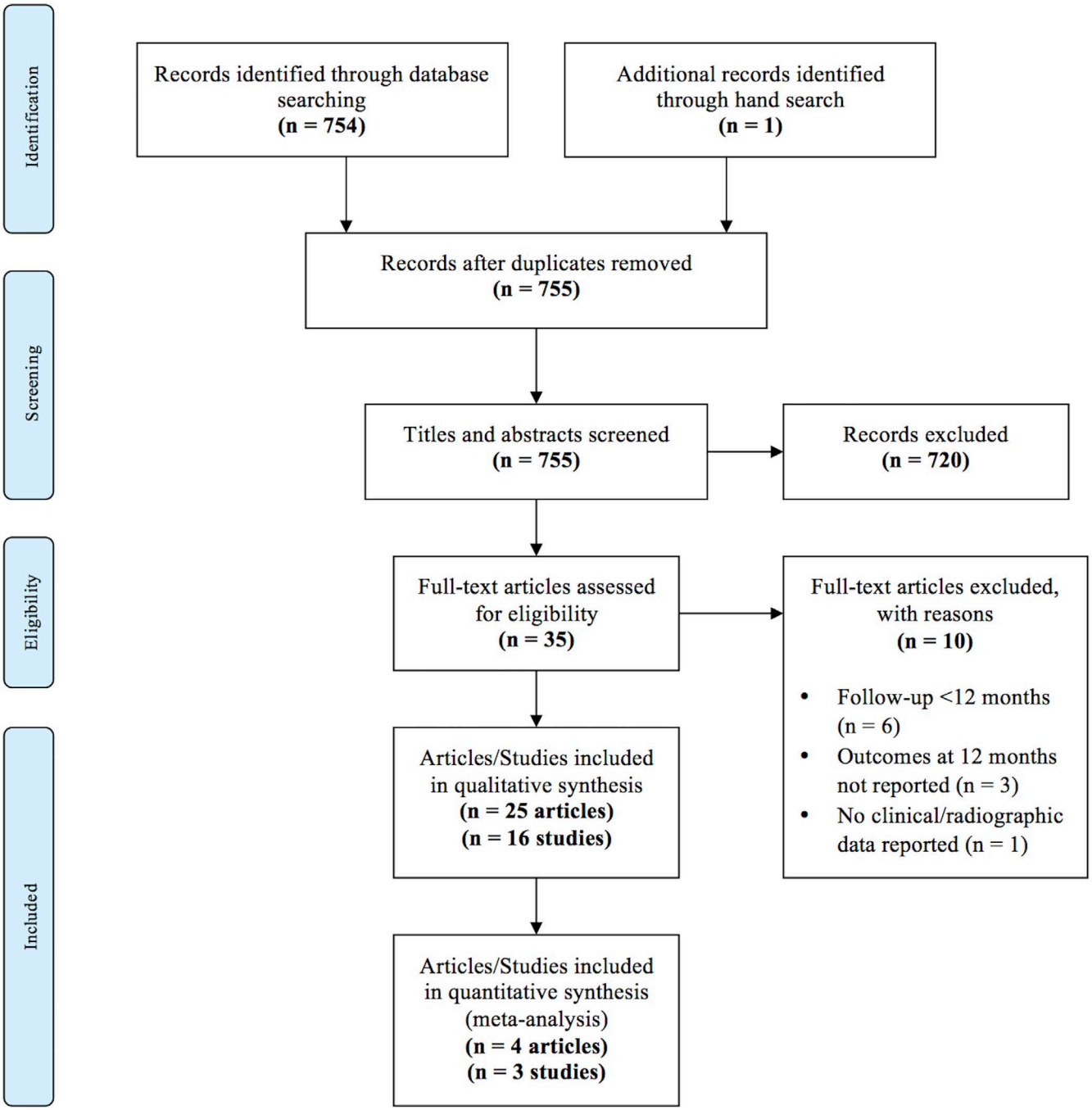


FIGURE 1 PRISMA flow diagram depicting the selection process

TABLE 1 Included studies: Outcomes reported in controlled studies (*n* = 4 articles, *n* = 3 studies)

Study	Arms	Number of observations *at 12 months*	Outcomes *at 12 months*	Benefit of test procedure *at 12 months*	Comments
Isehed et al. (2016)	Open-flap debridement	13 patients 13 implants	ΔMBL: −0.2 ± 1.1 mm ΔPD: −4.0 ± 2.9 mm ΔBOP% (implants): −20 ΔSUP% (implants): −36	ΔMBL: 0.5 mm ΔPD: 1.5 mm (in favour of control group) ΔBOP% (implants): 0 ΔSUP% (implants): 17	Mean ΔMBL and ΔPD kindly provided by the authors. BOP/SUP positive if present at any site of implant. REC and PROMs not reported. No systemic antibiotics prescribed.
	Enamel matrix derivative	12 patients 12 implants	ΔMBL: −0.7 ± 1.1 mm ΔPD: −2.5 ± 2.0 mm ΔBOP% (implants): −20 ΔSUP% (implants): −53		
Jepsen et al. (2016)	Open-flap debridement	26 patients 26 implants	ΔMBL: −1.0 ± 1.4 mm (mesial), −0.8 ± 1.1 mm (distal) %Defect fill: 23.1 ± 46.3 (mesial), 21.9 ± 30.2 (distal) ΔPD: −2.6 ± 1.4 mm ΔBOP% (sites): −44.9 ± 38.2 ΔBOP% (implants): −30.8 ΔSUP% (implants): −25.6 ± 32.7	ΔMBL: 2.6 mm (mesial), 2.7 mm (distal) %Defect fill: 55.9 (mesial), 52.3 (distal) ΔPD: 0.2 mm ΔBOP% (sites): 11.2 ΔBOP% (implants): 0 ΔSUP% (implants): 2.4 (in favour of control group)	Composite outcome (BOP-, PD < 5 mm and absence of additional bone loss) Control: 23.0% of implants Test: 30.3% of implants BOP% based on 6 sites/implant. BOP/SUP positive if present at any site of implant. REC and PROMs not reported. Systemic antibiotics prescribed
	Porous titanium granules	33 patients 33 implants	ΔMBL: −3.6 ± 2.1 mm (mesial), −3.5 ± 2.2 mm (distal) %Defect fill: 79.0 ± 29.9 (mesial), 74.2 ± 36.3 (distal) ΔPD: −2.8 ± 1.3 mm ΔBOP% (sites): −56.1 ± 30.5 ΔBOP% (implants): −30.3 ΔSUP% (implants): −23.2 ± 32.8		
Wohlfahrt et al. (2012) *12 months* also reported in: Andersen et al. (2017) *7 years*	Open-flap debridement	16 patients 16 implants	ΔMBL: −0.1 ± 1.9 mm %Defect fill: −14.8 ± 83.4 ΔPD: −2.0 ± 2.3 mm ΔBOP (sites): −0.56 ± 2.9	ΔMBL: 1.9 mm %Defect fill: 71.8 ΔPD: 0.3 mm (in favour of control group) ΔBOP (sites): 0.18 (in favour of control group)	BOP expressed as mean number of positive sites (out of 6) per implant. SUP, REC and PROMs not reported. Systemic antibiotics prescribed. Submerged healing for 6 months following surgery. 17/32 patients attended the 7-year examination: 3 implants in 3 patients (all in the test group) were lost during follow-up.
	Porous titanium granules	16 patients 16 implants	ΔMBL: −2.0 ± 1.7 mm %Defect fill: 57.0 ± 45.1 ΔPD: −1.7 ± 1.7 mm ΔBOP (sites): −0.38 ± 2.1		

Note. BOP: bleeding on probing; MBL: marginal bone level; PD: probing depth; REC: soft tissue level; PROMs: patient-reported outcome measures; SUP: suppuration on probing.

TABLE 2 Included studies: Outcomes reported in studies without controls (*n* = 21 articles, *n* = 13 studies)

Study	Groups	Number of observations *at 12 months*	Outcomes *at 12 months*	Comments
Aghazadeh et al. (2012)	Group 1: Autologous bone graft (particulate), resorbable membrane	22 patients 36 implants	ΔMBL: −0.2 mm (*SE*: 0.3) ΔPD: −2.0 mm (*SE*: 0.2) ΔBOP% (sites): −44.8 (*SE*: 6.3) ΔSUP% (sites): −11.5 (*SE*: 5.2)	Composite outcome 1 (BOP-, PD <5 mm and absence of additional bone loss) Group 1: 11.1% of implants Group 2: 20.5% of implants Composite outcome 2 (BOP+ at ≤1 site, PD <5 mm and absence of additional bone loss) Group 1: 13.9% of implants Group 2: 38.5% of implants BOP/SUP% based on 4 sites/implant. REC and PROMs not reported. Systemic antibiotics prescribed
	Group 2: Bovine bone mineral (particles), resorbable membrane	23 patients 39 implants	ΔMBL: −1.1 mm (*SE*: 0.3) ΔPD: −3.1 mm (*SE*: 0.2) ΔBOP% (sites): −50.4 (*SE*: 5.3) ΔSUP% (sites): −25.2 (*SE*: 4.2)	
Behneke et al. (2000)	Autologous bone graft (block or particulate), supporting screws or fibrin glue	Number of patients not reported 18 implants	ΔMBL: −3.9 mm ΔPD: −2.7 mm ΔCAL: −2.2 mm	*SE* or *SD* of mean changes not reported. BOP, SUP, REC and PROMs not reported. ΔREC calculated: 0.5 mm Outcomes at 12 months reported for subsample. Systemic antibiotics prescribed.
Khoury and Buchmann (2001)	Group 1: Autologous bone graft (block and particulate)	7 patients 12 implants	ΔMBL: −2.4 mm ΔPD: −5.4 mm ΔProbing bone level: −2.4 mm	*SE* or *SD* of mean changes not reported. BOP, SUP, REC and PROMs not reported. Systemic antibiotics prescribed
	Group 2: Autologous bone graft (block and particulate), ePTFE membrane	11 patients 20 implants	ΔMBL: −3.3 mm ΔPD: −4.8 mm ΔProbing bone level: −3.7 mm	
	Group 3: Autologous bone graft (block and particulate), collagen membrane	7 patients 9 implants	ΔMBL: −2.5 mm ΔPD: −3.3 mm ΔProbing bone level: −2.5 mm	
Matarasso et al. (2014)	Bovine bone mineral (particles), collagen membrane	11 patients 11 implants	ΔMBL: −2.8 mm %Defect fill: 93.3 ± 13.0 ΔREC: −1.3 mm ΔPD: −4.1 mm ΔCAL: −3.0 mm ΔBOP% (sites): −13.6	*SE* or *SD* of mean changes not reported. BOP% based on 6 sites/implant. 6 of 11 implants free of BOP prior to surgery. SUP and PROMs not reported. Systemic antibiotics prescribed
Nart et al. (2017)	Allograft (impregnated with vancomycin and tobramycine), collagen membrane	13 patients 17 implants	ΔMBL: −3.6 mm %Defect fill: 87.0 ± 18.2 ΔREC: −1.3 ± 0.5 mm ΔPD: −4.2 ± 1.5 mm ΔBOP% (sites): −70.6 ΔSUP% (sites): −100.0	*SE* or *SD* of mean changes not reported for all outcomes. BOP/SUP% based on 6 sites/implant. PROMs not reported. No systemic antibiotics prescribed

(Continued)

TABLE 2 (Continued)

Study	Groups	Number of observations *at 12 months*	Outcomes *at 12 months*	Comments
Roccuzzo et al. (2011) *12 months* also reported in: Roccuzzo et al. (2017) *7 years*	Group 1: TPS implants Bovine bone mineral (block)	14 patients 14 implants	ΔMBL: −1.6 ± 0.7 mm ΔPD: −2.1 ± 1.2 mm ΔBOP% (sites): −33.9 ΔSUP% (implants): −60.0	BOP% based on 4 sites/implant. SUP expressed as % of implants demonstrating suppuration. REC and PROMs not reported. Systemic antibiotics prescribed. 24/26 patients attended the 7-year examination: 4 implants in 4 patients (2 in each group) were lost during follow-up
	Group 2: SLA implants Bovine bone mineral (block)	12 patients 12 implants	ΔMBL: −1.9 ± 1.3 mm ΔPD: −3.4 ± 1.7 mm ΔBOP% (sites): −60.4 ΔSUP% (implants): −100.0	
Roccuzzo et al. (2016)	Bovine bone mineral (block)	71 patients 71 implants	ΔPD: −2.9 ± 1.7 mm ΔBOP% (sites): −53.2 ΔSUP% (implants): −35.5	Composite outcome 1 (BOP- and PD ≤5 mm) 49.3% of implants Composite outcome 2 (BOP- and PD ≤6 mm) 56.0% of implants BOP% based on 4 sites/implants. SUP expressed as % of implants demonstrating suppuration. MBL, REC and PROMs not reported. ΔREC for different defect categories varied from 0.5 mm to 0.9 mm. Estimated mean: 0.69 ± 0.76 mm. Systemic antibiotics prescribed
Roos-Jansåker et al. (2007a)	Hydroxyapatite, resorbable membrane	12 patients 16 implants	ΔMBL: −2.3 ± 1.2 mm ΔREC: −2.8 ± 1.4 mm ΔPD: −4.2 ± 1.5 mm ΔCAL: −1.4 ± 1.7 mm ΔBOP% (implants): −62.5	BOP expressed as % of bleeding at deepest site of implant. SUP and PROMs not reported. Systemic antibiotics prescribed. Submerged healing for 6 months following surgery.
Roos-Jansåker et al. (2007b) *12 months* also reported in: Roos-Jansåker, Lindahl, Persson, and Renvert (2011) *3 years* Roos-Jansåker et al. (2014) *5 years*	Group 1: Hydroxyapatite, resorbable membrane	17 patients 29 implants	ΔMBL: −1.5 ± 1.2 mm ΔREC: −1.3 ± 1.5 mm ΔPD: −2.9 ± 2.0 mm ΔCAL: −1.6 ± 2.0 mm ΔBOP% (sites): −57.7	BOP% based on 4 sites/implant. SUP and PROMs not reported. Systemic antibiotics prescribed. 25/38 patients attended the 5-year examination: no implants were lost during follow-up
	Group 2: Hydroxyapatite	19 patients 36 implants	ΔMBL: −1.4 ± 1.3 mm ΔREC: −1.6 ± 1.6 mm ΔPD: −3.4 ± 1.6 mm ΔCAL: −1.8 ± 1.4 mm ΔBOP% (sites): −67.9	

(Continued)

TABLE 2 (Continued)

Study	Groups	Number of observations *at 12 months*	Outcomes *at 12 months*	Comments
Schwarz et al. (2008) *2 years* also reported in: Schwarz, Bieling, Latz, Nuesry, and Becker (2006) *6 months* Schwarz, Sahm, Bieling, and Becker (2009) *4 years*	Group 1: Hydroxyapatite	9 patients 9 implants	ΔREC: −0.4 ± 0.2 mm ΔPD: −2.0 ± 0.5 mm ΔCAL: −1.6 ± 0.3 mm ΔBOP% (sites): −44	BOP% based on 6 sites/implant. MBL, SUP and PROMs not reported. No systemic antibiotics prescribed
	Group 2: Bovine bone mineral (particles), collagen membrane	11 patients 11 implants	ΔREC: −0.3 ± 0.4 mm ΔPD: −2.7 ± 0.6 mm ΔCAL: −2.4 ± 0.7 mm ΔBOP% (sites): −49	
Schwarz et al. (2010)	Bovine bone mineral (particles), collagen membrane	27 patients 27 implants	Defect Class Ib (*n* = 9) ΔREC: −0.4 ± 0.7 mm ΔPD: −1.6 ± 0.9 mm ΔCAL: −1.2 ± 1.1 mm ΔBOP% (sites): −39.9 ± 16.6 Defect Class Ic (*n* = 9) ΔREC: −0.5 ± 0.5 mm ΔPD: −1.6 ± 0.7 mm ΔCAL: −1.1 ± 0.9 mm ΔBOP% (sites): −25.9 ± 14.7 Defect Class Ie (n = 9) ΔREC: −0.3 ± 0.6 mm ΔPD: −2.7 ± 0.7 mm ΔCAL: −2.4 ± 1.0 mm ΔBOP% (sites): −61.1 ± 16.7	BOP% based on 6 sites/implant. MBL, SUP and PROMs not reported. No systemic antibiotics prescribed
Schwarz et al. (2012) *2 years* also reported in: Schwarz, Sahm, Iglhaut, and Becker (2011) *6 months* Schwarz, Hegewald, John, Sahm, and Becker (2013) *4 years* Schwarz et al. (2017) *7 years*	Group 1: Implant surface decontamination with plastic curettes, cotton pellets and sterile saline Bovine bone mineral (particles), collagen membrane	14 patients	ΔREC: −0.5 ± 0.4 mm ΔPD: −2.0 ± 1.6 mm ΔCAL: −1.5 ± 1.6 mm ΔBOP% (sites): −60.1 ± 26.6	BOP% based on 6 sites/implant. MBL, SUP and PROMs not reported. No systemic antibiotics prescribed. 15/32 patients attended the 7-year examination: 4 patients were excluded between years 2 and 3 due to severe re-infection. No information on implant loss
	Group 2: Implant surface decontamination with Er:YAG laser Bovine bone mineral (particles), collagen membrane	10 patients	ΔREC: −0.4 ± 0.2 mm ΔPD: −1.7 ± 1.2 mm ΔCAL: −1.3 ± 1.2 mm ΔBOP% (sites): −55.0 ± 28.4	
Wiltfang et al. (2012)	Autologous bone graft (particulate), xenogeneic bone graft	22 patients 36 implants	ΔDefect depth: −3.5 mm (95% CI: −4.3/−2.7) ΔREC: −1.3 mm ΔPD: −4.0 mm (95% CI: −4.6/−3.3) ΔBOP% (implants): −36 ΔSUP% (implants): −72	*SE*, *SD* or CI of mean changes not reported for all outcomes. BOP/SUP positive if present at any site of implant. 39% implants free of BOP prior to surgery. MBL and PROMs not reported. Systemic antibiotics prescribed.

Note. BOP: bleeding on probing; CAL: clinical attachment level; CI: confidence interval; MBL: marginal bone level; PD: probing depth; PROMs: patient-reported outcome measures; REC: soft tissue level; SUP: suppuration on probing; *SE*: standard error; *SD*: standard deviation.

included in the analysis), which was used to calculate prediction intervals (Borenstein, Higgins, Hedges, & Rothstein, 2017). Statistical significance was set to $p < 0.05$. All analyses were performed with Review Manager (RevMan version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3 | RESULTS

3.1 | Search

Results of the search are illustrated in Figure 1. The electronic search yielded 754 titles. One additional article (Hamzacebi, Oduncuoglu, & Alaaddinoglu, 2015) was identified through the hand search, rendering an initial selection of 755 records. Following screening of titles and abstracts, 35 articles were selected for full-text analysis (kappa = 0.86). An additional 10 articles were excluded, resulting in a final selection of 25 articles describing 16 different studies. The reasons for exclusion are given in Table A-1. The agreement on the final selection was kappa = 0.87.

3.2 | Description of selected studies

3.2.1 | Design

The included studies are described in Tables 1 and 2. Out of the 16 relevant studies, three included controls and were designed as randomized controlled trials (Isehed et al., 2016; Jepsen et al., 2016; Wohlfahrt et al., 2012). Each study included one single experimental group, and open-flap debridement was provided to controls.

Of the 13 studies without controls, three were designed as randomized trials (Aghazadeh, Persson, & Renvert, 2012; Schwarz, John, Mainusch, Sahm, & Becker, 2012; Schwarz et al., 2008), while the remaining were observational studies. A total of four studies included multiple interventional arms (Aghazadeh et al., 2012; Khoury & Buchmann, 2001; Roos-Jansåker, Renvert, Lindahl, & Renvert, 2007b; Schwarz et al., 2008), comparing different reconstructive techniques with each other. One additional study compared the outcomes of one reconstructive technique at two different types of implants (Roccuzzo, Bonino, Bonino, & Dalmasso, 2011), while another two reported outcomes of treatment at different defect configurations (Roccuzzo, Gaudioso, Lungo, & Dalmasso, 2016; Schwarz et al., 2010). Schwarz et al. (2012) assessed two methods of surface decontamination prior to one reconstructive approach. The remaining five studies did not include any comparative analyses (Behneke, Behneke, & d'Hoedt, 2000; Matarasso, Iorio Siciliano, Aglietta, Andreuccetti, & Salvi, 2014; Nart, de Tapia, Pujol, Pascual, & Valles, 2017; Roos-Jansåker, Renvert, Lindahl, & Renvert, 2007a; Wiltfang et al., 2012)

3.2.2 | Study samples

Sample sizes varied from 29 to 63 patients for the controlled studies and from 11 to 75 patients for the studies lacking controls. Roughly, every second study included selected participants, while the remaining studies described consecutive patient enrolment. In 10 studies, patients with medical conditions (e.g., uncontrolled diabetes) were excluded. Heavy smoking was an exclusion criterion in 5 studies.

All studies were based exclusively on samples from European populations. Four studies reported on patients treated in a private practice setting, while the others reported on patients treated in a specialist or university setting. One study (Jepsen et al., 2016) included multiple centres, while the remaining investigations were performed at single clinical centres. A formal power calculation was described in six (Aghazadeh et al., 2012; Isehed et al., 2016; Jepsen et al., 2016; Schwarz et al., 2010, 2012; Wohlfahrt et al., 2012) of the 16 included studies.

Mean age of included patients ranged from 48 to 71 years, and the ratio between males and females included varied from 0.9 to 0.1. The proportion of smokers ranged from 15% to 70%. In 5 studies, only one single type of implant was included, while 2 to 11 different implant brands were treated in the remaining studies. Prerequisites for the peri-implant defects to be treated varied considerably between studies. Eight studies, for instance, did not specify the presence of signs of inflammation (e.g., BOP) for inclusion. All studies but two (Roos-Jansåker et al., 2007a,b), however, required the presence of an angular bone defect. Requirements in terms of depth of the bone defect ranged from a minimum of 3 to 4 mm. Two studies (Jepsen et al., 2016; Nart et al., 2017) further specified the peri-implant defects in terms of configuration (for details, see Table A-2).

3.2.3 | Interventions

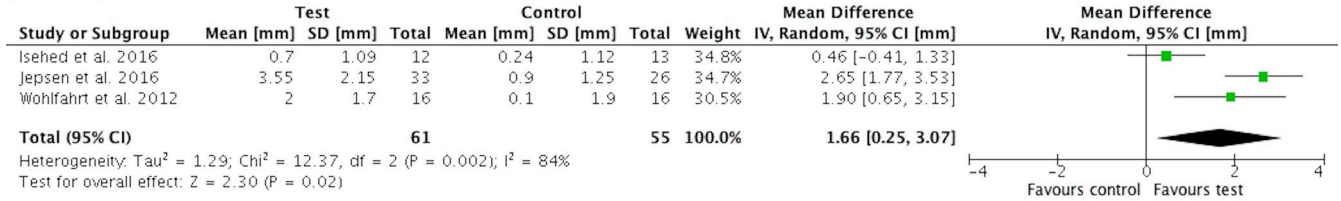
In two of the three controlled studies, porous titanium granules were used in the intervention groups (Jepsen et al., 2016; Wohlfahrt et al., 2012), while the third evaluated the potential benefit of enamel matrix derivate (Isehed et al., 2016).

All of the studies without controls used bone replacement grafts, either alone (Behneke et al., 2000; Khoury & Buchmann, 2001; Roccuzzo et al., 2011, 2016; Roos-Jansåker et al., 2007b; Schwarz et al., 2008; Wiltfang et al., 2012) or in combination with membranes (Aghazadeh et al., 2012; Khoury & Buchmann, 2001; Matarasso et al., 2014; Nart et al., 2017; Roos-Jansåker et al., 2007a,b; Schwarz et al., 2008, 2010, 2012). The most commonly used graft material was bovine bone mineral as particles (Aghazadeh et al., 2012; Matarasso et al., 2014; Schwarz et al., 2008, 2010, 2012) or as a block (Roccuzzo et al., 2011, 2016). Hydroxyapatite and autologous bone grafts were applied in 3 (Roos-Jansåker et al., 2007a,b; Schwarz et al., 2008) and four (Aghazadeh et al., 2012; Behneke et al., 2000; Khoury & Buchmann, 2001; Wiltfang et al., 2012) studies, respectively. One study described the use of an allograft (Nart et al., 2017).

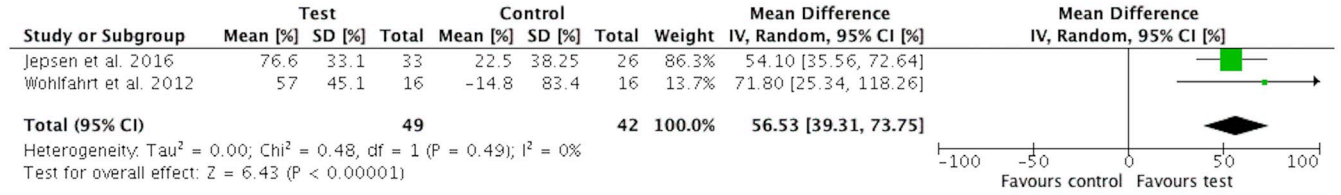
3.3 | Risk of bias in individual studies

The assessment of risk of bias in the included randomized trials is illustrated in Table A-3. A low risk of bias was noted in one study only (Isehed et al., 2016), based on the apparent difficulty to blind

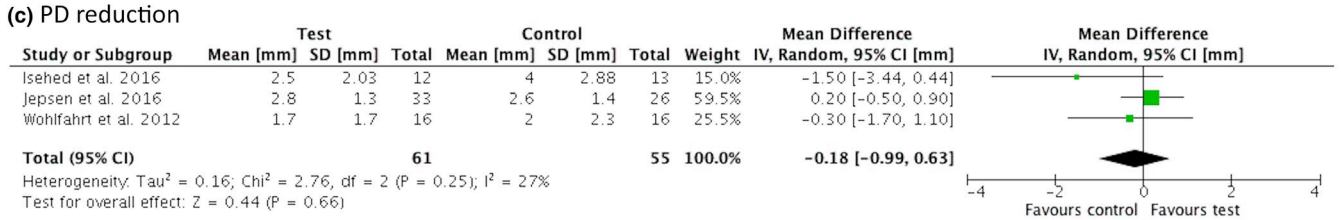
(a) Change of MBL



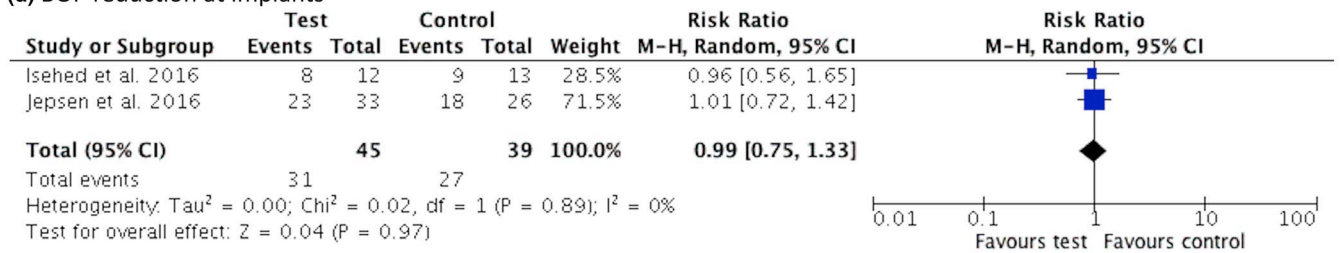
(b) Defect reduction/defect fill



(c) PD reduction



(d) BOP reduction at implants



(e) BOP reduction at implant sites

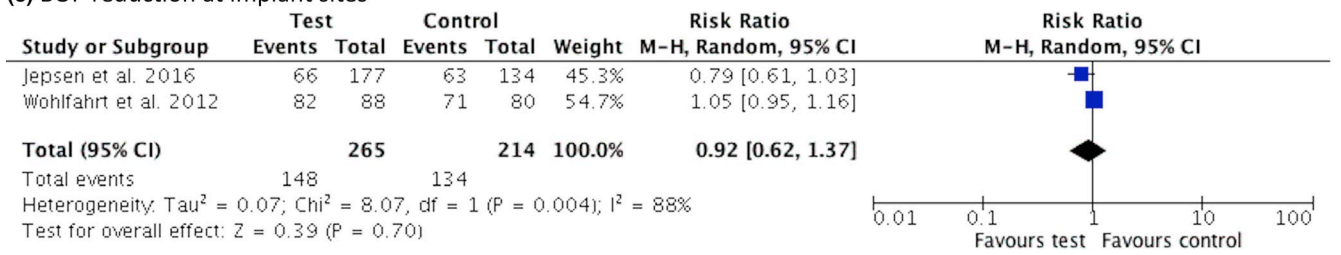


FIGURE 2 (a) Forest plot. Potential benefit in terms of change of MBL (studies with controls). Unit of analysis: implant. Additional data kindly provided by Isehed et al. (2016). For Jepsen et al. (2016): average of mesial and distal. (b) Forest plot. Potential benefit in terms of defect reduction/defect fill [%] (studies with controls). Unit of analysis: implant. For Jepsen et al. (2016): average of mesial and distal. (c) Forest plot. Potential benefit in terms of PD reduction (studies with controls). Unit of analysis: implant. Additional data kindly provided by Isehed et al. (2016). For Jepsen et al. (2016): average of mesial and distal. (d) Forest plot. Potential benefit in terms of BOP reduction at implants (studies with controls). Unit of analysis: implant. Number of events estimated based on reported percentages. (e). Forest plot. Potential benefit in terms of BOP reduction at implant sites (studies with controls). Unit of analysis: implant site. Number of events estimated based on reported percentages or numbers

the examiner during radiological assessments in the studies evaluating bone replacement grafts (detection bias). In addition, a substantial patient dropout was noted for the long-term follow-up (7 years) for two studies (Andersen, Aass, & Wohlfahrt, 2017; Schwarz et al., 2017). This, however, was not relevant for outcomes at 12 months.

The quality of reporting in the selected observational studies is depicted in Table A-4. Three of the studies (Roccuzzo et al., 2016; Schwarz et al., 2010; Wiltfang et al., 2012) met all of the quality categories.

3.4 | Risk of bias across studies

No significant publication bias was observed for the three controlled studies in terms of change of MBL and PD reduction (Figure A-1a and

b). Considering only reconstructive interventions from controlled and uncontrolled studies, the funnel plots indicated no significant publication bias for change of MBL but indicated a significant bias for PD reduction (Figure A-2a and b).

3.5 | Potential benefit of reconstructive surgical therapy

The analysis included a total of 116 implants for the primary outcome. For the secondary outcomes, the number of included implants varied from 84 to 116. Heterogeneity among studies expressed as I^2 varied from 0% to 88%, depending on the outcome measure.

3.5.1 | Primary outcome: change of radiographic marginal bone level

Figure 2a illustrates the results of the meta-analysis for changes of MBL. All three studies with controls reported on the primary outcome. A statistically significant benefit (WMD = 1.7 mm; 95% CI: 0.3/3.1; $p = 0.02$) was observed in favour of the reconstructive interventions.

3.5.2 | Secondary outcomes

Defect fill was reported in two of the studies with controls (Figure 2b), indicating a statistically significant greater fill at test sites (WMD = 56.5%; 95% CI: 39.3/73.8; $p < 0.001$). The analysis failed to identify a significant benefit in terms of PD reduction, based on data from all three studies (Figure 2c). Similar findings were made for BOP reduction. The RR for BOP reduction was 1.0 (95% CI: 0.8/1.3; $p = 0.97$) and 0.9 (95% CI: 0.6/1.4; $p = 0.70$) for implants and implant sites, respectively (Figures 2d and e). None of the studies with controls reported on changes of CAL, REC or PROMs. Implant survival over at least 5 years was described in one of the interventional studies (Andersen et al., 2017). Over a 7-year follow-up, 3 of 17 implants were lost in three patients, all belonging to the test group (porous titanium granules).

3.6 | Outcome of reconstructive surgical therapy

The analysis included a total of 433 implants for the primary outcome. For the secondary outcomes, the number of included implants varied from 147 to 821. Heterogeneity among studies, namely the percentage of variation due to a true variation between treatment effects in relation to the variation due to sampling error, varied from 51% to 95%.

3.6.1 | Primary outcome: change of radiographic marginal bone level

Figure 3a illustrates the reduction of MBL from baseline to 12 months postsurgery. Based on 11 arms in seven studies, the WMD amounted to 2.0 mm (95% CI: 1.3/2.7; $p < 0.001$). The prediction interval, that is the expected range of the outcome of treatment applied to a random subject of the overall studied population, was −0.4/4.4 mm. Estimates were consistent, regardless of study design.

3.6.2 | Secondary outcomes

A CAL gain of 1.8 mm (95% CI: 1.3/2.2; $p < 0.001$) with a prediction interval of 0.6/3.0 (Figure 3b) was observed based on findings from four studies. Change of REC was assessed in six studies (10 arms) and amounted to −0.7 mm (95% CI: −1.0/−0.3; $p < 0.001$) (Figure 3c). The prediction interval was −1.7/0.4. PD reduction is illustrated in Figure 3d. The weighted mean effect was 2.8 mm (95% CI: 2.3/3.4; $p < 0.001$) at 12 months, based on 21 arms in 13 studies. The prediction interval was estimated to be 0.4/5.3 mm. Reduction of inflammation at 12 months was statistically significant. The RR for BOP was 0.4 (95% CI: 0.2/0.8; $p = 0.004$) and 0.2 (95% CI: 0.2/0.4; $p < 0.001$) for implants and implant sites, respectively (Figure 3e and f). The respective prediction intervals were 0.1/2.3 and 0.0/1.7. Results of the sensitivity analysis revealed that the RR for BOP for implants was considerably lower in studies with controls (0.07; 95% CI: 0.0/0.5) than without (0.51; 95% CI: 0.3/0.8).

None of the studies without controls reported on defect fill or PROMs, while implant survival over at least 5 years was described in two. Results ranged from 83% (Roccuzzo et al., 2017) to 100% (Roos-Jansåker, Persson, Lindahl, & Renvert, 2014) on the implant level.

4 | DISCUSSION

The present systematic review aimed at evaluating the efficacy of reconstructive surgical therapy at peri-implantitis-related bone defects. The potential benefit of reconstructive techniques over control procedures was evaluated in three studies, representing a total of 116 implants. Altogether, 16 studies reported on the outcome of reconstructive measures at 12 months after surgery. The meta-analyses identified a statistically significant larger MBL gain (WMD = 1.7 mm) and defect fill (WMD = 57%) for test procedures, but found no differences for clinical measures (PD reduction, BOP reduction). Changes of clinical attachment and soft tissue levels were not considered.

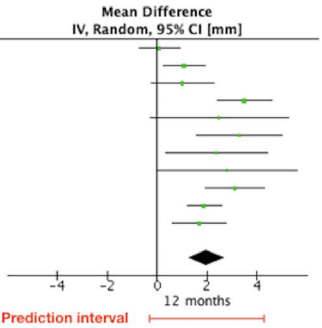
In terms of overall outcome, therapy resulted in improved MBL (WMD = 2.0 mm) and CAL (WMD = 1.8 mm), in recession (WMD = 0.7 mm), in reduced PD (WMD = 2.8 mm) and in reduced BOP (Implants: RR = 0.4/Sites: RR = 0.2). None of the included studies addressed patient-reported outcome measures.

Results of the present meta-analyses are in line with calculations presented in previously published systematic reviews on the topic (Chan, Lin, Suárez, MacEachern, & Wang, 2014; Khoshkam et al., 2013, 2016; Sahrmann, Attin, & Schmidlin, 2011). The present analysis suggests that reconstructive therapy at peri-implantitis-related defects is a feasible concept, but it is also obvious that the available evidence is limited. The majority of studies identified in the present review was observational and had the characteristics of case series.

(a) Change of MBL

Study or Subgroup	Baseline Mean [mm]	Baseline SD [mm]	Baseline Total	12 months Mean [mm]	12 months SD [mm]	12 months Total	Weight	Mean Difference IV, Random, 95% CI [mm]
Aghazadeh et al. 2012 (Autologous bone graft)	5.85	1.7	36	5.75	1.8	36	11.8%	0.10 [-0.71, 0.91]
Aghazadeh et al. 2012 (Bovine bone material)	5.25	1.8	39	4.15	1.87	39	11.7%	1.10 [0.29, 1.91]
Isehed et al. 2016	5.83	1.92	15	4.8	1.39	12	9.8%	1.03 [-0.22, 2.28]
Jepsen et al. 2016	5.48	2.51	33	1.97	1.97	33	10.5%	3.51 [2.42, 4.60]
Khoury & Buchmann 2001 (Autologous bg & col mem)	6.4	3.2	9	3.9	2.8	9	4.5%	2.50 [-0.28, 5.28]
Khoury & Buchmann 2001 (Autologous bg & ePTFE)	5.1	3.1	20	1.8	2.4	20	7.8%	3.30 [1.58, 5.02]
Khoury & Buchmann 2001 (Autologous bone graft)	3.5	3.4	12	1.1	1.2	12	6.6%	2.40 [0.36, 4.44]
Matarasso et al. 2013	8	3.7	11	5.2	3	11	4.5%	2.80 [-0.01, 5.61]
Nart et al. 2017	4.29	2.11	17	1.16	1.34	17	10.1%	3.13 [1.94, 4.32]
Roccuzzo et al. 2011 (SLA implants)	3	0.9	12	1.1	0.8	12	12.3%	1.90 [1.22, 2.58]
Roccuzzo et al. 2011 (TPS implants)	3.9	1.6	14	2.2	1.3	14	10.5%	1.70 [0.62, 2.78]
Total (95% CI)			**218**			**215**	**100.0%**	**1.99 [1.27, 2.71]**

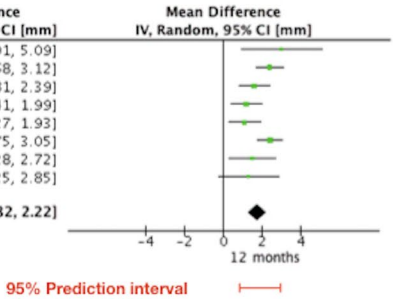
Heterogeneity: Tau² = 0.99; Chi² = 39.42, df = 10 (P < 0.0001); I² = 75%
Test for overall effect: Z = 5.40 (P < 0.00001)



(b) CAL gain

Study or Subgroup	Baseline Mean [mm]	Baseline SD [mm]	Baseline Total	12 months Mean [mm]	12 months SD [mm]	12 months Total	Weight	Mean Difference IV, Random, 95% CI [mm]
Matarasso et al. 2013	9.7	2.5	11	6.7	2.5	11	4.0%	3.00 [0.91, 5.09]
Schwarz et al. 2008 (Bone graft & membrane)	7.5	1	11	5.1	0.7	11	16.7%	2.40 [1.68, 3.12]
Schwarz et al. 2008 (Bone graft)	7.3	0.8	9	5.7	0.9	9	15.4%	1.60 [0.81, 2.39]
Schwarz et al. 2010 (Class Ib)	7.1	0.9	9	5.9	0.8	9	15.4%	1.20 [0.41, 1.99]
Schwarz et al. 2010 (Class Ic)	7.5	0.9	9	6.4	0.9	9	14.6%	1.10 [0.27, 1.93]
Schwarz et al. 2010 (Class Ie)	7.5	0.8	9	5.1	0.6	9	18.0%	2.40 [1.75, 3.05]
Schwarz et al. 2012 (Hand instruments)	6.5	2	14	5	1.2	14	9.3%	1.50 [0.28, 2.72]
Schwarz et al. 2012 (Laser)	6.4	2	10	5.1	1.5	10	6.6%	1.30 [-0.25, 2.85]
Total (95% CI)			**82**			**82**	**100.0%**	**1.77 [1.32, 2.22]**

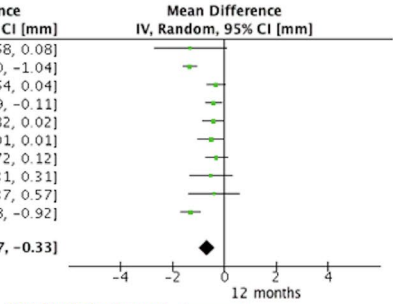
Heterogeneity: Tau² = 0.18; Chi² = 13.00, df = 7 (P = 0.07); I² = 46%
Test for overall effect: Z = 7.70 (P < 0.00001)



(c) REC

Study or Subgroup	Baseline Mean [mm]	Baseline SD [mm]	Baseline Total	12 months Mean [mm]	12 months SD [mm]	12 months Total	Weight	Mean Difference IV, Random, 95% CI [mm]
Matarasso et al. 2013	1.7	1.5	11	3	1.8	11	3.9%	-1.30 [-2.68, 0.08]
Nart et al. 2017	0.1	0.31	17	1.42	0.5	17	12.8%	-1.32 [-1.60, -1.04]
Schwarz et al. 2008 (Bone graft & membrane)	0.4	0.3	11	0.7	0.5	11	12.2%	-0.30 [-0.64, 0.04]
Schwarz et al. 2008 (Bone graft)	0.4	0.2	9	0.8	0.4	9	12.7%	-0.40 [-0.69, -0.11]
Schwarz et al. 2010 (Class Ib)	0.4	0.5	9	0.8	0.4	9	11.4%	-0.40 [-0.82, 0.02]
Schwarz et al. 2010 (Class Ic)	0.4	0.5	9	0.9	0.6	9	10.4%	-0.50 [-1.01, 0.01]
Schwarz et al. 2010 (Class Ie)	0.5	0.5	9	0.8	0.4	9	11.4%	-0.30 [-0.72, 0.12]
Schwarz et al. 2012 (Hand instruments)	1.3	1.1	14	1.8	1.1	14	7.4%	-0.50 [-1.31, 0.31]
Schwarz et al. 2012 (Laser)	1.5	1	10	1.9	1.2	10	6.2%	-0.40 [-1.37, 0.57]
Wiltfang et al. 2012	0.7	0.6	36	2	1	36	11.8%	-1.30 [-1.68, -0.92]
Total (95% CI)			**135**			**135**	**100.0%**	**-0.65 [-0.97, -0.33]**

Heterogeneity: Tau² = 0.19; Chi² = 45.04, df = 9 (P < 0.00001); I² = 80%
Test for overall effect: Z = 3.99 (P < 0.0001)



(d) PD reduction

Study or Subgroup	Baseline Mean [mm]	Baseline SD [mm]	Baseline Total	12 months Mean [mm]	12 months SD [mm]	12 months Total	Weight	Mean Difference IV, Random, 95% CI [mm]
Aghazadeh et al. 2012 (Autologous bone graft)	6	1.3	36	3.8	1.2	36	5.0%	2.20 [1.62, 2.78]
Aghazadeh et al. 2012 (Bovine bone material)	6.2	1.4	39	3.3	1.25	39	5.0%	2.90 [2.31, 3.49]
Isehed et al. 2016	6.83	0.99	15	4.25	1.56	12	4.4%	2.58 [1.57, 3.59]
Jepsen et al. 2016	6.3	1.3	33	3.5	1.5	33	4.9%	2.80 [2.12, 3.48]
Khoury & Buchmann 2001 (Autologous bg & col mem)	7.7	0.5	9	4.4	0.8	9	5.0%	3.30 [2.68, 3.92]
Khoury & Buchmann 2001 (Autologous bg & ePTFE)	8.2	1	20	3.4	1.2	20	4.9%	4.80 [4.12, 5.48]
Khoury & Buchmann 2001 (Autologous bone graft)	8	0.5	12	2.6	0.5	12	5.2%	5.40 [5.00, 5.80]
Matarasso et al. 2013	8.1	1.8	11	4	1.3	11	4.0%	4.10 [2.79, 5.41]
Nart et al. 2017	6.48	1.26	17	3.45	0.43	17	4.9%	3.03 [2.40, 3.66]
Roccuzzo et al. 2011 (SLA implants)	6.8	1.2	12	3.4	1	12	4.6%	3.40 [2.52, 4.28]
Roccuzzo et al. 2011 (TPS implants)	7.2	1.5	14	5.1	2	14	4.0%	2.10 [0.79, 3.41]
Roccuzzo et al. 2016	7.17	1.61	71	4.24	1.36	71	5.1%	2.93 [2.44, 3.42]
Schwarz et al. 2008 (Bone graft & membrane)	7.1	0.8	11	4.4	0.6	11	5.0%	2.70 [2.11, 3.29]
Schwarz et al. 2008 (Bone graft)	6.9	0.6	9	4.9	0.8	9	4.9%	2.00 [1.35, 2.65]
Schwarz et al. 2010 (Class Ib)	6.7	0.7	9	5.1	0.6	9	5.0%	1.60 [1.00, 2.20]
Schwarz et al. 2010 (Class Ic)	7.1	0.6	9	5.5	0.5	9	5.1%	1.60 [1.09, 2.11]
Schwarz et al. 2010 (Class Ie)	7	0.5	9	4.3	0.5	9	5.1%	2.70 [2.24, 3.16]
Schwarz et al. 2012 (Hand instruments)	5.2	1.5	14	3.2	0.4	14	4.7%	2.00 [1.19, 2.81]
Schwarz et al. 2012 (Laser)	4.9	1.4	10	3.2	0.8	10	4.5%	1.70 [0.70, 2.70]
Wiltfang et al. 2012	7.5	1.77	36	3.5	1.18	36	4.9%	4.00 [3.31, 4.69]
Wohlfahrt et al. 2012	6.5	1.9	16	4.9	1.8	16	4.0%	1.60 [0.32, 2.88]
Total (95% CI)			**412**			**409**	**100.0%**	**2.84 [2.32, 3.37]**

Heterogeneity: Tau² = 1.34; Chi² = 265.60, df = 20 (P < 0.00001); I² = 92%
Test for overall effect: Z = 10.64 (P < 0.00001)

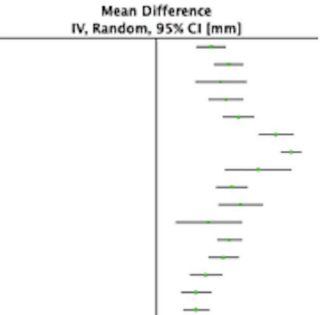
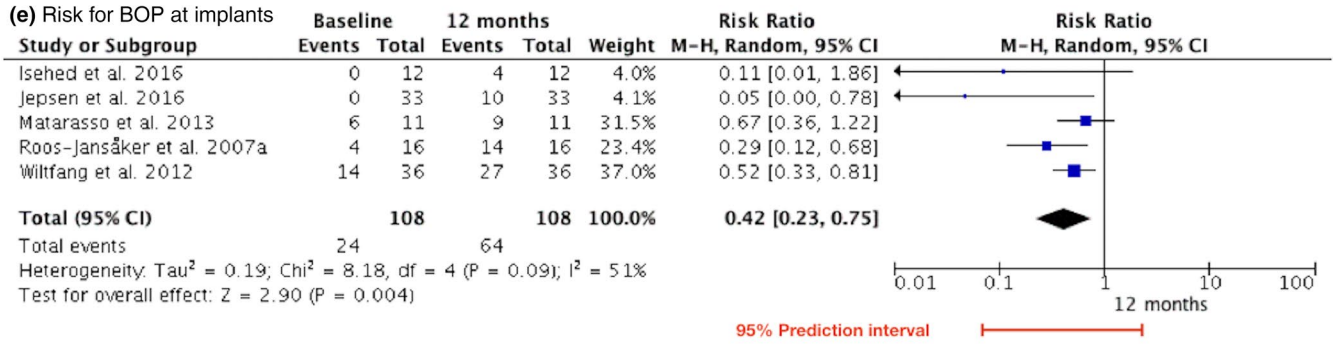


FIGURE 3 (continued)

Only three of the included studies were randomized controlled trials addressing the scientific question of the present review, that is the potential benefit of reconstructive measures over open-flap debridement alone. None of the included study samples originated from outside of Europe, which represents a limitation in terms of generalizability. In addition, most studies were conducted at specialist or university clinics. The significant heterogeneity within and between samples may in part be attributed to the different techniques and materials used and



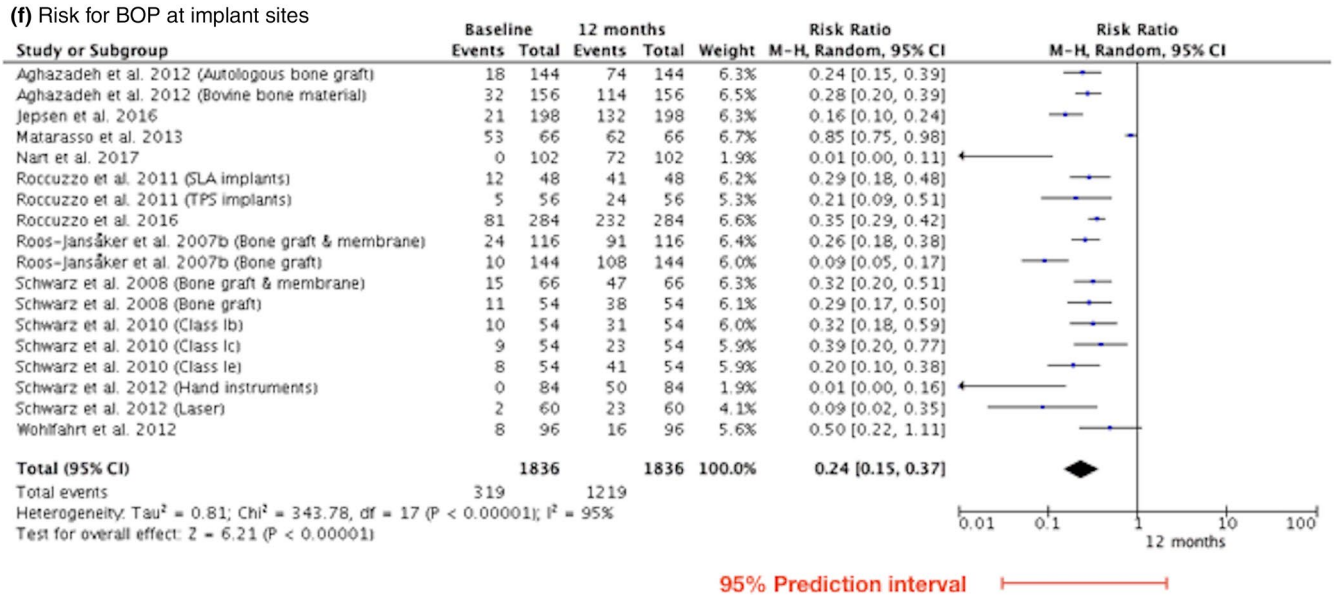


FIGURE 3 (a) Forest plot. Reduction of MBL (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Additional data kindly provided by Isehed et al. (2016). Not considered: Baseline and/or 12-month bone levels (mean) not reported: Roccuzzo et al. (2016), Roos-Jansåker et al. (2007a,b), Schwarz et al. (2008, 2010, 2012), Wiltfang et al. (2012), Wohlfahrt et al. (2012). *SE* or *SD* of mean values not reported: Behneke et al. (2000). (b) Forest plot. CAL gain (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Not considered: Baseline and/or 12-month clinical attachment levels (mean) not reported: Aghazadeh et al. (2012), Isehed et al. (2016), Jepsen et al. (2016), Khoury and Buchmann (2001), Nart et al. (2017), Roccuzzo et al. (2011, 2016), Roos-Jansåker et al. (2007a,b), Wiltfang et al. (2012), Wohlfahrt et al. (2012). *SE* or *SD* of mean values not reported: Behneke et al. (2000). (c) Forest plot. Change of soft tissue level (REC) (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Not considered: Soft tissue levels (mean) at baseline and/or 12 months not reported: Aghazadeh et al. (2012), Behneke et al. (2000), Isehed et al. (2016), Jepsen et al. (2016), Khoury and Buchmann (2001), Roccuzzo et al. (2011, 2016), Roos-Jansåker et al. (2007a,b), Wohlfahrt et al. (2012). (d) Forest plot. PD reduction (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Additional data kindly provided by Isehed et al. (2016). Not considered: Baseline and/or 12-month PD (mean) not reported: Roos-Jansåker et al. (2007a,b). *SE* or *SD* of mean values not reported: Behneke et al. (2000). (e) Forest plot. Risk for BOP at implants (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant. Not considered: BOP% (implants) at baseline and/or 12 months not reported: Aghazadeh et al. (2012), Behneke et al. (2000), Khoury and Buchmann (2001), Nart et al. (2017), Roccuzzo et al. (2011, 2016), Roos-Jansåker et al. (2007b), Schwarz et al. (2008, 2010, 2012), Wohlfahrt et al. (2012). (f) Forest plot. Risk for BOP at implant sites (reconstructive interventions from controlled and uncontrolled studies). Unit of analysis: implant site. Not considered: BOP% (sites) at baseline and/or 12 months not reported: Behneke et al. (2000), Isehed et al. (2016), Khoury and Buchmann (2001), Roos-Jansåker et al. (2007a), Wiltfang et al. (2012)

to inconsistent inclusion/exclusion criteria. The gender ratio among selected study populations varied considerably, as did the proportion of smokers and patients with systemic conditions. There was also a noteworthy discrepancy in terms of selection of grafting material among the included articles. The most commonly used material in the uncontrolled, observational studies was bovine bone mineral, while none of the controlled studies evaluated this specific product.

The variation of outcomes between study samples was explored by I^2, illustrating the proportion of variance exceeding the sampling error (true variance) (Higgins & Thompson, 2002; Higgins et al., 2003). The prediction intervals observed in the present meta-analyses showed a wide range of expected effects, also indicating a significant variability between the included studies (Borenstein et al., 2017; IntHout, Ioannidis, Rovers, & Goeman, 2016). For

example, in terms of MBL changes, the expected outcome ranged from no effect at all (0 is included) or bone loss to improvement of marginal bone level of 4.4 mm. It should be kept in mind that the 95% CI of the estimate simply reflects the precision of the estimation of the mean value. The prediction interval, however, is an index of dispersion, indicating how widely the effect varies across a given population (Borenstein et al., 2017).

In the consensus report from the 8th European Workshop on Periodontology, it was suggested to use composite outcomes to describe results of peri-implantitis therapy (Sanz & Chapple, 2012). These should ideally include clinical measures of inflammation and radiographic assessments of bone-level alterations. Following these recommendations, studies applying pocket elimination techniques (Carcuac et al., 2016, 2017) or reconstructive techniques (Aghazadeh et al., 2012; Jepsen et al., 2016) have reported results accordingly. An additional goal of reconstructive therapy is the maintenance of soft tissue height. None of the controlled studies, however, reported data on soft tissue alterations. The recession observed in observational studies (WMD = 0.7 mm) was statistically significant and corresponded well with findings reported in studies on periodontal reconstructive therapy (Heden, Wennström, & Lindhe, 1999; S. Jepsen et al., 2008; Tonetti et al., 2004, 2002; Trombelli, Simonelli, Minenna, Rasperini, & Farina, 2017). It remains unclear, however, whether the reconstructive techniques applied at peri-implant defects resulted in a better aesthetic outcome as compared to controls.

Studies with controls indicated a benefit of 1.7 mm in favour of reconstructive measures for changes of marginal bone level. It should be kept in mind, however, that two of the three controlled studies (Jepsen et al., 2016; Wohlfahrt et al., 2012) used porous titanium granules as bone replacement graft in the test groups. It is obvious that blinding of the examiner during radiographic assessments in such studies was not possible. Further, it is unclear how the presence of a radiopaque grafting material affected the assessment of marginal bone levels as neither study reported measurement errors. Isehed et al. (2016), who used enamel matrix derivative in the test group, reported a moderate benefit of 0.5 mm. Considering all different reconstructive interventions included in the present review, marginal bone levels were improved by 2.0 mm on average. However, the prediction interval was wide and included 0, indicating a high degree of variability.

Despite the observed potential benefit in radiographic appearance, reconstructive therapy did not provide any benefit in terms of reduction of PD and BOP. Considering overall changes from baseline to 12 months, however, peri-implant inflammation was significantly reduced by the surgical treatment. The analysis showed that it was more likely to arrest bleeding at a single site (RR = 0.2) than to achieve peri-implant health at all aspects of the affected implant (RR = 0.4). Data reported by Jepsen et al. (2016) further illustrate this observation. While the percentage of bleeding sites was reduced by 45% and 56% in control and test groups, respectively, the proportion of implants free of any bleeding at 12 months was 30% for both groups. Similar figures have been described in studies applying pocket elimination techniques. Thus, Carcuac et al. (2017) and Heitz-Mayfield et al. (2018) reported 40% of implants to be completely free of bleeding at 3 and 5 years, respectively. Again, a high variation in terms of expected change of BOP at site and implant levels was testified, as illustrated by wide prediction intervals.

The present work suffers from a number of shortcomings. Data from pre-clinical (e.g., Albouy et al., 2011; Carcuac et al., 2015) and clinical studies (e.g., Berglundh et al., 2018; Roccuzzo et al., 2017) on surgical therapy of peri-implantitis pointed towards the impact of implant surface characteristics on treatment outcomes. Further, inclusion criteria in regard to the configuration of peri-implant defects differed between studies, which may have influenced subsequent healing (Schwarz et al., 2010). And finally, the frequency and quality of maintenance therapy following reconstructive procedures may also have been of importance as has been demonstrated for periodontitis patients (Cortellini, Pini Prato, & Tonetti, 1994). Neither of these factors was, however, considered in the present meta-analyses. In the secondary calculation of the overall changes, measures from baseline and 12 months were handled as independent data sets. It may be argued that treatment outcomes are, in fact, correlated to the initial situation. In addition, different treatment arms originating from the same study were considered to be independent of each other. This may have affected assessment of heterogeneity.

In conclusion, the available evidence on reconstructive therapy at peri-implantitis-related defects is limited by (a) the low number of controlled studies, (b) the lack of controlled studies for commonly used procedures, (c) the heterogeneity between studies and (d) the choice of outcome measures. A high variability for predicted outcomes at 12 months was noted. The interpretation of the demonstrated larger MBL gain for test procedures is difficult as graft material may not be distinguishable from newly formed bone. Potential aesthetic and patient-reported advantages remain to be demonstrated.

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CONFLICT OF INTEREST

The authors declare no conflict of interest with respect to the authorship and/or publication of this article.

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SUPPORTING INFORMATION

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

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II

Artículo 2:

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Objetivo:

Evaluar el beneficio potencial de la utilización de un sustituto óseo en la terapia quirúrgica reconstructiva de la periimplantitis.

Material y métodos:

En este ensayo clínico aleatorizado multicéntrico, se trataron quirúrgicamente 138 pacientes portadores de 147 implantes. La aleatorización se realizó mediante el lanzamiento de una moneda asignándose así a control (cirugía de acceso) o test (cirugía reconstructiva con sustituto óseo). Las variables clínicas se registraron en basal y a 6 y 12 meses de seguimiento, incluyendo profundidades de sondaje (PPD), sangrado y supuración al sondaje (BOP y SOP), así como la recesión de tejidos blandos (REC). Los niveles óseos marginales, se midieron en radiografías intra-orales y la satisfacción de los pacientes (PROs) se registró en basal y a 12 meses. No se realizó cegamiento a la asignación de grupos. La variable respuesta primaria a 12 meses fue una variable compuesta que incluía (1) permanencia del implante en boca, (2) ausencia de BOP/SOP en todos los aspectos del implante, (3) PPD ≤ 5mm en todos los aspectos del implante y (4) ≤ 1mm de recesión de la mucosa marginal en el aspecto vestibular o bucal del implante. Se incluyeron variables secundarias (1) cambios en niveles óseos marginales, (2) cambios en profundidades de sondaje, BOP%, mucosa queratinizada (KM) vestibular, (3) recesión vestibular/bucal y (4) satisfacción de los pacientes.

Resultados:

A lo largo del seguimiento, 4 implantes (1 en el grupo test, 3 en el grupo control) tuvieron que ser explantados debido a la progresión de la patología. A 12 meses, se examinaron un total de 69 implantes en el grupo test y 68 implantes en el grupo control. 16.4% y 13.5% de los implantes en los grupos test y control respectivamente, cumplían con todas las variables que incluía la variable compuesta. La reducción de PPD y ganancia de MBL fue de 3.7mm y alrededor de 1.0mm en ambos grupos. La media de reducción de BOP% varió entre 45% (Test) y 50% (Control), sin diferencias estadísticamente significativas entre grupos. La recesión vestibular fue menos pronunciada en el grupo test (M=0.7, SD=0.9mm), comparado con control (M=1.1, SD=1.5mm). La satisfacción de los pacientes fue favorable en ambos grupos sin diferencias estadísticamente significativas. Se registró un caso de reacción alérgica a la terapia antibiótica. No se registró ningún otro efecto adverso.

Conclusiones:

La terapia quirúrgica reconstructiva de la periimplantitis mejoró la situación clínica y radiográfica a 12 meses de seguimiento. Mientras que el uso de un sustituto óseo no mejoró la reducción de las profundidades de sondaje ni del sangrado al sondaje, la recesión vestibular fue menos pronunciada para el grupo test. La satisfacción de los pacientes fue elevada en ambos grupos.

Palabras clave:

Injerto óseo, implante dental, periimplantitis, terapia reconstructiva, terapia quirúrgica.

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CLINICAL ORAL IMPLANTS RESEARCH WILEY

ORIGINAL ARTICLE

Reconstructive surgical therapy of peri-implantitis: A multicenter randomized controlled clinical trial

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Abstract

Objective: To evaluate the potential benefit of the use of a bone substitute material in the reconstructive surgical therapy of peri-implantitis.

Methods: In this multicenter randomized clinical trial, 138 patients (147 implants) with peri-implantitis were treated surgically, randomized by coin toss to either a control (access flap surgery) or a test group (reconstructive surgery using bone substitute material). Clinical assessments, including probing pocket depth (PPD), bleeding and suppuration on probing (BOP & SOP) as well as soft tissue recession (REC), were recorded at baseline, 6 and 12 months. Marginal bone levels (MBL), measured on intraoral radiographs, and patient-reported outcomes (PROs) were recorded at baseline and 12 months. No blinding to group allocation was performed. The primary outcome at 12 months was a composite measure including (i) implant not lost, (ii) absence of BOP/SOP at all aspects, (iii) PPD ≤5 mm at all aspects and (iv) ≤1 mm recession of mucosal margin on the buccal aspect of the implant. Secondary outcomes included (i) changes of MBL, (ii) changes of PPD, BOP%, and buccal KM, (iii) buccal REC and (iv) patient-reported outcomes.

Results: During follow-up, four implants (one in the test group, three in the control group) in four patients were removed due to disease progression. At 12 months, a total of 69 implants in the test and 68 implants in the control group were examined. Thus, 16.4% and 13.5% of implants in the test and control group, respectively, met all predefined criteria of the composite outcome. PPD reduction and MBL gain were 3.7 mm and about 1.0 mm in both groups. Reduction in mean BOP% varied between 45% (test) and 50% (control), without significant differences between groups. Buccal REC was less pronounced in the test group (M = 0.7, SD = 0.9 mm) when compared to controls (M = 1.1, SD = 1.5 mm). PROs were favorable in both groups without significant differences. One case of allergic reaction to the antibiotic therapy was recorded. No other adverse events were noted.

Conclusions: Surgical therapy of peri-implantitis effectively improved the clinical and radiographic status at 12 months. While the use of a bone substitute material did not improve reductions of PPD and BOP, buccal REC was less pronounced in the test group. Patient satisfaction was high in both groups.

KEYWORDS
bone graft, dental implant, peri-implantitis, reconstructive therapy, surgical therapy

1 | INTRODUCTION

Peri-implantitis is characterized by bleeding/suppuration on probing together with loss of supporting bone and affects about 15% of implant-carrying patients (Derks et al., 2016). The primary goal of the treatment of peri-implantitis is to resolve the inflammatory lesion in peri-implant tissues, which was shown to be possible in preclinical in vivo experiments (Albouy et al., 2011; Carcuac et al., 2015). Successful management of peri-implantitis, as indicated by the reduction in bleeding on probing and/or absence of further bone loss, has also been demonstrated both in observational studies (e.g., Berglundh et al., 2018; Roccuzzo et al., 2017; Schwarz et al., 2017) and in randomized controlled trials (e.g., Carcuac et al., 2016; Carcuac et al., 2017; Hentenaar et al., 2022).

In addition to the resolution of the peri-implantitis lesion, a desirable outcome is the regeneration of supporting tissues lost during disease progression. The use of reconstructive procedures in the surgical treatment of periodontitis has been extensively evaluated (Nibali et al., 2020), and the technique is an established option for the management of angular defects around teeth (Sanz et al., 2020). A similar approach in the treatment of peri-implantitis-associated defects may be relevant not only for the longevity of the implant but also for the esthetic appearance post-therapy.

In a systematic review on reconstructive measures as part of surgical treatment of peri-implantitis, it was reported that evidence from controlled trials is limited (Tomasi et al., 2019). While no clinical benefits of reconstructive measures over access flap alone were observed, the use of bone substitute materials resulted in improved radiographic bone levels and defect fill (K. Jepsen et al., 2016; Wohlfahrt et al., 2012). Interpretation of such findings, however, is complex due to the difficulty in distinguishing graft material from newly formed bone on radiographs. In a consensus report from the 15th European Workshop on Periodontology on bone regeneration, the importance of including outcomes related to soft tissue dimensions and esthetics in studies on reconstructive techniques used at peri-implantitis-associated bony defects was highlighted (S. Jepsen et al., 2019). While some studies (Isehed et al., 2016; Jepsen et al., 2016; Wohlfahrt et al., 2012) did not consider esthetic parameters in their clinical evaluations, two publications (Renvert et al., 2018; Renvert et al., 2021) found no differences in soft tissue recession between test and control groups. Furthermore, the degree of patient satisfaction was not dependent on treatment modality (Renvert et al., 2021).

Thus, the limited evidence, specifically in terms of soft tissue recession and patient-reported outcomes, calls for further investigation. The aim of the present randomized controlled trial was to evaluate the potential benefit of the use of a bone substitute material in the reconstructive surgical therapy of peri-implantitis. Hence, the null hypothesis was the absence of any difference between access flap alone and access flap combined with a bone substitute material.

2 | MATERIALS AND METHODS

The study was designed as a multicenter, parallel group, randomized, controlled trial conducted at 6 centers located in Sweden, Italy, Spain, and Germany. The protocol was approved by the responsible authorities in the respective countries (Gothenburg: 1192–16; Bilbao: 06/2017; Málaga: 27/09/2017; Perugia: 3173/18; Trento: 21390; Munich: 17028) and registered at clinicaltrials.gov (NCT03077061). Interim analyses for efficacy/futility were carried out. No changes to the study protocol were performed after trial commencement. CONSORT guidelines were followed (Schulz et al., 2010).

2.1 | Study population

Eligible participants were subjects aged 18 years or over, presenting with peri-implantitis at ≥1 implant (≥1 year of function). Target sites presented with peri-implant probing pocket depth (PPD) of ≥7 mm, bleeding and/or suppuration on probing (BOP/SOP) and radiographically confirmed bone loss of ≥3 mm. For cases lacking reference radiographs, bone levels ≥3 mm were considered. Peri-implant osseous defects were circumferential and ≥3 mm deep, as confirmed during surgery. No minimum number of bony walls was required. Exclusion criteria were (i) surgical therapy of peri-implantitis and/or use of systemic/local antibiotics during the previous 6 months, (ii) untreated periodontitis, (iii) systemic conditions/medication affecting peri-implant tissues and/or impeding surgical intervention (e.g., uncontrolled diabetes, immunosuppressive medication).

In all, 165 subjects were invited and a total of 138, presenting with 147 target implants, were eventually included in the study (Figure 1). Patient and implant/site characteristics are illustrated in Table 1.

2.2 | Setting

The study took place at 6 clinical centers. All study-related procedures were performed by experienced clinicians with specialty degrees in periodontics (JD, AOV, AG, MD, DS, CT, KK, IA & TB), oral

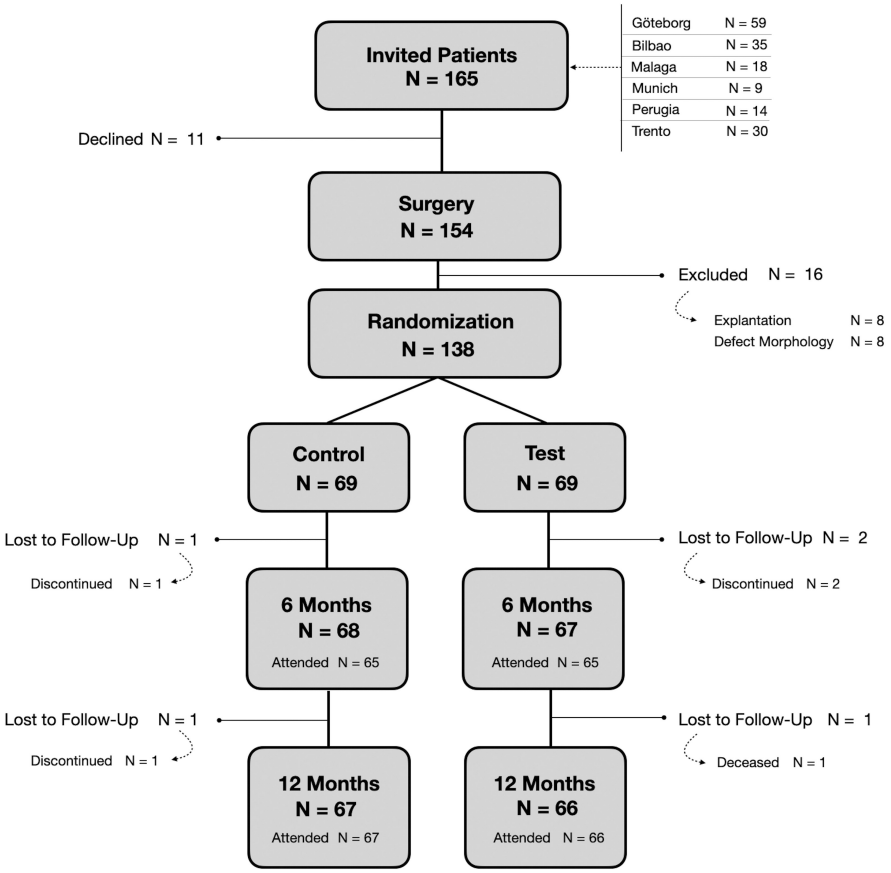

FIGURE 1 Flow-chart illustrating the process of enrollment, treatment allocation and follow-up

surgery (PG), or orthodontics (EB). All clinicians met for discussion of the study protocol and calibration purposes at the primary study center (Gothenburg) prior to study initiation.

Patients meeting the inclusion criteria were invited on a consecutive basis. Upon signed consent, participants were enrolled and assigned a unique identification number. At the time of surgical intervention, subjects were randomly allocated to either the test or control group. In case of multiple implants per patient, all implants were allocated to the same group. Randomization sequence was determined by coin toss and was stratified by smoking with a 1:1 allocation using a block size of 4. Smokers were those subjects reporting daily tobacco smoking. Randomization lists were prepared at the primary study center and distributed together with clinical record forms. Allocation was concealed through the use of sealed, opaque envelopes. During follow-up, neither clinicians nor participants were blinded to group allocation. Surgical interventions were performed between July 2017 and February 2021.

2.3 | Interventions

Patients first received tailored, non-surgical peri-implantitis therapy including oral hygiene instructions, possible adjustments to implant-borne prostheses and instrumentation performed with titanium curettes and polishing cups. Once demonstrating adequate self-performed infection control (full-mouth plaque score ≤20%), patients underwent surgical therapy at peri-implantitis sites. A 10-day antibiotic regimen (Amoxicillin 2 × 750 mg daily) was initiated 3 days prior to surgery. When feasible, prostheses were disconnected. Following local anesthesia, full-thickness access flaps were carefully elevated and inflamed tissue was removed from the peri-implant defect(s). Implant surfaces were cleaned by titanium curettes and a rotating titanium brush (Nano NiTi Brush, HANS KOREA CO. Ltd) used at ≤1200 rpm under continuous irrigation with saline. Upon surface decontamination, allocation to test or control was revealed. In controls, flaps were simply replaced at their initial position and sutured. At test sites, peri-implant bony defects were filled with a bone substitute material (Bio-Oss Collagen®, Geistlich, Lucerne, Switzerland) to the level of the bone crest prior to suturing. In both groups, the aim was to achieve primary closure through careful adaptation of tissue margins (Figure 2). Prostheses were reconnected and patients were advised to abstain from mechanical plaque control measures and rinse with a 0.2% solution of chlorhexidine digluconate until suture removal at 2 weeks. For additional details on the surgical procedures, see Table A1. Follow-up visits including oral hygiene reinforcement and polishing by rubber cup (targeting the whole dentition) were scheduled at 6 weeks and at 6 and 12 months (Figure A1).

2.4 | Clinical examination

Clinical assessments were carried out at baseline (prior to surgery) and at 6 and 12 months. Assessments included measurements of PPD,

TABLE 1 Patient and implant/site characteristics at baseline by group

		Test			Control			Total		
		n	%/mean (SD)	Min to max	*n*	%/mean (SD)	Min to max	*n*	%/mean (SD)	Min to max
Gender	Female	41	59.4%			47	68.1%	88	63.8%	
	Male	28	40.6%			22	31.9%	50	36.2%	
Current smoker (self-reported)	No	53	76.8%			48	69.6%	101	73.2%	
	Yes	16	23.2%			21	30.4%	37	26.8%	
History of periodontitis	No	23	33.3%			24	34.8%	47	34.1%	
	Yes	46	66.7%			45	65.2%	91	65.9%	
Diabetes	No	67	97.1%			66	95.7%	133	96.4%	
	Yes	2	2.9%			3	4.3%	5	3.6%	
Age at surgery (years)		69	62.4 (11.3)	34 to 88	69	59.3 (11.5)	24 to 79	138	60.8 (11.5)	24 to 88
Implant years		68	10.1 (5.1)	2 to 22	68	10.5 (5.8)	1 to 30	136	10.3 (5.5)	1 to 30
Number of implants included per patient		69	1.1 (0.2)	1 to 2	69	1.1 (0.3)	1 to 2	138	1.1 (0.2)	1 to 2[a]
Jaw	Maxilla	36			33	44.6%		69	46.9%	
	Mandible	37			41	55.4%		78	53.1%	
Location	Anterior (canine to canine)	15			14	18.9%		29	19.7%	
	Posterior	58	49.3%		60	81.1%		118	80.3%	
Implant brand	Nobel Biocare	10	50.7%		16	21.6%		26	17.7%	
	Astra Tech	35	20.5%		28	37.8%		63	42.9%	
	Straumann	14	79.5%		17	23.0%		31	21.1%	
	Other	9	13.7%		9	12.2%		18	12.2%	
	Unclear	5	47.9%		4	5.4%		9	6.1%	
Surface characteristics	Modified	72	19.2%		71	95.9%		143	97.3%	
	Nonmodified	1	12.3%		3	4.1%		4	2.7%	
Retention	Cemented	31	6.8%		32	43.2%		63	42.9%	
	Conometric	1	98.6%		4	5.4%		5	3.4%	
	Screw-retained	41	1.4%		38	51.4%		79	53.7%	
PPD (mm)		73	42.5%	7.0 to 13.0	74	8.5 (1.6)	7.0 to 13.0	147	8.6 (1.6)	7.0 to 13.0
BOP (%)		73	1.4%	25.0 to 100.0	74	91.9 (19.5)	25.0 to 100.0	147	90.0 (20.8)	25.0 to 100.0
SOP (%)		73	56.2%	0.0 to 100.0	74	31.1 (38.3)	0.0 to 100.0	147	34.9 (40.4)	0.0 to 100.0
Plaque (%)		73	20.2 (37.0)	0.0 to 100.0	74	17.2 (29.5)	0.0 to 00.0	147	18.7 (33.3)	0.0 to 100.0

TABLE 1 (Continued)

	Test			Control			Total		
	n	%/mean (SD)	Min to max	*n*	%/mean (SD)	Min to max	*n*	%/mean (SD)	Min to max
Buccal soft tissue level (mm)	73	0.4 (1.4)	−3.0 to 5.0	74	0.5 (1.3)	−2.0 to 6.0	147	0.5 (1.3)	−3.0 to 6.0
Buccal KM (mm)	73	2.3 (1.8)	0.0 to 6.0	74	2.3 (1.9)	0.0 to 7.0	147	2.3 (1.8)	0.0 to 6.0
MBL (mm)	73	5.9 (1.9)	2.3 to 10.2	74	6.2 (2.0)	2.7 to 12.9	147	6.1 (2.0)	2.3 to 12.9

Note: $N = 138$ patients; $n = 147$ implants/sites.

Abbreviations: BOP, bleeding on probing; KM, keratinized mucosa; MBL, marginal bone level; PPD, probing pocket depth (deepest site); SD, standard deviation; SOP, suppuration on probing.

[a]Nine patients contributed with two implants.

BOP, SOP, soft tissue levels and presence of plaque at 4 aspects per implant using a metal periodontal probe. The width of keratinized mucosa (KM) and the distance between the mucosal margin and a reference landmark (the shoulder of the implant or the prosthetic margin) were evaluated on the buccal aspect. PPD, soft tissue levels and KM were recorded to the nearest millimeter, while BOP, SOP (within 15 s following probing) and plaque were scored dichotomously (yes/no). Clinical examinations were performed with prostheses in place and intraoral photographs were obtained at baseline and follow-up visits.

During surgery, dimensions of the peri-implant bony defect(s) were measured by probe. Thus, defect depth (bony crest to the bottom of defect) and width as well as bone levels relative to implant shoulder were evaluated at four aspects per implant. Defects were categorized according to (i) defect geometry and (ii) presence/absence of the buccal bony wall (Table A2).

2.5 | Radiographic examination

Intra- radiographic images were obtained by long-cone parallel technique prior to surgery (≤4 weeks) and at 12 months. Marginal bone levels (MBL) were assessed by two trained and blinded investigators (JD & YI) using an image analysis software (ImageJ 2.0.0-rc-69/1.52n; National Institutes of Health). Pictures were calibrated either by the known inter-thread distance or the implant length/diameter. MBLs were measured on the mesial and distal aspect relative to a fixed landmark and expressed in mm (Figure A2).

For 34 implant sites, MBL assessments were repeated. The absolute difference between two assessments was used to express the measurement error. Intra- and inter-rater comparisons revealed mean measurement errors of 0.33 ± 0.37 mm (±: standard deviation) and 0.49 ± 0.46 mm. A two-way mixed-effect model with consistency agreement reported intraclass correlation coefficients of 0.97 (95% CI 0.96/0.98; CI: confidence interval) and 0.95 (95% CI 0.92/0.97), respectively.

2.6 | Patient-reported outcomes

Participants completed a written questionnaire prior to surgery, at 2 weeks and at 12 months. Responses were scored on a visual analog scale (VAS, 100 mm, Figure A3). Questions were translated into respective languages. Adverse events were recorded. In addition to an overall comparison by group allocation, we performed a sub-analysis of satisfaction at 12 months considering only subjects treated at implant sites located in the esthetic zone (second premolar to second premolar in the maxilla).

2.7 | Data analysis

According to an *a priori* power calculation, a total of 122 patients (61 per group) were required to detect (power 0.8; alpha 0.05) a

FIGURE 2 Images illustrating interventions by group allocation

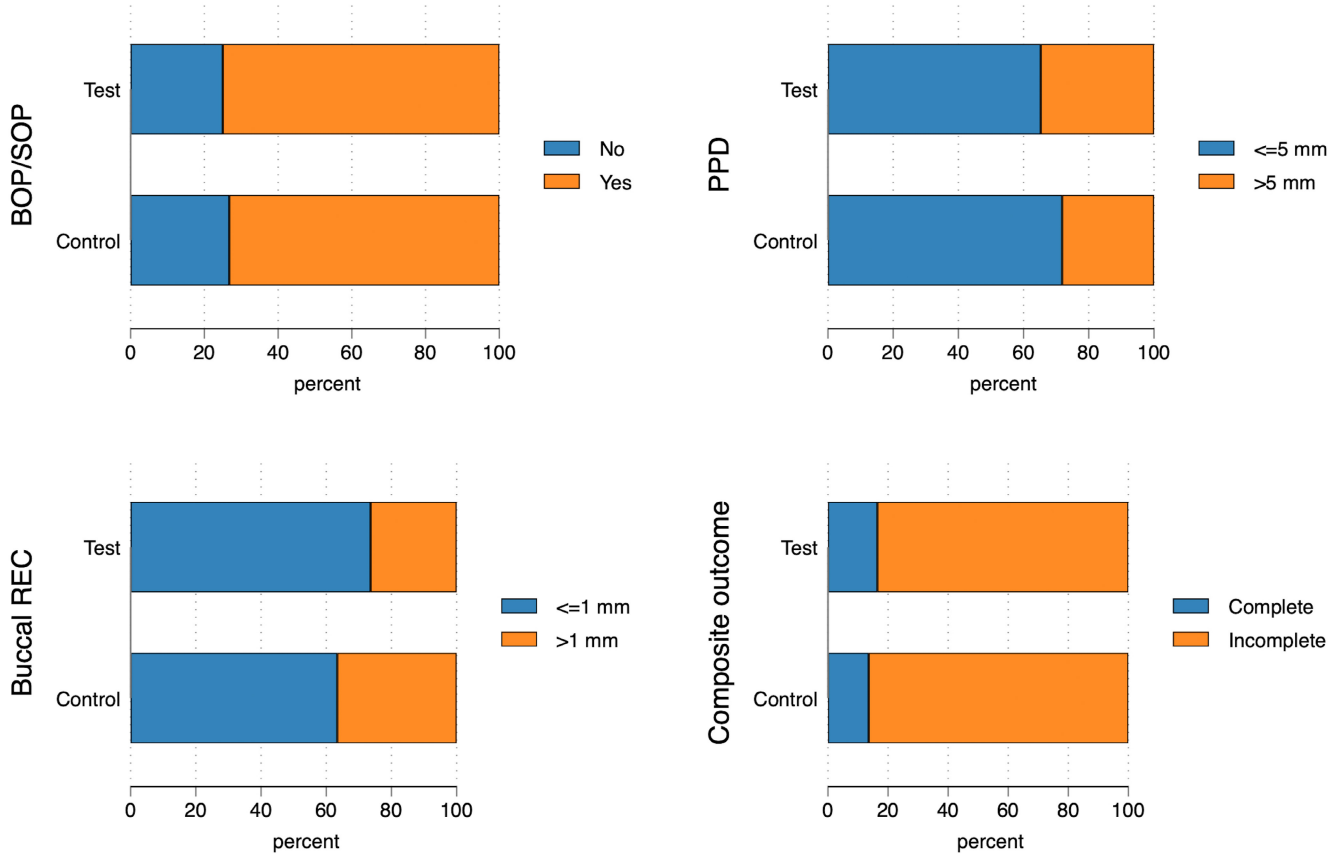

FIGURE 3 Threshold and composite outcomes at 12 months. $N = 147$ implants, the four implants lost due to disease progression are considered. Composite outcome defined as implant not lost, no bleeding on probing (BOP), no suppuration on probing (SOP), probing pocket depth (PPD) ≤5 mm and buccal recession (REC) ≤1 mm. For further details, see Table A3.

difference of 1 mm in PPD change between groups, considering a standard deviation of 1.97 (Carcuac et al., 2016). To compensate for possible drop-out, the enrollment of 140 study participants was planned. At the time of study planning, no relevant data on composite outcomes were available for appropriate power analysis.

The unit of analysis for clinical and radiographic evaluations was the implant. For MBL and PPD, the deepest measurement at each evaluation point was chosen, while for soft tissue level and KM, the buccal aspect was representative of the implant. For BOP and SOP, the percentage of positive aspects (out of four sites) per implant was calculated.

TABLE 2 Continuous outcomes at 12 months by group (intention to treat)

	Test			Control			Total		
	n	Mean (SD)	Min to max	*n*	Mean (SD)	Min to max	*n*	Mean (SD)	Min to max
PPD Change (mm)	72	−3.7 (2.1)	−8.0 to 3.0	71	−3.7 (2.3)	−9.0 to 6.0	143	−3.7 (2.2)	−9.0 to 6.0
BOP% Change	72	−44.8 (36.6)	−100.0 to 50.0	71	−49.6 (41.1)	−100.0 to 75.0	143	−47.2 (38.8)	−100.0 to 75.0
Buccal REC (mm)	72	0.7 (0.9)	−1.0 to 3.0	71	1.1 (1.5)	−3.0 to 7.0	143	0.9 (1.2)	−3.0 to 7.0
Buccal KM Change (mm)	72	−0.1 (1.3)	−5.0 to 4.0	71	−0.5 (1.1)	−4.0 to 3.0	143	−0.3 (1.2)	−5.0 to 4.0
MBL Change (mm)	72	1.1 (1.4)	−4.4 to 5.2	71	1.1 (1.0)	−2.3 to 3.9	143	1.1 (1.2)	−4.4 to 5.2
Plaque (%) – per protocol	69	20.3 (33.8)	0.0 to 100.0	68	19.9 (31.6)	0.0 to 100.0	137	20.1 (32.6)	0.0 to 100.0

Note: $N = 143$ implants. The four implants lost due to disease progression are not considered. For statistical testing, see Table A5.

Abbreviations: BOP, bleeding on probing; KM, keratinized mucosa; MBL, marginal bone level; PPD, probing pocket depth; REC, recession; SD, standard deviation.

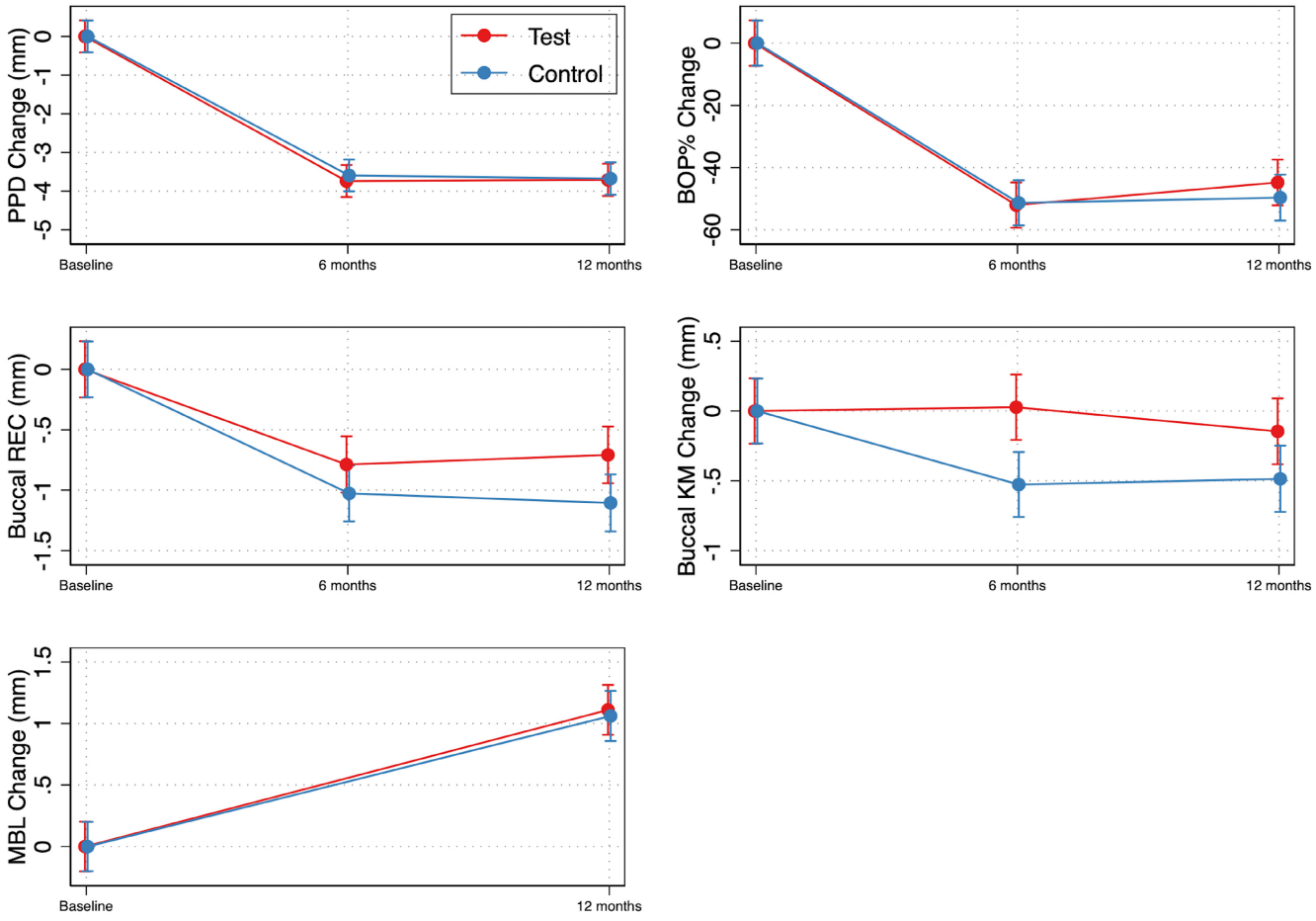

FIGURE 4 Changes of probing pocket depth (PPD), bleeding on probing% (BOP%), buccal keratinized mucosa (KM), marginal bone level (MBL) and buccal recession (REC) following the surgical intervention. $N = 143$ implants, the 4 implants lost due to disease progression are not considered. Results are based on regressions analyses also illustrated in Table A5. Whiskers indicate 95% CIs.

The primary outcome at 12 months was a composite measure including all of the following features: (i) implant not lost, (ii) absence of BOP/SOP at all aspects, (iii) PPD ≤5 mm at all aspects and (iv) ≤1 mm recession of mucosal margin on the buccal aspect (buccal REC) of the implant. Secondary outcomes included (i) changes (i.e., from baseline to 12 months) of MBL, (ii) changes of PPD, BOP%, buccal KM, (iii) buccal REC and (iv) patient-reported outcomes.

We used logistic (for the primary outcome) and linear regression analyses to assess differences between test and control groups. Results of the logistic regression were expressed as odds ratio (OR). For continuous data, group allocation and time points (baseline, 6 and 12 months) were entered as main effects and interaction terms to the respective models (STATA 17.0, StataCorp). We predicted outcomes including 95% CIs and analyzed potential differences through

pairwise comparisons (α: 0.05). We used Bonferroni correction for multiple comparisons. To address the potential clustering effect of multiple implants within patients, we confirmed initial estimates through multilevel modeling.

Analyses were performed according to the intention-to-treat principle. In case of missing data, the last available observation was carried forward under the assumption of "missing completely at random." An evaluation of missingness was performed. Patient-reported outcomes demonstrated skewed distributions and were analyzed per-protocol using the Mann–Whitney U test. Finally, the potential effect of center on the composite outcome and on changes of PPD and MBL was evaluated by adding "Center" as an independent parameter to both the logistic and the respective linear regression analyses.

3 | RESULTS

Out of the initially included 138 participants (147 implants), five subjects (six implants) were lost to follow-up prior to the 12-month evaluation (Figure 1). A total of four implants (one in the test group, three in the control group) in four patients were removed prior to the final examination due to continuous loss of MBL. One case of allergic reaction to the antibiotic therapy was recorded. No other adverse events related to any study intervention were noted.

At 12 months, the different components of the composite outcome were met at varying degrees. In all, the majority of implants presented with shallow PPD (≤5 mm; 68.5%) and minor buccal REC (≤1 mm; 68.5%). In contrast, the complete absence of BOP/SOP was achieved only for a minority of implants (25.9%). Accordingly, a composite outcome for all predefined criteria (implant not lost, absence of BOP/SOP, PPD ≤5 mm and buccal REC ≤1 mm) was noted for 16.4% and 13.5% of implants in the test and control group, respectively (Figure 3 & Table A3). Differences between groups were not statistically significant (OR 0.79; 95% CI 0.32/1.97; $p = .62$; Table A4). PPD reduction and MBL gain were 3.7 mm and about 1.0 mm in both groups. The reduction in mean BOP% varied between 45% and 50%. No statistically significant differences between groups were observed. Test implants demonstrated less buccal REC (mean difference: 0.40 mm, 95% CI 0.06/0.73; $p = .02$) and less buccal KM change (mean difference: 0.34 mm, 95% CI 0.01/0.67; $p = .05$) than controls (Table 2, Figure 4, Table A5 and Figure A4).

Pronounced MBL gain of >2 mm was noted at 22.2% of test and at 18.3% of control implants. In all, 3 implants (2.1%), in addition to the four implants that were removed, demonstrated MBL loss >1 mm between surgery and the 12-month evaluation (Table A3).

Responses to the questionnaires were not normally distributed (Figure 5 & Table A6).

At 12 months, the overall satisfaction with treatment outcomes (median and interquartile range) was rated at 97.5 (20.0) and 91.5 (20.0) in the test and control groups, respectively. Corresponding satisfaction with the esthetic outcome was 95.0 (24.0) and 95.0 (30.0). Postsurgical pain at 2 weeks was scored as 10.0 (20.0) and 10.0 (21.0). Differences between test and control groups were not statistically significant.

Clinical and radiographic outcomes at the 51 implants located in the esthetic zone revealed no statistically significant differences when compared to other sites (Table A7). In addition, differences between treatment groups in terms of buccal REC in the esthetic zone were consistent with overall findings (Table A8). No statistically significant differences in patient satisfaction were observed (Figure A5). No association between the degree of "satisfaction with therapy" and "satisfaction with esthetic outcome" and buccal REC was found (Figure A6).

The analysis of a potential center effect revealed no statistically significant differences in terms of composite outcome and PPD change between centers. Differences in MBL change by center were observed (Figure A7 & Tables A9–A12).

Details of the number of missing values (nonattendance) by time point are illustrated in Table A13.

4 | DISCUSSION

In the present study, the potential benefit of the use of a bone substitute material in the reconstructive surgical therapy of peri-implantitis was evaluated. Treatment resulted in pronounced improvements at 12 months as illustrated by reductions of PPD and BOP as well as by marginal bone level gain. For these parameters, no differences between groups were observed. Complete absence of BOP/SOP was observed at about 25% of implants, which limited the proportion of implants matching all predefined criteria for the composite outcome, irrespective of treatment group. Buccal soft tissue recession, however, was less pronounced in the test group when compared to controls. Patient-reported outcomes were favorable in both groups without significant differences.

The results of the present study provide relevant information on the management of peri-implantitis-associated osseous defects. The currently available evidence in the field is limited not only due to the small number of controlled studies but also due to the heterogeneity in the choice of reconstructive technique. Thus, Wohlfahrt et al. (2012) and Jepsen et al. (2016) used a bone substitute material consisting of titanium granules, while Renvert et al. (2021; 2018) filled the bony defects at test sites with a xenograft. Isehed et al. (2016, 2018), on the other hand, applied a biological agent. Irrespective of technique, no differences in reduction of PPD or BOP scores were observed between test and control groups. Although this observation is in agreement with our results, the overall magnitude of PPD reduction in the present study was greater than in the aforementioned studies. This difference may be explained by the severity of peri-implantitis in the presently included patient sample, illustrated by a PPD of 8.6 mm and an osseous defect depth of 6.0 mm prior to therapy. This explanation is supported by data presented by Tapia et al. (2019), who reported a similarly marked PPD reduction following reconstructive surgical therapy of peri-implantitis at sites with a pre-surgical PPD of 8.5 mm.

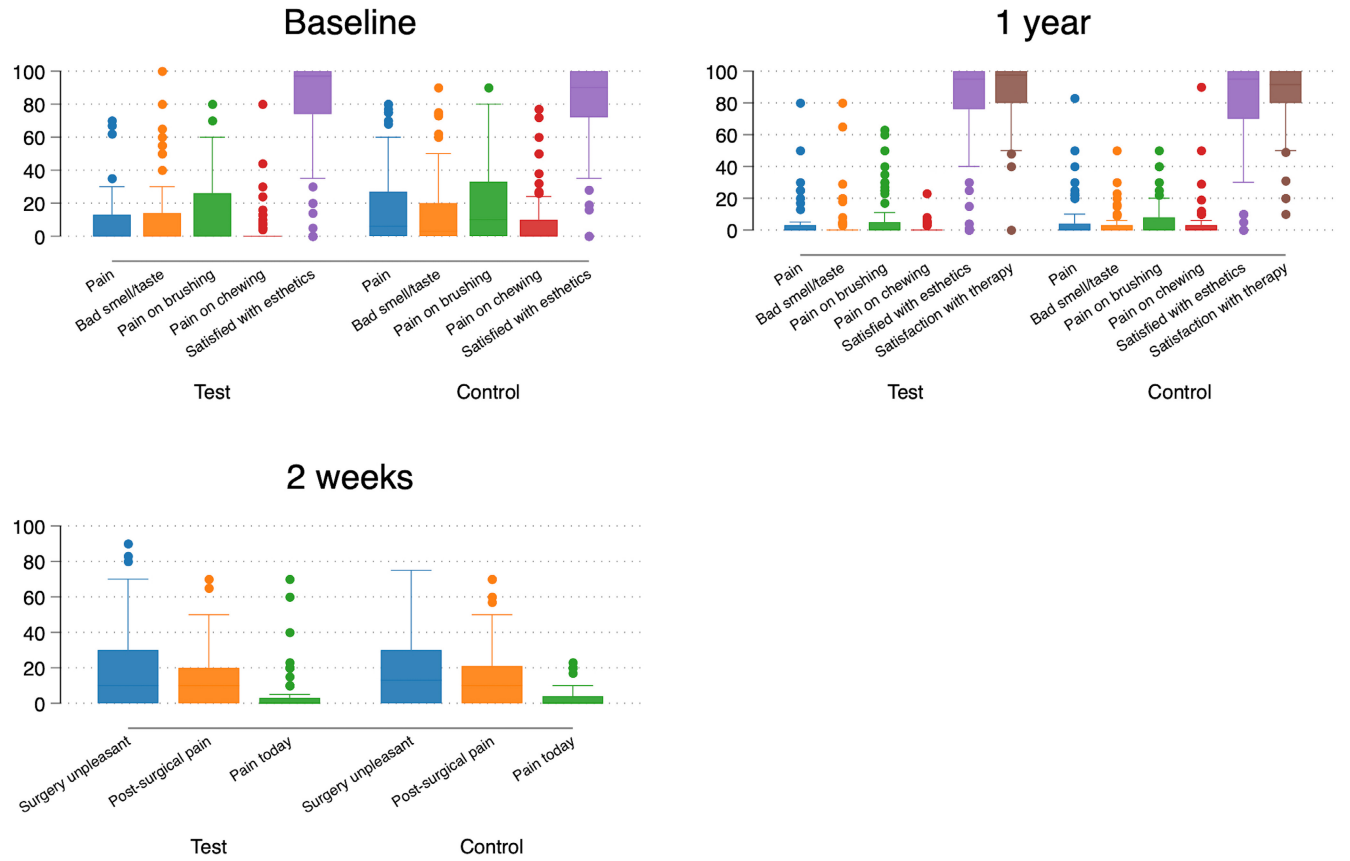

FIGURE 5 Patient-reported outcomes at baseline, at 2 weeks and at 12 months by group. Outcomes were scored on a VAS (100 mm). More details are reported in Table A6.

While the lack of differences in reduction of PPD and BOP scores between test and control sites in the current trial was consistent with findings from previous controlled studies, our data on MBL changes were more ambiguous. The MBL improvement at 12 months was about 1 mm in both groups, which corresponds well with previously described observations at control sites but not with data reported from test sites. Thus, Jepsen et al. (2016) and Renvert et al. (2021) reported an MBL improvement at test sites varying between 2.7 and 3.5 mm, while corresponding data for control sites were 0.9–1.4 mm. The reasons for the different results on MBL changes at test sites are not fully understood but may be related to variations in choice of reconstructive techniques/materials and in morphology of the peri-implantitis-associated bony defects. As already pointed out, difficulties in distinguishing a bone filler material from newly formed bone may influence the interpretation of bone levels on radiographs. In addition, peri-implant osseous defects may present with configurations ranging from fully contained to "open," i.e., absence of buccal and lingual bony walls. In the present study, the inclusion criteria allowed for cases with peri-implant defects lacking buccal and/or lingual bone walls. In fact, almost 40% of all defects were classified as "open." This figure may be considered as high, as the corresponding proportion in an observational study on reconstructive surgical therapy of peri-implantitis was 18% (Roccuzzo et al., 2016). In the study by Renvert et al. (2021), 62% of sites had a fully contained defect configuration, whereas similar conditions in the present study were identified in 24% of cases.

Although a substantial reduction in BOP was observed after treatment in the present study, a complete resolution of inflammation, as indicated by the complete absence of BOP, was not achieved. This finding is not unique for the current investigation. Indeed, previous studies on surgical treatment of peri-implantitis have reported persisting BOP at follow-up (Carcuac et al., 2016; Carcuac et al., 2017; Carcuac et al., 2020; Heitz-Mayfield et al., 2012; Heitz-Mayfield et al., 2018). Persisting BOP may be explained by the difficulties for patients to achieve proper access during home care coupled with the complex anatomy of exposed implant components following treatment. In the present study, residual BOP scores had a critical influence on the composite outcome. Difficulties in obtaining high composite outcome scores were also reported elsewhere (Carcuac et al., 2016; Jepsen et al., 2016).

There are limited data on the alterations of the soft tissue margin in previous controlled studies on reconstructive surgical therapy of peri-implantitis. While Renvert et al. (2021; 2018) did not observe differences in soft tissue recession between test and control sites, the results in the present study pointed to more favorable outcomes at test sites. The mean difference between groups was 0.4 mm and pronounced soft tissue recession of >1 mm occurred in a larger proportion of control than test sites (37% vs.

26%). Although the reason for the difference in soft tissue recession between groups is not fully understood, the potential influence of the graft material on the tissue volume in the bucco-lingual dimension after therapy should be considered. In this context, it should be pointed out, however, that the clinical relevance of this finding at 12 months may be limited, as patient satisfaction in terms of esthetic appearance after treatment was high, irrespective of allocation to test or control procedures. This general observation is in agreement with data presented by Renvert et al. (2021). We further confirmed the lack of association between patient satisfaction and soft tissue recession in our sub-analysis on implants in the esthetic zone.

The multicenter design and the large sample size are strengths of the present study. No critical center effects were observed. When interpreting the findings, the reader should also consider some limitations. The relevance of persisting, albeit reduced, BOP and PPD, and the importance of soft tissue recession on long-term outcomes and patient satisfaction require evaluations beyond the current time frame of 12 months. The lack of blinding of investigators and patients may have introduced a risk of bias. In addition, the power calculation was based on changes of PPD rather than our primary outcome, due to a lack of relevant data on composite outcomes at the time of study design. Further, evaluations of MBL after the use of bone substitute materials are challenging and may have influenced the accuracy of radiographic assessments. Results from a preclinical in vivo study, however, indicated that the identification of marginal bone levels on conventional radiographic images is a reliable method, also after reconstructive therapy of peri-implantitis (Almohandes et al., 2022).

5 | CONCLUSIONS

Surgical therapy of peri-implantitis effectively improved the clinical and radiographic status at 12 months. While the use of a bone substitute material did not improve reductions of PPD and BOP, buccal REC was less pronounced in the test group. Patient satisfaction was high in both groups.

AUTHOR CONTRIBUTIONS

JD and TB contributed to study conception and design. All authors contributed to data collection. ER, YI, and CD acted as study monitors and were responsible for data management. JD, CT, and TB contributed to data analysis and interpretation. All authors contributed to drafting and revision of the manuscript.

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CONFLICT OF INTEREST

Dr. Derks reports speakers honoraria from Osteology Foundation, Dentsply Sirona Implants, Straumann Group and received research grants from Eklund Foundation and Electro Medical Systems. Dr. Ortiz-Vigón reports speakers honoraria from Straumann Group and Arrow Development research and financial support from Thinking Perio research. Dr. Guerrero reports honoraria from Inibsa and Dentsply Sirona Implants. Dr. Donati reports speakers honoraria from Dentsply Sirona Implants and received research grants from Dentsply Sirona Implants. Dr. Bressan reports speakers honoraria from Dentsply Sirona Implants and Sweden & Martina. Dr. Ghensi reports speakers honoraria from Geistlich Pharma AG and BioHorizons Camlog. Dr. Schaller reports speakers honoraria from Zimmer Biomet. Dr. Tomasi reports speakers honoraria from Dentsply Sirona Implants, Straumann Group, Geistlich Pharma AG and Sweden & Martina. Dr. Karlsson reports speakers honoraria from Dentsply Sirona Implants. Dr. Abrahamsson received research grants from Dentsply Sirona Implants. Dr. Berglundh reports honoraria from Dentsply Sirona Implants, speakers honoraria from Osteology Foundation and received research grants from Dentsply Sirona Implants and Geistlich Pharma AG.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request made to the corresponding author.

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Apéndice

APPENDIX A

TABLE A1 Details regarding surgical interventions by group. *N* = 138 patients

		Test			Control			Total		
		n	% mean (SD)	Min-max	*n*	% mean (SD)	Min-max	*n*	% Mean (SD)	Min-max
Prosthesis	Not removed	22	31.9%		21	30.4%		43	31.2%	
	Removed	47	68.1%		48	69.6%		95	68.8%	
Surgical access	Limited access	1	1.4%		1	1.4%		2	1.4%	
	Full access	68	98.6%		68	98.6%		136	98.6%	
Surgical assessment	Not fully satisfied	0	0%		0	0%		0	0%	
	Fully satisfied	69	100.0%		69	100.0%		138	100.0%	
Surgery duration (min)		69	53.0 (12.8)	25–105	69	49.6 (16.3)	10–145	138	51.3 (14.7)	10–145

TABLE A2 Characteristics of peri-implant defects assessed intrasurgically by group

		Test			Control			Total		
		n	% mean (SD)	Min-max	*n*	% mean (SD)	Min-max	*n*	% Mean (SD)	Min-max
Bone crest to bottom of defect (mm)		73	6.0 (1.9)	3–13	74	6.0 (2.1)	3–14	147	6.0 (2.0)	3–14
Implant shoulder to bottom of defect (mm)		73	6.7 (2.1)	3–14	74	6.7 (2.4)	3–15	147	6.7 (2.3)	3–15
Defect width (mm)		73	3.1 (1.0)	1–7	74	3.1 (1.0)	2–9	147	3.1 (1.0)	1–9
Defect configuration	Open[a] at buccal and lingual aspect	27	37.0%		30	40.5%		57	38.8%	
	Open[a] at either buccal or lingual aspect	32	43.8%		22	29.7%		54	36.7%	
	Contained	14	19.2%		22	29.7%		36	24.5%	
Buccal bone wall	Intact	36	49.3%		35	47.3%		71	48.3%	
	Partially missing[b]	20	27.4%		12	16.2%		32	21.8%	
	Missing[b]	17	23.3%		27	36.5%		44	29.9%	

Note: *N* = 147 implants.

[a]Defect configuration: "Open" is defined as implant exposure >2 mm (Implant shoulder to bottom of defect - Crest to bottom of defect >2 mm).

[b]Buccal bone wall: "Partially missing" is defined as buccal implant exposure >2 and ≤4 mm. "Missing" is defined as buccal implant exposure >4 mm.

TABLE A3 Threshold and composite outcomes at 12 months by group (intention to treat)

		Test		Control		Total	
		n	%	*n*	%	*n*	%
Implant loss	No	72	98.6%	71	95.9%	143	97.3%
	Yes	1	1.4%	3	4.1%	4	2.7%
BOP	No	18	25.0%	19	26.8%	37	25.9%
	Yes	54	75.0%	52	73.2%	106	74.1%
SOP	No	64	88.9%	62	87.3%	126	88.1%
	Yes	8	11.1%	9	12.7%	17	11.9%
PPD	≤5 mm	47	65.3%	51	71.8%	98	68.5%
	>5 mm	25	34.7%	20	28.2%	45	31.5%
Buccal REC	≤1 mm	53	73.6%	45	63.4%	98	68.5%
	>1 mm	19	26.4%	26	36.6%	45	31.5%
Composite outcome	Complete[a]	12	16.4%	10	13.5%	22	15.0%
	Incomplete	61	83.6%	64	86.5%	125	85.0%
MBL Change ≥0 mm	No	9	12.5%	7	9.9%	16	11.2%
	Yes	63	87.5%	64	90.1%	127	88.8%
MBL Gain >1 mm	No	36	50.0%	35	49.3%	71	49.7%
	Yes	36	50.0%	36	50.7%	72	50.3%
MBL Gain >2 mm	No	56	77.8%	58	81.7%	114	79.7%
	Yes	16	22.2%	13	18.3%	29	20.3%
MBL Loss >1 mm	No	71	98.6%	69	97.2%	140	97.9%
	Yes	1	1.4%	2	2.8%	3	2.1%

Note: *N* = 147 implants.

Abbreviations: BOP, bleeding on probing;KM, keratinized mucosa; MBL, marginal bone level; PPD, probing pocket depth; REC, recession; SOP, suppuration on probing.

[a]Complete defined as implant not lost; no BOP, no SOP, PPD ≤5 mm and buccal REC ≤1 mm.

TABLE A4 Logistic regression: Composite outcome at 12 months (intention to treat)

	Odds ratio	95% Confidence interval	*p*-Value
Test	1	-	-
Control	0.79	0.32/1.97	.620
Intercept	0.30	0.11/0.37	<.001

Note: *N* = 147 implants.

TABLE A5 Results of the regression analysis: Continuous outcomes (intention to treat)

		Test		Control		
		Predicted value	95% Confidence interval	Predicted value	95% Confidence interval	*p*-Value
PPD Change (mm)	6 months	−3.74	−4.15/−3.33	−3.60	−4.01/−3.18	-
	12 months	−3.71	−4.13/−3.29	−3.68	−4.10/−3.26	.91
BOP% Change	6 months	−52.06	−59.34/−44.77	−51.35	−58.59/−44.11	-
	12 months	−44.79	−52.13/−37.45	−49.65	−57.04/−42.26	.36
MBL Change (mm)	12 months	1.11	0.91/1.31	1.06	0.86/1.27	.73
Buccal REC (mm)	6 months	0.79	0.56/1.02	1.03	0.80/1.26	-
	12 months	0.71	0.47/0.94	1.11	0.87/1.34	.02
Buccal KM Change (mm)	6 months	0.03	−0.21/0.26	−0.53	−0.76/−0.30	-
	12 months	−0.15	−0.39/0.09	−0.49	−0.72/−0.25	.05

Note: *N* = 143 implants. The four implants lost due to disease progression are not considered.

Abbreviations: BOP, bleeding on probing; KM, keratinized mucosa; MBL, marginal bone level; PPD, probing pocket depth; REC, recession.

TABLE A6 Patient-reported outcomes at baseline, 2 weeks, and 12 months by group (per protocol)

		Test							Control							Total						
		n	Med	IQR	Mean	SD	Min	Max	*n*	Med	IQR	Mean	SD	Min	Max	*n*	Med	IQR	Mean	SD	Min	Max
Baseline	Pain	69	0.0	13.0	9.1	15.5	0	70	69	6.0	27.0	17.3	23.7	0	80	138	2.0	20.0	13.2	20.4	0	80
	Bad smell/taste	69	0.0	14.0	11.9	21.9	0	100	69	3.0	20.0	15.4	22.6	0	90	138	0.0	20.0	13.7	22.3	0	100
	Pain on brushing	69	0.0	26.0	13.5	20.1	0	80	69	10.0	33.0	20.3	25.5	0	90	138	5.0	30.0	16.9	23.1	0	90
	Pain on chewing	69	0.0	0.0	3.8	12.0	0	80	69	0.0	10.0	9.4	17.5	0	77	138	0.0	5.0	6.6	15.2	0	80
	Satisfied with esthetics	69	97.0	26.0	76.7	34.8	0	100	68	90.0	28.0	80.1	27.5	0	100	137	92.0	26.0	78.4	31.3	0	100
1 year	Pain	65	0.0	3.0	4.6	12.9	0	80	65	0.0	4.0	6.0	14.2	0	83	130	0.0	3.0	5.3	13.5	0	83
	Bad smell/taste	65	0.0	0.0	4.1	13.5	0	80	65	0.0	3.0	3.5	8.4	0	50	130	0.0	2.0	3.8	11.2	0	80
	Pain on brushing	65	0.0	5.0	7.5	15.0	0	63	65	0.0	8.0	6.0	11.0	0	50	130	0.0	7.0	6.7	13.1	0	63
	Pain on chewing	64	0.0	0.0	1.0	3.3	0	23	65	0.0	3.0	4.3	13.3	0	90	129	0.0	0.0	2.7	9.8	0	90
	Satisfied with esthetics	63	95.0	24.0	79.1	31.5	0	100	65	95.0	30.0	79.8	29.6	0	100	128	95.0	28.5	79.5	30.4	0	100
	Satisfaction with therapy	64	97.5	20.0	87.3	19.5	0	100	64	91.5	20.0	85.0	21.9	10	100	128	95.0	20.0	86.2	20.7	0	100
2 weeks	Surgery unpleasant	69	10.0	30.0	20.0	25.2	0	90	68	13.0	30.0	19.6	21.3	0	75	137	11.0	30.0	19.8	23.3	0	90
	Postsurgical pain	69	10.0	20.0	13.2	17.1	0	70	68	10.0	21.0	14.6	17.6	0	70	137	10.0	20.0	13.9	17.3	0	70
	Pain today	69	0.0	3.0	5.3	12.9	0	70	68	0.0	4.0	3.2	6.2	0	23	137	0.0	3.0	4.3	10.2	0	70

Note: $N = 138$ patients. Results are graphically illustrated in Figure 5

TABLE A7 Clinical and radiographic outcomes at 12 months by location (intention to treat)

	Esthetic zone					Other					Total				
	n	Mean	SD	Min	Max	*n*	Mean	SD	Min	Max	*n*	Mean	SD	Min	Max
PPD Change (mm)	51	−3.9	(2.1)	−9.0	0.0	92	−3.6	(2.3)	−8.0	6.0	143	−3.7	(2.2)	−9.0	6.0
BOP% Change	51	−51.0	(36.4)	−100.0	50.0	92	−45.1	(40.1)	−100.0	75.0	143	−47.2	(38.8)	−100.0	75.0
Buccal REC (mm)	51	1.0	(1.0)	−1.0	4.0	92	0.9	(1.4)	−3.0	7.0	143	0.9	(1.2)	−3.0	7.0
Buccal KM Change (mm)	51	−0.4	(1.1)	−2.0	3.0	92	−0.3	(1.3)	−5.0	4.0	143	−0.3	(1.2)	−5.0	4.0
MBL Change (mm)	51	1.1	(1.1)	−1.0	3.5	92	1.1	(1.3)	−4.4	5.2	143	1.1	(1.2)	−4.4	5.2

Note: *N* = 143 implants. Maxillary sites in the area from second premolar to second premolar were considered to be located in the esthetic zone.

Abbreviations: BOP, bleeding on probing; KM, keratinized mucosa; MBL, marginal bone level; PPD, probing pocket depth; REC, recession.

TABLE A8 Buccal REC in the esthetic zone by the treatment group (intention to treat)

	Test					Control					Total				
	n	Mean	SD	Min	Max	*n*	Mean	SD	Min	Max	*n*	Mean	SD	Min	Max
Buccal REC (mm)	27	0.8	(1.0)	−1.0	3.0	24	1.2	(1.0)	0.0	4.0	51	1.0	(1.0)	−1.0	4.0

Note: *N* = 51 implants.

Abbreviation: REC, recession.

TABLE A9 Evaluation of center effect. (A) Continuous parameters at baseline by center. $N = 147$ implants. (B) Continuous outcomes at 12 months by center (intention to treat). $N = 143$ implants

	Bilbao			Gothenburg			Malaga			Munich			Perugia			Trento			Total		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
(A)																					
PPD (mm)	32	8.7	(1.4)	49	8.1	(1.2)	19	10.1	(1.8)	7	8.3	(2.0)	10	8.0	(1.2)	30	8.9	(1.8)	147	8.6	(1.6)
BOP (%)	32	83.6	(27.4)	49	94.9	(12.5)	19	98.7	(5.7)	7	92.9	(18.9)	10	95.0	(15.8)	30	80.8	(26.8)	147	90.0	(20.8)
SOP (%)	32	31.2	(42.1)	49	54.1	(43.7)	19	26.3	(28.2)	7	28.6	(36.6)	10	15.0	(33.7)	30	20.8	(31.5)	147	34.9	(40.4)
Plaque (%)	32	29.7	(39.9)	49	4.1	(17.9)	19	18.4	(21.8)	7	25.0	(38.2)	10	70.0	(48.3)	30	12.5	(24.3)	147	18.7	(33.3)
Buccal soft tissue level (mm)	32	1.0	(1.4)	49	0.2	(1.7)	19	0.5	(0.8)	7	0.6	(0.8)	10	0.5	(1.2)	30	0.3	(1.0)	147	0.5	(1.3)
Buccal KM (mm)	32	1.5	(1.7)	49	2.4	(1.8)	19	3.0	(2.3)	7	3.0	(2.8)	10	2.8	(1.2)	30	2.3	(1.4)	147	2.3	(1.8)
MBL (mm)	32	6.5	(2.2)	49	5.9	(1.8)	19	7.3	(1.4)	7	5.7	(1.9)	10	5.8	(2.3)	30	5.4	(1.9)	147	6.1	(2.0)
(B)																					
PPD Change (mm)	32	−3.4	(2.4)	48	−4.1	(1.5)	18	−4.2	(2.8)	6	−2.7	(2.3)	9	−3.9	(1.7)	30	−3.1	(2.6)	143	−3.7	(2.2)
BOP% Change	32	−48.4	(46.6)	48	−54.2	(36.2)	18	−55.6	(35.9)	6	0.0	0.0	9	−61.1	(39.7)	30	−35.0	(30.5)	143	−47.2	(38.8)
Buccal REC (mm)	32	0.7	(1.5)	48	1.2	(0.9)	18	0.7	(1.0)	6	0.3	(0.8)	9	1.3	(1.3)	30	0.7	(1.5)	143	0.9	(1.2)
Buccal KM Change (mm)	32	0.0	(1.9)	48	−0.3	(0.9)	18	−0.6	(0.9)	6	0.0	(1.3)	9	−0.8	(0.8)	30	−0.5	(0.9)	143	−0.3	(1.2)
MBL Change (mm)	32	0.9	(0.9)	48	1.4	(1.3)	18	1.1	(1.4)	6	1.6	(2.0)	9	0.5	(0.8)	30	0.8	(1.2)	143	1.1	(1.2)
Plaque at 12 months – pp[a]	32	27.3	(33.2)	47	4.8	(14.4)	17	30.9	(40.0)	4	43.8	(42.7)	9	38.9	(48.6)	28	21.4	(33.8)	137	20.1	(32.6)

Abbreviations: BOP, bleeding on probing; KM, keratinized mucosa; MBL, marginal bone level; REC—recession; PPD, probing pocket depth; REC, recession.

[a]Plaque at 12 months is reported per protocol.

TABLE A10 Composite outcome at 12 months by center (intention to treat)

		Bilbao		Gothenburg		Malaga		Munich		Perugia		Trento		Total	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Composite outcome	Complete[a]	6	18.8%	6	12.2%	2	10.55	0	0.0%	2	20.0%	6	20.0%	22	15.0%
	Incomplete	26	81.2%	43	87.8%	17	89.5%	7	100.0%	8	80.0%	24	80.0%	125	85.0%

Note: N = 147 implants.

[a]Complete defined as implant not lost, no bleeding on probing, no suppuration on probing, probing pocket depth ≤5 mm, and buccal recession ≤1 mm.

TABLE A11 Logistic regression: Composite outcome at 12 months comparing centers (intention to treat)

	Odds ratio	95% Confidence interval	*p*-Value
Bilbao	1.00	-	-
Gothenburg	0.60	0.18/2.07	.423
Malaga	0.51	0.09/2.83	.441
Munich	[a]		
Perugia	1.08	0.18/6.46	.930
Trento	1.08	0.31/3.82	.901
Intercept	0.23	0.09/0.56	.001

Note: $N = 147$ implants.

[a]One cell with 0 observations.

TABLE A12 Regression analysis of continuous outcomes comparing centers, adjusted for multiple comparisons (Bonferroni) (intention to treat)

	Contrast	Standard error	*t*-Value	*p*-Value
PPD change				
Gothenburg versus Bilbao	−0.69	0.40	−1.70	1.00
Malaga versus Bilbao	−0.78	0.52	−1.51	1.00
Munich versus Bilbao	0.77	0.79	0.98	1.00
Perugia versus Bilbao	−0.45	0.67	−0.68	1.00
Trento versus Bilbao	0.34	0.45	0.75	1.00
Malaga versus Gothenburg	−0.10	0.49	−0.20	1.00
Munich versus Gothenburg	1.46	0.77	1.90	.86
Perugia versus Gothenburg	0.24	0.64	0.37	1.00
Trento versus Gothenburg	1.03	0.41	2.49	.20
Munich versus Malaga	1.56	0.83	1.87	.94
Perugia versus Malaga	0.33	0.72	0.46	1.00
Trento versus Malaga	1.12	0.53	2.13	.51
Perugia versus Munich	−1.22	0.93	−1.31	1.00
Trento versus Munich	−0.43	0.79	−0.55	1.00
Trento versus Perugia	0.79	0.67	1.17	1.00
MBL change				
Gothenburg versus Bilbao	0.48	0.20	2.42	.24
Malaga versus Bilbao	0.12	0.25	0.48	1.00
Munich versus Bilbao	0.68	0.38	1.78	1.00
Perugia versus Bilbao	−0.45	0.32	−1.37	1.00
Trento versus Bilbao	−0.11	0.22	−0.52	1.00
Malaga versus Gothenburg	−0.35	0.24	−1.49	1.00
Munich versus Gothenburg	0.21	0.37	0.56	1.00
Perugia versus Gothenburg	−0.92	0.31	−2.94	.05
Trento versus Gothenburg	−0.59	0.20	−2.94	.05
Munich versus Malaga	0.56	0.41	1.39	1.00
Perugia versus Malaga	−0.57	0.35	−1.61	1.00
Trento versus Malaga	−0.23	0.26	−0.91	1.00
Perugia versus Munich	−1.13	0.45	−2.49	.20
Trento versus Munich	−0.80	0.39	−2.07	.59
Trento versus Perugia	0.33	0.33	1.01	1.00

Note: $N = 143$ implants. Outcomes are graphically illustrated in Figure A7.

TABLE A13 Missing values for the different parameters by time point

	Test			Control			Total		
	Baseline	6 months	12 months	Baseline	6 months	12 months	Baseline	6 months	12 months
PPD	0	4	3	0	5	3	0	9	6[a]
BOP	0	4	3	0	5	3	0	9	6[a]
Buccal Soft Tissue Level	0	4	3	0	5	3	0	9	6[a]
Buccal KM	0	4	3	0	5	3	0	9	6[a]
MBL	0	-	3	0	-	3	0	-	6[a]

Note: Unit of analysis: Implant.

Abbreviations: BOP, bleeding on probing; KM, keratinized mucosa; MBL, marginal bone level; PPD, probing pocket depth.

[a]Six implants in five patients.

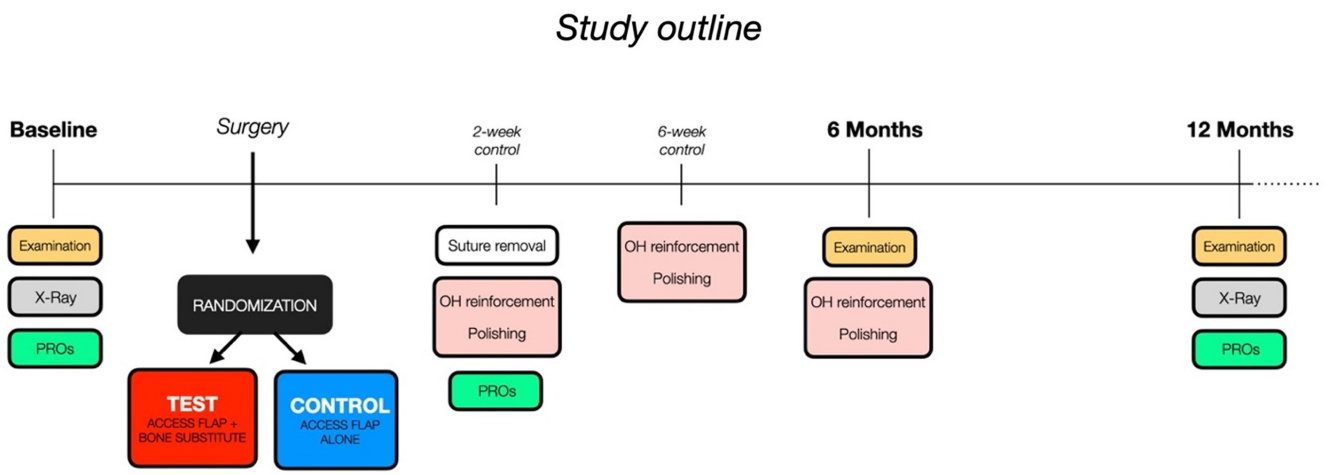

FIGURE A1 Flowchart illustrating the study outline

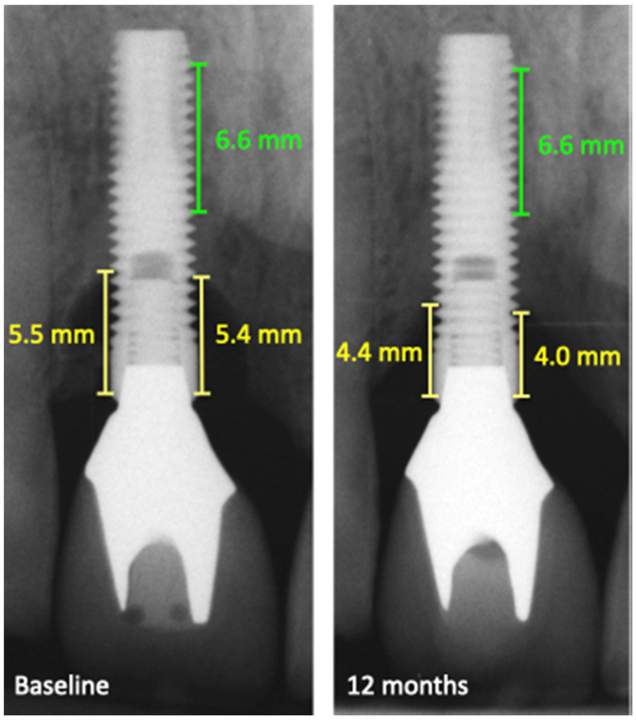

FIGURE A2 Illustration of radiographic evaluation of marginal bone levels at baseline and at 1 year. Images were calibrated by known distances (green line).

Questionnaire
Baseline (prior to surgery)

1. Are you experiencing any discomfort or pain from the implant(s) scheduled for surgery?

0 No pain/discomfort — 100 Substantial pain/discomfort

2. Are you experiencing any bad taste or smell from the implant(s) scheduled for surgery?

0 No bad taste/smell — 100 Substantial bad taste/smell

3. Are you experiencing any discomfort or pain when brushing the implant(s) scheduled for surgery?

0 None — 100 Substantial pain/discomfort

4. Are you experiencing any discomfort or pain when chewing with the implant(s) scheduled for surgery?

0 No pain/discomfort — 100 Substantial pain/discomfort

5. Are you satisfied with the esthetic appearance of the implant(s) scheduled for surgery?

0 Not at all satisfied — 100 Fully satisfied

Questionnaire
2 weeks after surgery

1. How would you describe the surgery?

0 Not unpleasant at all — 100 Very unpleasant

2. Did you experience discomfort/pain following the surgery?

0 No discomfort/pain — 100 Substantial discomfort/pain

3. Are you still experiencing discomfort/pain?

0 No discomfort/pain — 100 Substantial discomfort/pain

4. Comment (Eg "adverse events"):

Questionnaire
1 year after surgery

1. Are you experiencing any discomfort or pain from the implant(s) that were treated surgically?

0 No pain/discomfort — 100 Substantial pain/discomfort

2. Are you experiencing any bad taste or smell from the implant(s) that were treated surgically?

0 No bad taste/smell — 100 Substantial bad taste/smell

3. Are you experiencing any discomfort or pain when brushing the implant(s) that were treated surgically?

0 No pain/discomfort — 100 Substantial pain/discomfort

4. Are you experiencing any discomfort or pain when chewing with the implant(s) that were treated surgically?

0 No pain/discomfort — 100 Substantial pain/discomfort

5. Are you satisfied with the esthetic appearance of the implant(s) that were treated surgically?

0 Not at all satisfied — 100 Fully satisfied

6. How do you judge the outcome of therapy?

0 Failure — 100 Complete success

FIGURE A3 Questionnaires provided to study participants at baseline, at 2 weeks and at 12 months

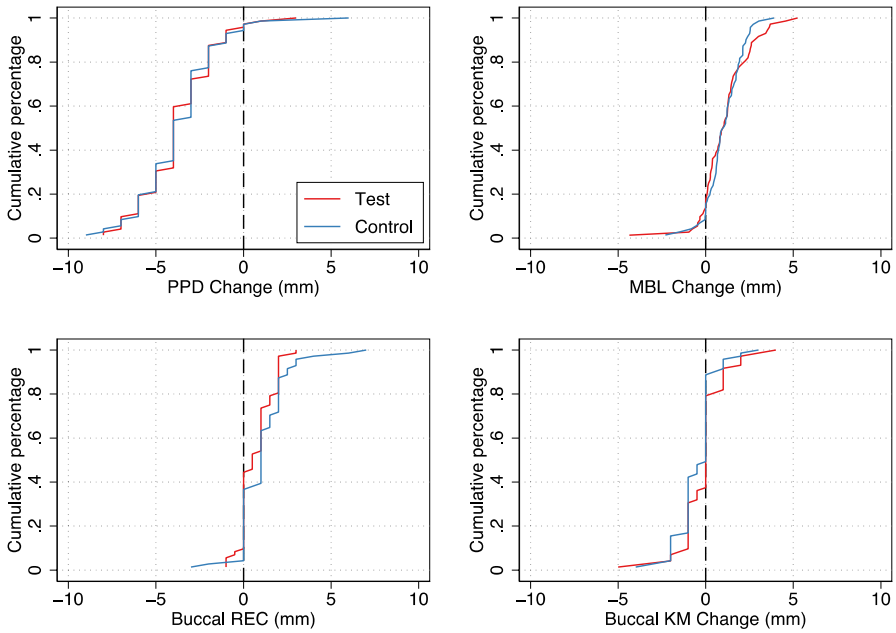

FIGURE A4 Cumulative curves of continuous outcomes at 12 months by group. *N* = 143 implants. KM, keratinized mucosa; MBL, marginal bone level; PPD, probing pocket depth; REC, recession.

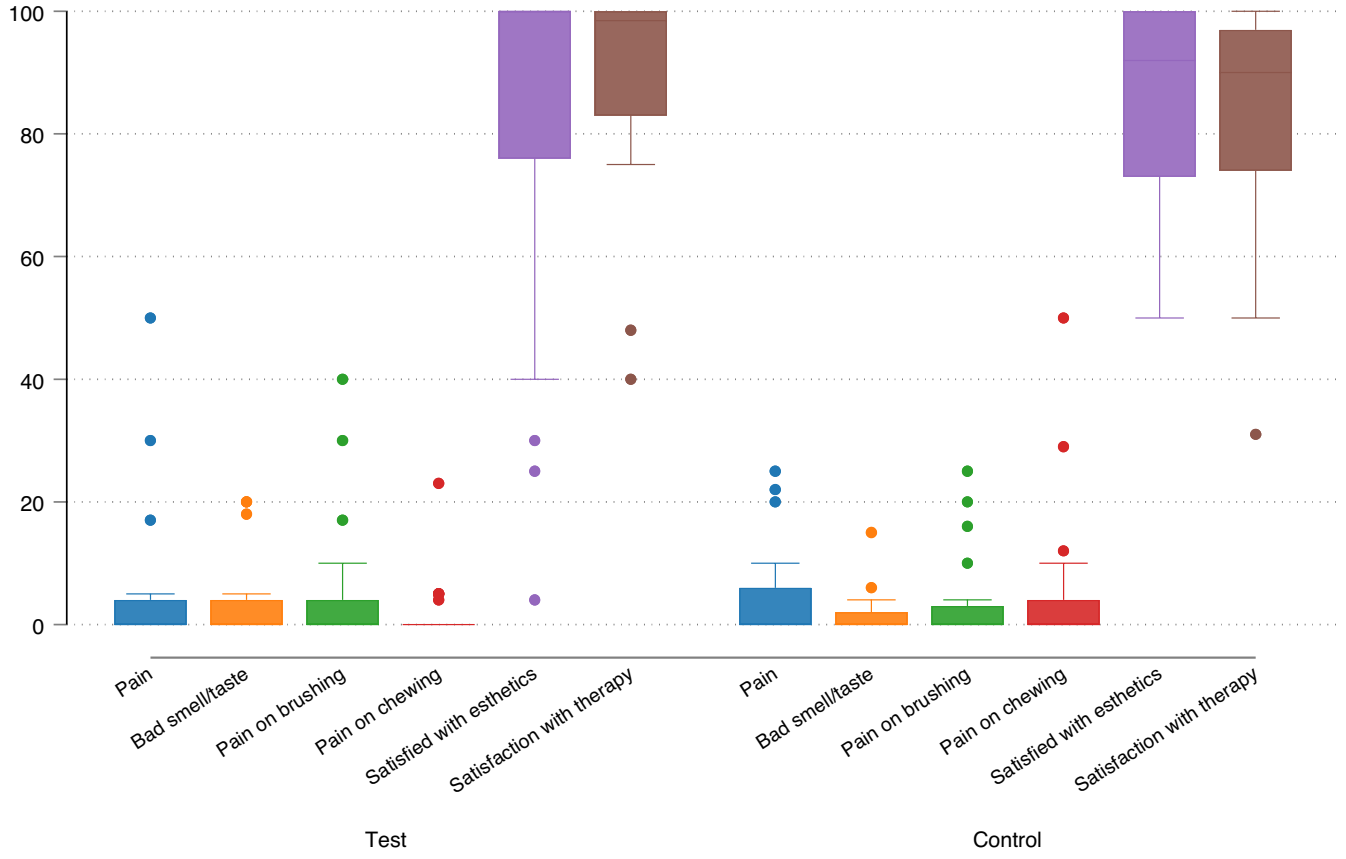

FIGURE A5 Patient-reported outcomes at 12 months by group considering only subjects with treated implant sites in the esthetic zone (second premolar to second premolar in the maxilla). Outcomes were scored on a VAS (100 mm). $N = 47$ patients

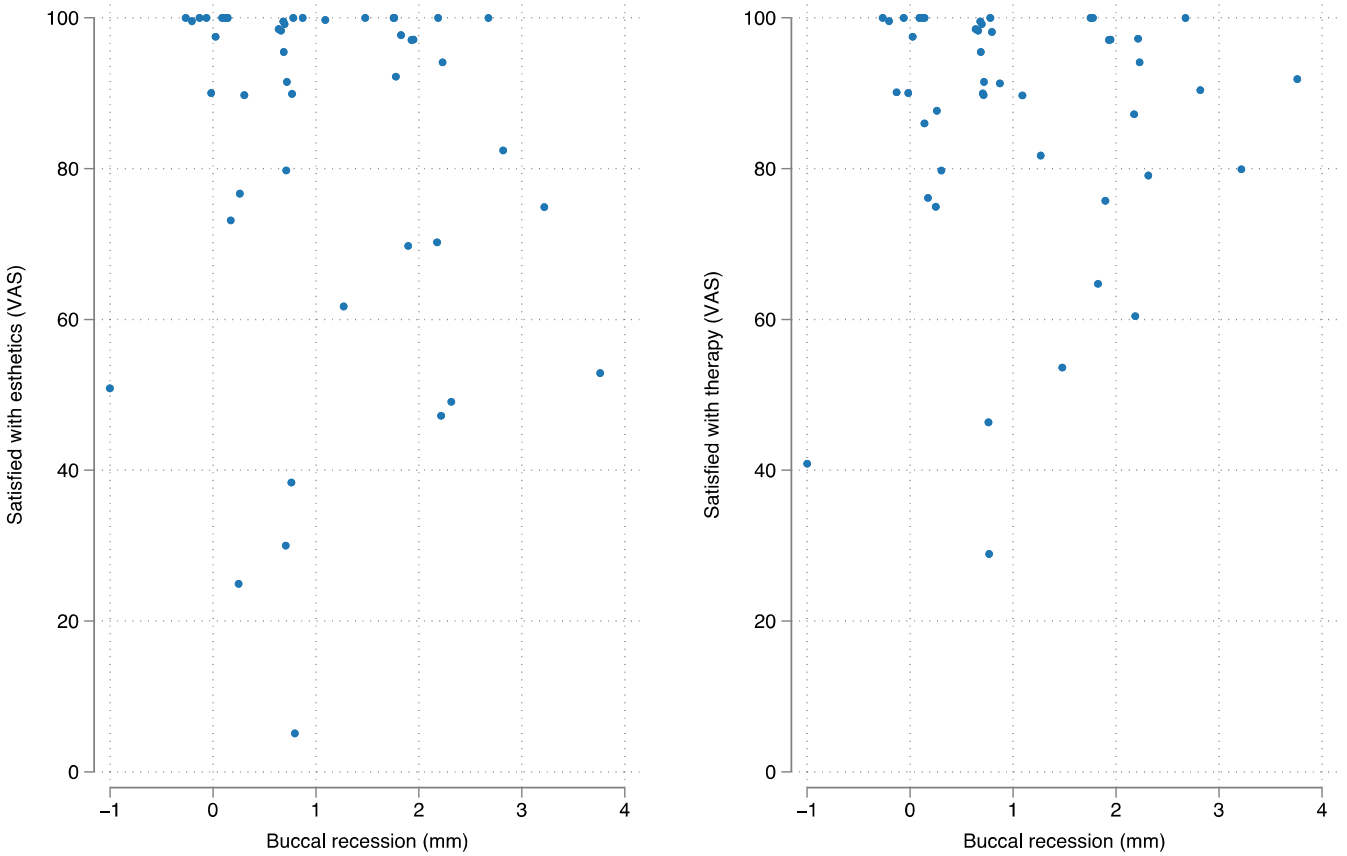

FIGURE A6 Patient satisfaction by soft tissue recession considering only subjects with treated implant sites in the esthetic zone (second premolar to second premolar in the maxilla). *N* = 47 patients. VAS, visual analog scale

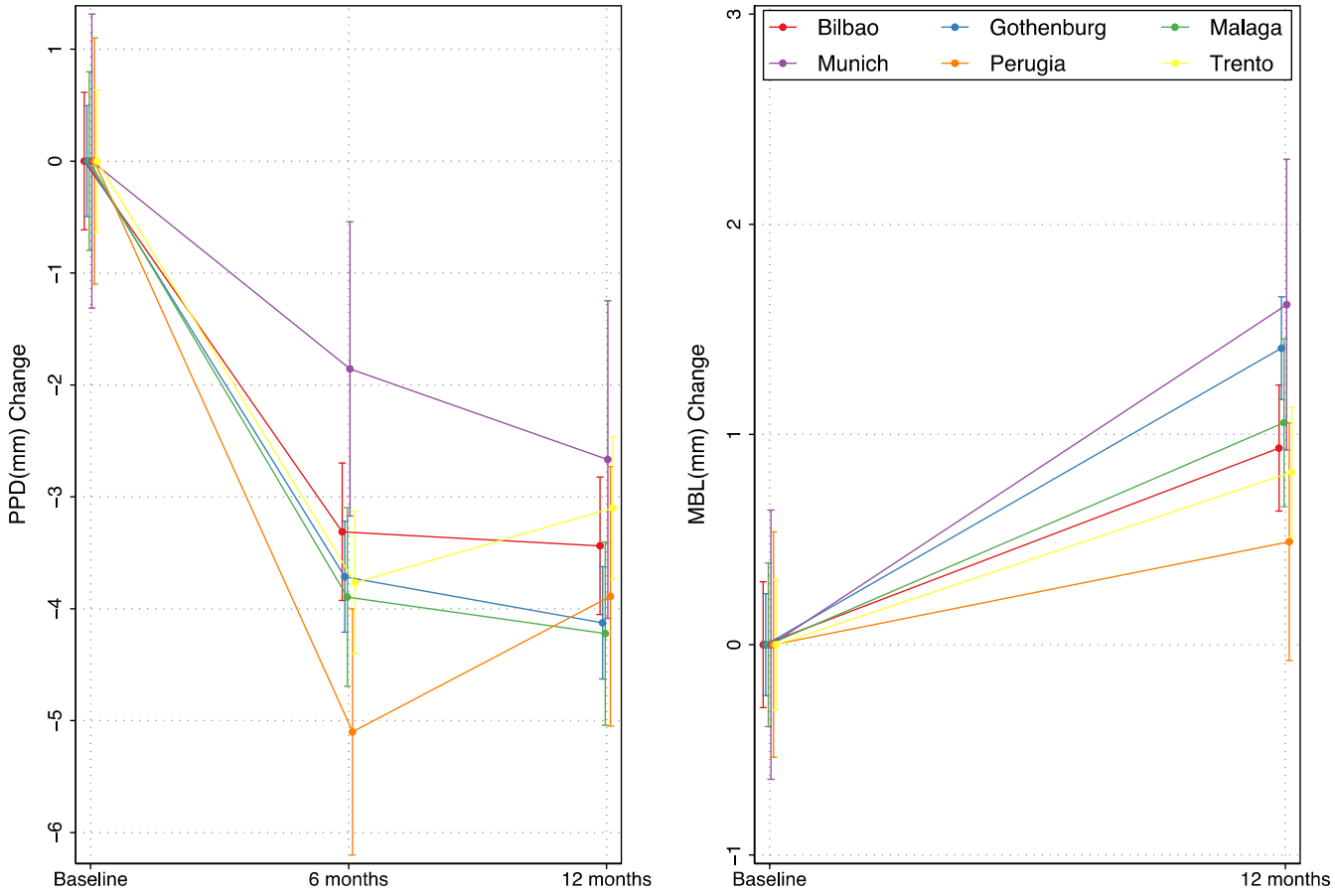

FIGURE A7 Illustration of potential center effect: Probing pocket depth change and marginal bone level change by center. $N = 143$ implants. Results of the statistical testing are illustrated in Table A12. MBL, marginal bone level; PPD, probing pocket depth.

III

Artículo 3:

Regidor, E., Ortiz-Vigon, A., Romandini, M., Dionigi, C., Derks, J., & Sanz, M. (2023). The adjunctive effect of a resorbable membrane to a xenogeneic bone replacement graft in the reconstructive surgical therapy of peri-implantitis: A randomized clinical trial. Journal of Clinical Periodontology, 1–19. https://doi.org/10.1111/jcpe.13796

Objetivo:

Evaluar el potencial añadido de utilizar una membrana de colágeno reabsorbible recubriendo un sustituto óseo xenogénico en la terapia reconstructiva de la periimplantitis.

Material y métodos:

Se trataron 43 pacientes diagnosticados de periimplantitis asociada a defectos intraóseos mediante un tratamiento quirúrgico reconstructivo utilizando un sustituto óseo xenogénico. Adicionalmente en el grupo test se utilizó una membrana de colágeno reabsorbible cubriendo las partículas del injerto óseo. Se midieron profundidades de sondaje (PPD), indices de sangrado y supuración al sondaje (BoP/SoP), nivel de tejidos blandos y mucosa queratinizada (KMW) a 6 y 12 meses tras la intervención. Los niveles óseos periimplantarios radiográficos (MBL) y los resultados reportados por los pacientes se midieron a 12 meses del procedimiento quirúrgico. Tras 12 meses también se registró una variable de éxito compuesta que incluía ausencia de sangrado y/o supuración, profundidad de sondaje igual o inferior a 5mm y que la reducción de los niveles de tejido blando vestibulares (recesión/dehiscencia vestibular) fuera igual o inferior a 1mm.

Resultados:

A 12 meses de seguimiento no se registró la perdida de ningún implante y se observó el éxito del tratamiento en el 36.8% y 45% de los implantes en el grupo test y control respectivamente. De igual manera, no hubo diferencias estadísticamente significativas en PPD, BoP/SoP. KMW, MBL o recesión vestibular.

Conclusiones:

El uso adicional de una membrana reabsorbible recubriendo un sustituto óseo en la terapia reconstructiva de defectos intraóseos provocados por la periimplantitis no ofreció ningún beneficio ni a nivel clínico ni a nivel radiográfico.

Palabras clave:

Membrana barrera, regeneración ósea, ensayo clínico, defecto periimplantario, periimplantitis, terapia reconstructiva.

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ORIGINAL ARTICLE

Journal of Clinical Periodontology WILEY

The adjunctive effect of a resorbable membrane to a xenogeneic bone replacement graft in the reconstructive surgical therapy of peri-implantitis: A randomized clinical trial

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Arrow Development S.L.

Abstract

Aim: To evaluate the potential adjunctive effect of a resorbable collagen membrane covering a xenogeneic bone replacement graft in the reconstructive surgical therapy of peri-implantitis.

Materials and Methods: Forty-three patients (43 implants) diagnosed with peri-implantitis associated with intra-bony defects were treated with a surgical reconstructive approach that included a xenogeneic bone substitute material. Additionally, resorbable collagen membranes were placed over the grafting material at sites randomly allocated to the test group; conversely, no membranes were placed in the control group. Clinical outcomes, namely probing pocket depth (PPD), bleeding and suppuration on probing (BoP and SoP), marginal mucosal level (REC) and keratinized mucosa width (KMW), were recorded at baseline and 6 and 12 months after surgery. Radiographic marginal bone levels (MBLs) and patient-reported outcomes (PROs) were assessed at baseline and 12 months. A composite outcome (success) was evaluated at 12 months, which included the absence of BoP/SoP, PPD ≤5 mm and reduction of buccal marginal mucosal level (buccal REC) of ≤1 mm.

Results: At 12 months, no implants were lost and treatment success was observed at 36.8% and 45.0% of implants in the test and control groups, respectively ($p = .61$). Similarly, there were no significant differences between groups in terms of changes of PPD, BoP/SoP, KMW, MBL or buccal REC. Post-surgical complications were observed in the test group only (e.g., soft tissue dehiscence, exposure of particulate bone graft and/or resorbable membrane). Longer surgical times (~10 min; $p < .05$) and higher levels of self-reported pain at 2 weeks ($p < .01$) were observed in the test group.

Conclusions: This study failed to demonstrate the presence of added clinical or radiographic benefits of the use of a resorbable membrane to cover a bone substitute material within the reconstructive surgical therapy of peri-implantitis associated with intra-bony defects.

KEYWORDS

barrier membrane, bone regeneration, clinical trial, peri-implant defect, peri-implantitis, reconstructive therapy

Clinical Relevance

Scientific rationale for study: It remains unclear whether the use of a resorbable membrane provides any benefits when used to cover bone substitute material in the reconstructive surgical therapy of peri-implantitis.

Principal findings: The adjunctive use of a resorbable membrane was associated with longer surgical times, higher levels of post-surgical pain and complications. However, there were no clinical or radiographic benefits 1 year post-operatively when compared to bone substitute material alone.

Practical implications: The use of a resorbable membrane in the reconstructive surgical therapy of peri-implantitis should be questioned given the lack of benefit on short-term clinical and radiographic outcomes.

1 | INTRODUCTION

Peri-implantitis is a highly prevalent disease characterized by the inflammation of peri-implant mucosa and subsequent progressive loss of the supporting bone (Rodrigo et al., 2018; Romandini et al., 2019; Romandini, Lima, Pedrinaci, Araoz, Costanza Soldini, & Sanz, 2021; Tomasi & Derks, 2012; Vignoletti et al., 2019). If left untreated, it may ultimately lead to implant and restoration loss (Derks et al., 2016). Its treatment aims at the resolution of inflammation and the prevention of further bone loss. In this regard, non-surgical sub-marginal instrumentation has shown limited efficacy, which typically results in the need for surgical therapy to access implant surfaces (Karlsson et al., 2019; Romandini et al., 2022).

Intra-bony defects associated with peri-implantitis may be treated with reconstructive approaches during the surgical intervention (Tomasi et al., 2019). Recently, a large multi-centre randomized clinical trial (RCT) reported that the adjunctive use of a bone substitute material resulted in similar radiographic outcomes when compared to open-flap debridement (OFD) and that the added value of the reconstructive approach was limited to the reduction of buccal marginal mucosal recession (Derks, Ichioka, et al., 2022; Derks, Ortiz-Vigón, et al., 2022). It remains unclear, however, whether the use of a resorbable membrane covering the bone substitute material could provide any additional benefit. Indeed, the additional use of membranes has shown clear benefits over the use of bone substitute materials alone in the context of guided bone regeneration simultaneous to implant placement (Sanz-Sánchez et al., 2015). However, the inherent different defect morphologies and aspects related to soft tissue management may limit the value of adding a membrane to reconstructive surgery at peri-implantitis-associated intra-bony defects. It was, therefore, the aim of the present RCT to evaluate this potential benefit within the reconstructive surgical therapy of peri-implantitis.

2 | MATERIALS AND METHODS

This study is reported following the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines (Schulz, Altman & Moher, 2010). The protocol of the trial was registered in advance at isrctn.com (ISRCTN67095066; https://www.isrctn.com/ISRCTN67095066) and approved by the Ethical Committee of Clinical Investigations of the Basque Country (CEICm-E PS2019012). All participants were informed in detail about the study protocol and provided written informed consent prior to inclusion.

2.1 | Trial design

The present study was designed as a randomized, single-centre clinical trial with two parallel groups, a 1:1 allocation ratio and a follow-up of 12 months.

2.2 | Participants

All patients participating in this RCT were treated in a private specialist clinic (Clinic Ortiz-Vigón Periocentrum Bilbao, Bilbao, Spain) once they fulfilled the following entrance criteria:

- Adult patients (≥18 years of age) willing to participate in the RCT, once being appropriately informed and after signing the informed consent approved by the local Ethical Committee;
- Diagnosis of peri-implantitis at ≥1 implant in function for >1 year displaying a peri-implant probing pocket depth (PPD) ≥7 mm, bleeding and/or suppuration on probing (BoP/SoP) and radiographically documented marginal bone loss (MBL) ≥3 mm. In the absence of reference radiographs, a bone level ≥3 mm was utilized (Romandini, Berglundh, Derks, Sanz, & Berglundh, 2021);
- Target implants were selected on the basis of absence of mobility and presence of no more than one site with residual BoP after non-surgical sub-marginal instrumentation;
- Target implants had to also demonstrate the presence of a peri-implant intra-bony defect with a depth ≥3 mm and width ≤4 mm, as assessed on radiographs and confirmed intra-surgically. In addition, the bony defect should present with a minimum of two walls (mesial and distal). No requirements as to the presence/absence of buccal and/or lingual walls were applied (defect types II-III b-c according to Monje et al., 2019 were eligible);

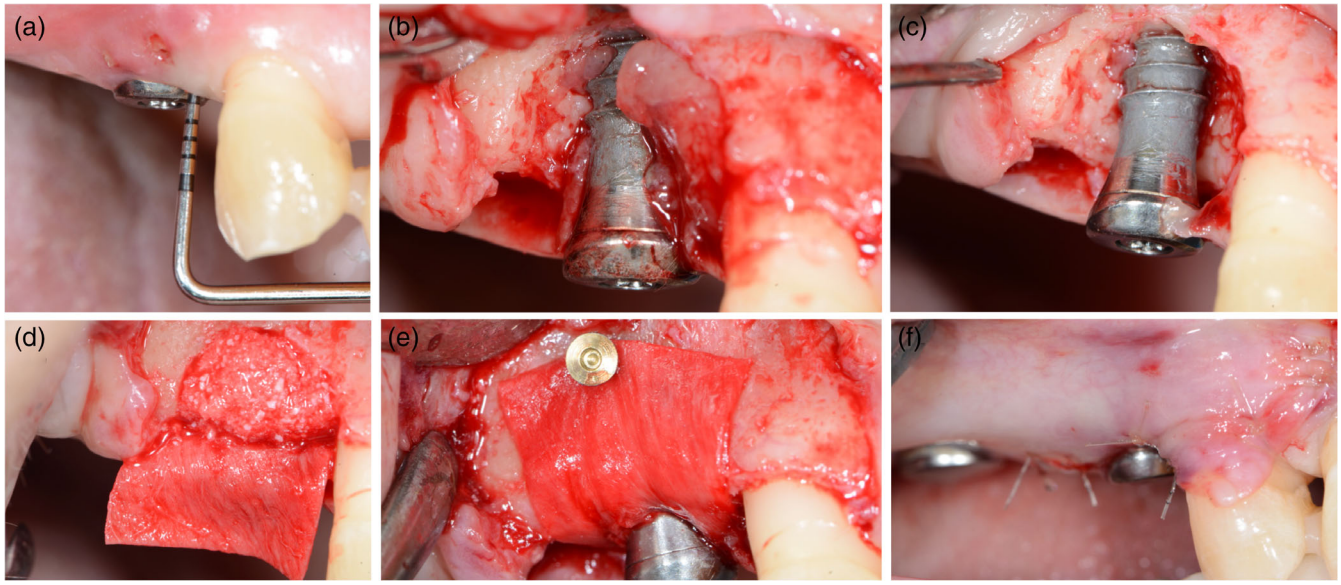

FIGURE 1 Surgical intervention of a patient in the control group. (a) Clinical assessment at baseline (after non-surgical therapy and removal of implant-supported prosthesis). (b) Full-thickness flap elevation. (c) Peri-implantitis defect after removal of inflammation tissue. (d, e) Particulate bone graft applied to the peri-implant bony defect. (f) Repositioning and suturing of the flaps.

- In the presence of more than one implant fulfilling the inclusion criteria, one of the implants was randomly selected and included in the study.

Patients were excluded if presenting systemic diseases representing a contraindication for oral surgery (e.g., recent myocardial infarction, active treatment of malignancy, uncontrolled diabetes, radiotherapy of the head or neck within the last 5 years, etc.), untreated periodontitis, current smoking of >10 cigarettes/day, current pregnancy or lactation, allergy to collagen or current use of medications such as analgesics/anti-inflammatory nonsteroidal drugs, immune-suppressive drugs (e.g., corticosteroids) or bisphosphonates.

2.3 | Interventions

After providing individualized oral hygiene instructions, supra- and submarginal instrumentation was performed at the affected implants with a combination of plastic ultrasonic scalers (PI Teflon-coated tips, Electro Medical Systems, Nyon, Switzerland) and air polishing with erythritol powder containing 0.3% chlorhexidine (Air-Flow PLUS, mean grain size of 14 μm). When necessary, implant-supported restorations were adjusted to allow proper access for oral hygiene procedures.

Approximately 4 weeks later, a 10-day systemic antibiotic treatment (Amoxicillin 2 × 750 mg daily) was initiated 3 days prior to the surgical intervention. All surgeries were performed by one experienced EFP-board certified periodontist (AOV) between July 2019 and February 2021. After applying local anaesthesia and, whenever possible, temporary removal of the implant-supported prosthesis, intrasulcular incisions were made and full-thickness flaps were carefully elevated. Once the inflammation tissue was removed from the peri-implant bony defect with titanium curettes, the implant surfaces were thoroughly decontaminated using a rotating titanium brush (Nano NiTi Brush, HANS KOREA CO. Ltd, Goyang, South Korea) at ≤1200 rpm under continuous irrigation with saline. The peri-implant bony defect was then filled with a xenogeneic bone replacement graft combined with collagen (Bio-Oss Collagen, Geistlich, Lucerne, Switzerland) up to the level of the bone crest (Figures 1 and A1; Appendix A). In the test group (see below for details on random allocation), a resorbable natural collagen membrane (Bio-Guide, Geistlich) was customized to fully cover the peri-implant defect and bone substitute material and was then stabilized by one or more fixing pins (Figures 2 and A2). Periosteal incisions were made to allow tensionless flap adaptation and suture of the soft tissue margins, aiming at primary closure. In cases when implant-supported restorations were removed, a healing abutment was used for at least 2 weeks.

Following surgery, sutures were removed at 2 weeks, and during this time patients were advised to abstain from mechanical plaque control and to rinse with a 0.12% chlorhexidine and 0.05% cetylpyridinium chloride oral mouthwash (Perio-Aid; Dentaid). Patients were then enrolled in a maintenance care programme including oral hygiene instructions as well as professional plaque removal using plastic ultrasonic scalers and air polishing. Follow-up visits were scheduled at 4 and 6 weeks, as well as at 6 and 12 months (Figure A3).

2.4 | Data collection

2.4.1 | Clinical outcome measurements

The following clinical variables were recorded by a blinded examiner (ER) with restorations in place and using a 15-mm metal University

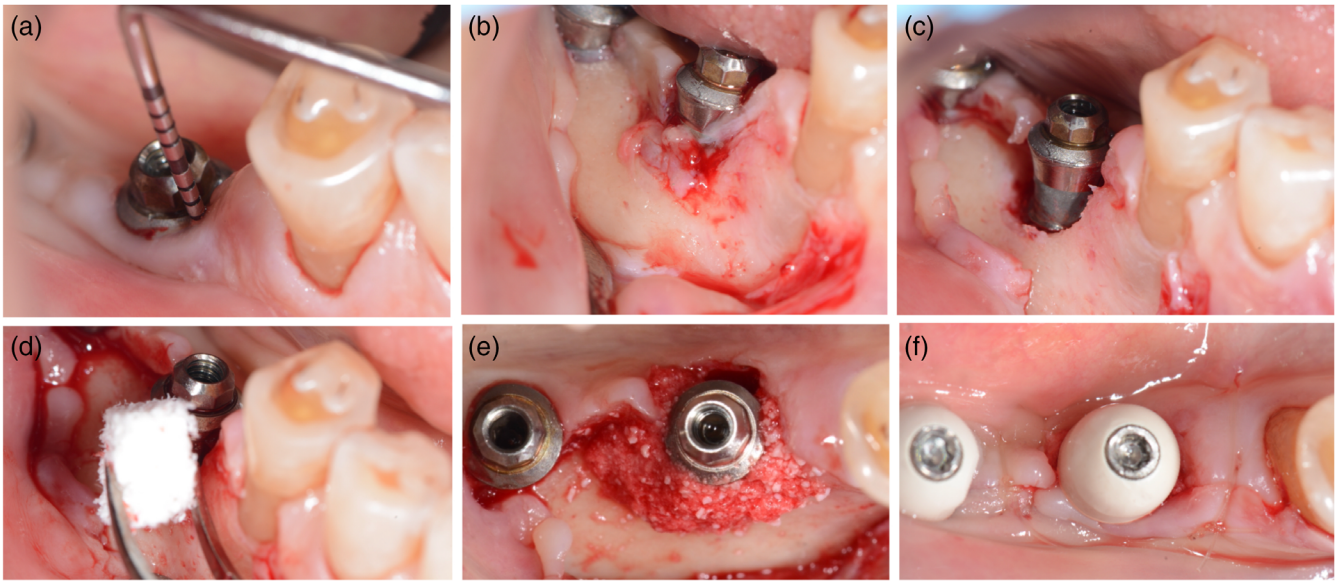

FIGURE 2 Surgical intervention of a patient in the test group. (a) Clinical measurement at baseline (after non-surgical therapy and removal of implant-supported prosthesis). (b) Full-thickness flap elevation. (c) Peri-implantitis defect after removal of inflammation tissue. (d) Particulate bone graft applied to the peri-implant bony defect. (e) Fixation of the resorbable collagen membrane covering the entire defect. (f) Repositioning and suturing of the soft tissue flaps.

North Carolina (UNC) periodontal probe (Hu-Friedy) at baseline (just before surgery) and at 6 and 12 months: PPD, BoP, SoP (within 15 s following probing), presence of plaque at four aspects per implant, marginal mucosal level (i.e., measured from the prosthetic margin to the peri-implant mucosal margin Romandini, Pedrinaci, Lima, Soldini, Araoz, & Sanz, 2021) and keratinized mucosa width (KMW) at the mid-buccal aspect. PPD, marginal mucosal level and KMW were recorded to the nearest millimetre, while BoP, SoP and plaque were scored dichotomously (yes/no).

During surgery, the depth (bony crest to bottom of defect) and width of the bony defect, as well as bone levels relative to the implant shoulder, were evaluated at four aspects per implant using a periodontal probe. Defect configuration was classified as "non-contained" (i.e., open at buccal and/or lingual aspect – types II-IIIb according to Monje et al., 2019) or "contained" (i.e., circumferential defects – types II-IIIc according to Monje et al., 2019). The buccal bony wall was categorized as "intact" if ≤2 mm (relative to the implant shoulder) was lost, as "partially missing" if 2–4 mm of the buccal aspect of the implant was exposed and "missing" if >4 mm was exposed.

2.4.2 | Radiographic outcome measurements

Intra-oral radiographic images were obtained using a long-cone parallel technique before surgery and at 12 months. MBLs were measured by a trained, calibrated, blinded investigator (CD) using an image analysis software (ImageJ 2.0.0-rc-69/1.52 n; National Institutes of Health, Bethesda, MD, USA). Calibration was performed using 20 implant sites. Repeated MBL assessments revealed an intra-rater measurement error of 0.31 ± 0.19 mm (standard deviation) and an intra-class correlation coefficient of 0.99 (95% confidence interval [CI]: 0.99–1.00).

Images were calibrated according to the known inter-thread distance and implant length/diameter. MBLs were measured on the mesial and distal aspects relative to a fixed landmark (i.e., implant shoulder or prosthetic margin) and expressed in mm (Figure A4).

2.4.3 | Patient-reported outcomes (PROs)

PROs were recorded using customized questionnaires completed by patients at baseline, 2 weeks and 12 months after surgery (Derks, Ichioka, et al., 2022; Derks, Ortiz-Vigón, et al., 2022). These questionnaires were based on visual analogue scales (VAS) and answered privately prior to the collection of the clinical data (Figure A5).

2.4.4 | Complications

The following post-operative complications were recorded two weeks after surgery: soft tissue dehiscence, exposure of the resorbable membrane and/or bone substitute material, post-operative infections and sensory disturbance (Figure A6).

2.5 | Primary and secondary outcomes

The primary outcome was a composite measure assessed at the affected implant at 12 months, which included (i) implant not lost, (ii) absence of BoP/SoP at all sites, (iii) PPD ≤5 mm at all sites and

(iv) change of buccal marginal mucosal level (buccal REC) ≤1 mm. As secondary outcomes, the following variables were measured at 12 months: changes of PPD, BoP, SoP, KMW, buccal REC, MBL and PROs. Furthermore, the duration of the surgical intervention and the occurrence of post-operative complications and adverse events were assessed.

2.6 | Sample size calculation

When planning this investigation, no clinical study using a composite outcome as primary outcome of efficacy of a reconstructive surgical intervention for the treatment of periimplantitis was available. Therefore, a minimum sample size of 20 patients per group was estimated a priori as having a statistical power of 93% to detect a relevant difference between groups in gain of MBL of 1.5 mm, assuming a common standard deviation of 1.2 mm (Renvert et al., 2018; Roos-Jansåker et al., 2007). In order to compensate for possible drop-outs, 43 patients were included.

2.7 | Randomization and blinding procedures

Study participants were randomly allocated to the test or control group during surgery, just after completing implant decontamination procedures. The randomization sequence was determined using a block size of 4 with a 1:1 allocation. Allocation was concealed through the use of sealed, opaque envelopes. Outcome assessors (ER and CD) and patients were blinded to group allocation.

2.8 | Data analysis

For MBL and PPD, the deepest measurement at each evaluation time was chosen, while for marginal mucosal level and KMW, the buccal aspect was representative of the implant. For BoP and SoP, both the presence and the extent (i.e., the percentage of positive aspects per implant – Verket et al., 2023) were considered. Changes between baseline and 6 and 12 months were calculated for all parameters. Reduction of buccal marginal mucosal level was interpreted as recession (buccal REC).

Analyses were carried out according to the "complete case" principle using STATA 17.0 software (StataCorp, College Station, TX, USA), as missing data were considered "missing completely at random" and sensitivity analyses applying the "intention-to-treat" principle (imputation with the last observed value) yielded similar results. Descriptive key characteristics of the study participants and implants were summarized. Thus continuous variables, with the exception of PROs, were expressed through means and standard deviations, while categorical parameters were described by frequency and percentage.

Differences between groups were tested through logistic (binary) or linear (continuous) regression analyses, using two-sided hypotheses and an $\alpha < 0.05$ level of significance. Group allocation and time point (baseline, 6 or 12 months) were entered as main effects and interaction terms to the respective models. Results of pairwise comparisons were expressed as differences in means (MD) or odds ratios (ORs), together with 95% CIs.

PROs were analysed using the Mann–Whitney test because of skewed data distribution and presented as median and interquartile range (IQR).

3 | RESULTS

Forty-three subjects (22 in the control and 21 in the test group, each contributing with one implant), were included at baseline (Figure 3). Details on the study sample and implant-related information are given in Tables 1 and A1. The study population consisted mainly of female patients (55.8%) with a mean age at baseline of 61.1 (± 9.6) years; deepest PPD and MBL at baseline were 9.1 (2.1) mm and 6.0 (1.9) mm, respectively. Restorations could not be removed during surgery in 25.6% of the cases (27.3% and 23.8% in the control and test groups, respectively), while 32.6% of the defects were categorized as contained (45.5% and 19.0% in the control and test groups, respectively).

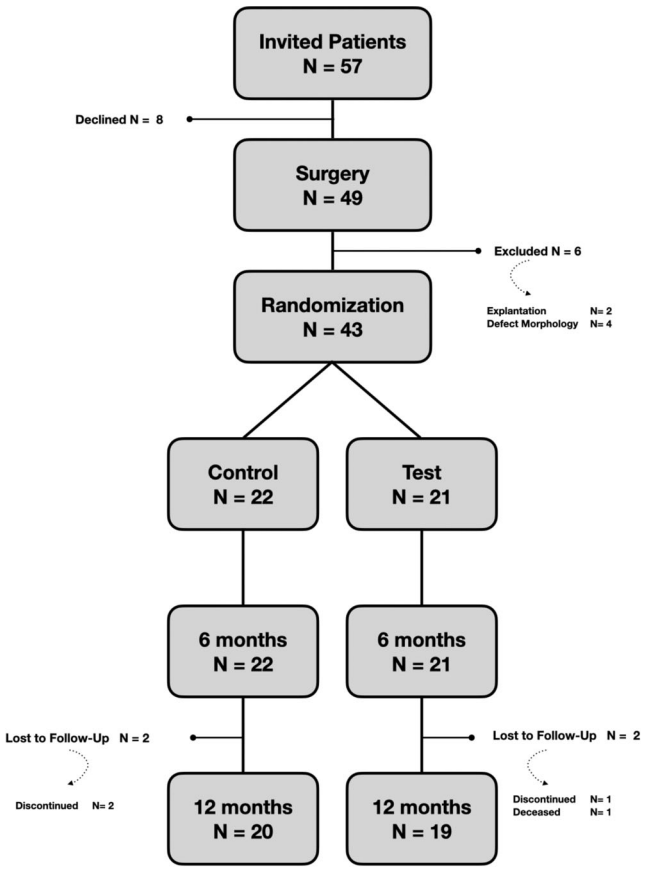

FIGURE 3 Flow-chart illustrating the process of enrollment, treatment allocation and follow-up.

TABLE 1 Patient and implant/site characteristics at baseline by group.

Patient-level characteristics															
	Control					Test					Total				
	n	% /mean	SD	Min.	Max.	*n*	% /mean	SD	Min.	Max.	*n*	% /mean	SD	Min.	Max.
Gender															
Female	14	63.6%				10	47.6%				24	55.8%			
Male	8	36.4%				11	52.4%				19	44.2%			
Smoker															
No	21	95.5%				18	85.7%				39	90.7%			
Yes	1	4.5%				3	14.3%				4	9.3%			
Age	22	62.2	(10.2)	31	74	21	60.0	(9.0)	38	78	43	61.1	(9.6)	31	78
Implant years	18	11.5	(5.2)	2	22	13	10.4	(4.5)	3	19	31	11.0	(4.9)	2	22
Implant-level characteristics															
	Control					Test					Total				
	n	% /mean	SD	Min.	Max.	*n*	% /mean	SD	Min.	Max.	*n*	% /mean	SD	Min.	Max.
Jaw															
Maxilla	10	45.5%				12	57.1%				22	51.2%			
Mandible	12	54.5%				9	42.9%				21	48.8%			
Location 1															
Anterior (3–3)	2	9.1%				1	4.8%				3	7.0%			
Posterior	20	90.9%				20	95.2%				40	93.0%			
Location 2															
Aesthetic zone (15–25)	7	31.8%				9	42.9%				16	37.2%			
Other	15	68.2%				12	57.1%				27	62.8%			
Retention															
Screw-retained	12	54.5%				13	61.9%				25	58.1%			
Cemented	10	45.5%				8	38.1%				18	41.9%			
Implant brand															
Straumann	18	81.8%				13	61.9%				31	72.1%			
Astra Tech	0	0.0%				1	4.8%				1	2.3%			
Unclear	4	18.2%				7	33.3%				11	25.6%			
Implant brand															
Non-modified	0	0.0%				0	0.0%				0	0.0%			
Modified	18	81.8%				14	66.7%				32	74.4%			
Unclear	4	18.2%				7	33.3%				11	25.6%			
PPD (mm)	22	8.8	(2.0)	6.0	13.0	21	9.4	(2.2)	6.0	14.0	43	9.1	(2.1)	6.0	14.0
BoP%	22	93.2	(23.4)	0.0	100.0	21	94.0	(22.2)	0.0	100.0	43	93.6	(22.6)	0.0	100.0
SoP%	22	21.6	(39.6)	0.0	100.0	21	48.8	(47.1)	0.0	100.0	43	34.9	(45.0)	0.0	100.0
Buccal marginal mucosal level (mm)	22	0.9	(1.3)	0.0	4.0	21	0.9	(1.1)	0.0	3.0	43	0.9	(1.2)	0.0	4.0
Buccal KMW (mm)	22	2.8	(2.0)	0.0	7.0	21	2.9	(2.2)	0.0	8.0	43	2.8	(2.1)	0.0	8.0
Baseline MBL (mm)	22	5.3	(1.8)	1.9	9.1	21	6.8	(1.9)	3.6	10.0	43	6.0	(1.9)	1.9	10.0

All patients received the allocated interventions and attended the 2-week and 6-month examinations. Four patients, two in each group, did not attend the 12-month examination (lost to follow-up). No adverse events were registered in relation to any study intervention.

At 12 months, no implants were lost, and all criteria of the composite outcome were met at 45.0% and 36.8% of implant sites in the control and test groups, respectively (OR = 0.71; 95% CI: 0.20–2.57; $p = .61$) (Figure 4 and Table A2). Overall, most of the

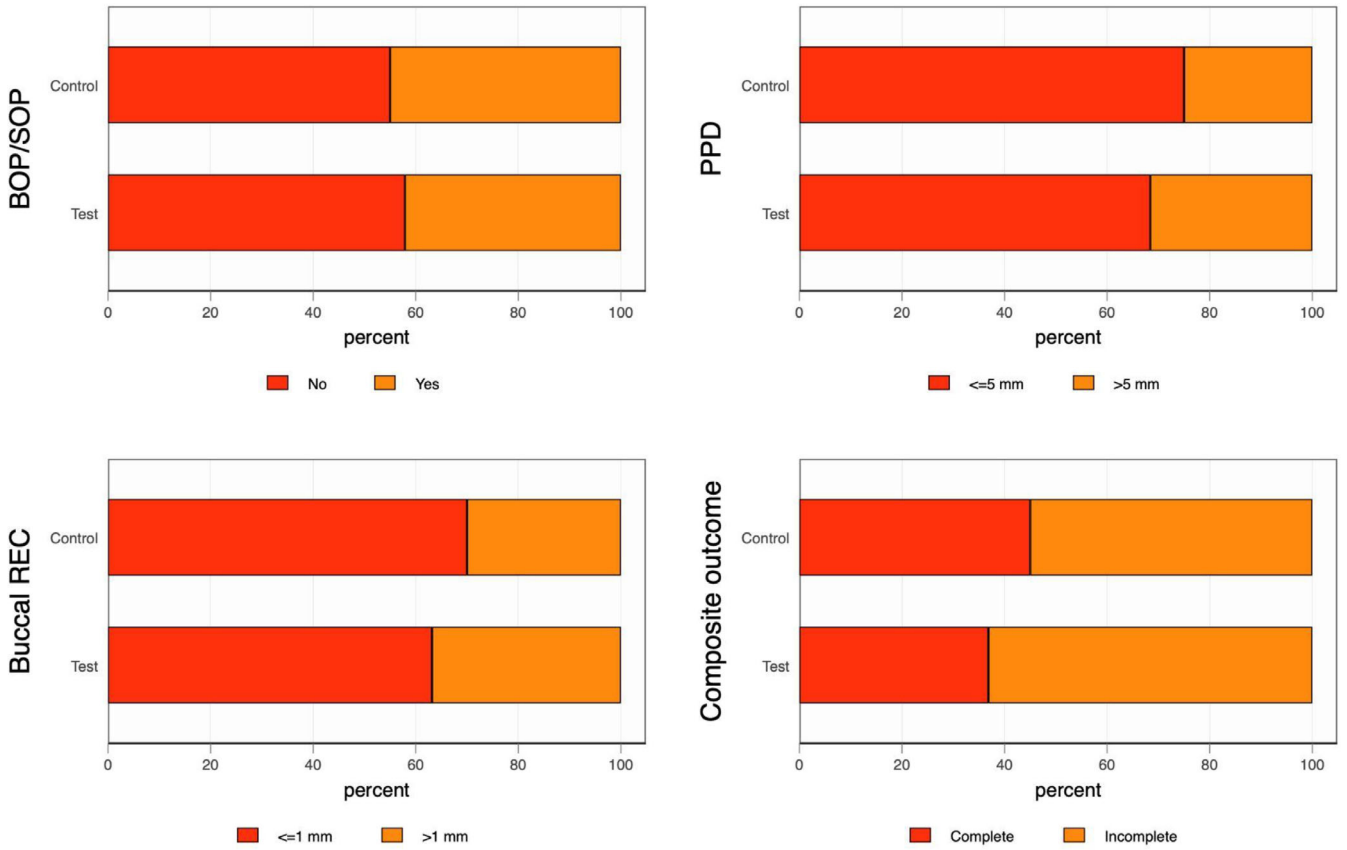

FIGURE 4 Composite outcomes at 12 months.

implants presented with PPD ≤5 mm (71.8%), absence of BoP/SoP (56.4%) and buccal REC ≤1 mm (66.7%). Differences between groups for these parameters were not statistically significant (Table A2).

Overall, PPD and BoP% were reduced at 12 months by 4.4 ± 2.3 mm and 67.3 ± 39.4%, respectively. Buccal REC and KMW changes were 0.1 ± 0.8 mm and 0.9 ± 1.3 mm, respectively. An overall bone gain (MBL change) of 1.2 ± 1.8 mm was observed. Differences between groups were not statistically significant (Figures 5 and A7 and Table A3).

Two weeks after the surgical intervention, patients in the test group reported significantly higher pain scores (median: 20.0; IQR: 70.0) compared to the control group (median: 5.0; IQR: 30.0) ($p < .01$). At 12 months, the overall satisfaction with therapy was 85 (IQR: 30.0) in the control group and 70 (IQR: 20.0) in the test group. A similar distribution was observed for "satisfaction with aesthetics" with medians of 80.0 (IQR: 50.0) and 60.0 (IQR: 40.0) in control and test groups, respectively (Figure 6 and Table A4).

Treatment time in the test group was slightly longer than in the control group (48.3 min vs. 38.3 min).

Complications related to the surgical interventions were noted only in the test group. The most frequent complications were soft tissue dehiscence (19.0%), exposure of the resorbable membrane (9.5%) and exposure of the bone substitute (4.8%) (Table A5).

4 | DISCUSSION

The present RCT was designed to evaluate the potential adjunctive benefit of a resorbable membrane covering a bone replacement graft in the reconstructive surgical therapy of peri-implantitis associated with intra-bony defects. Results indicated that the use of the membrane did not result in any improvement of clinical, radiographic or PROs evaluated 12 months post-operatively. Rather, longer treatment times and more post-surgical complications, such as higher post-surgical pain scores, were noted in the test group. Patient satisfaction was high, regardless of treatment group.

Although observational studies on reconstructive therapy of peri-implantitis (e.g., Galarraga-Vinueza et al., 2020; La Monaca et al., 2018; Monje et al., 2020) have suggested positive outcomes when combining different bone replacement grafts with resorbable membranes, the potential added value of membranes has not been extensively evaluated in randomized controlled trials (Tomasi et al., 2019). In one of the few comparative evaluations, Roos-Jansåker et al. (2007, 2011, 2014) assessed the 5-year clinical and radiographic outcomes of combining a resorbable membrane with a bone substitute material as opposed to use of bone replacement graft alone. The authors reported no significant differences between groups, as was the case in our dataset limited to a 12-month follow-up. Similarly, a recent RCT reported no added clinical or radiographic benefit with the use of a resorbable membrane at 12 months (Monje

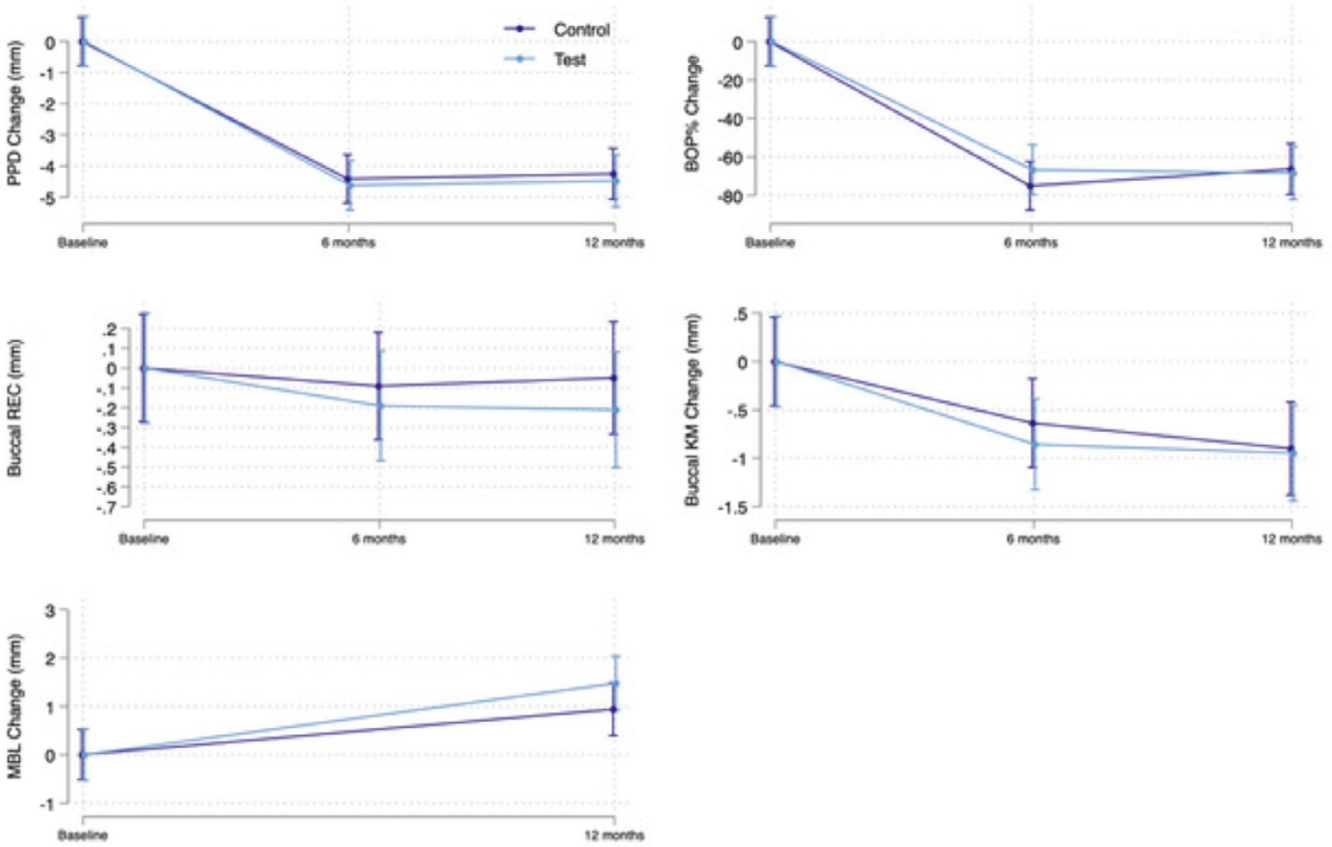

FIGURE 5 Changes of PPD, BoP, buccal REC, KMW and MBL from baseline to 12 months. Whiskers indicate 95% CIs.

et al., 2022). Although PPD and bone level changes were similar to the ones reported in the present study, a higher rate of treatment success was observed. This difference may be explained by the different decontamination procedures (Baima et al., 2022) and by the more permissive composite outcome definition employed.

Other evaluations made at 12 months following reconstructive therapy of peri-implantitis (Derks, Ortiz-Vigón, et al., 2022; Isehed et al., 2016; Isehed et al., 2018; Jepsen et al., 2016; Renvert et al., 2018; Renvert et al., 2021; Wohlfahrt et al., 2012) revealed significant reductions of PPD and BoP%, which are in line with the results reported in this clinical trial; minor differences in the magnitude of these reductions may be attributable to differences in data handling (e.g., mean vs. deepest values of PPD; Derks, Ichioka, et al., 2022). Specifically, the surgical technique we applied, including the surface decontamination protocol and choice of bone substitute material, was, apart from the use of the barrier membrane in the test group, identical with the methodology reported by Derks, Ortiz-Vigón, et al. (2022). It is therefore interesting to note that the magnitude of PPD reduction (~4 mm) and MBL gain (~1 mm) were similar. We did, however, observe a more pronounced reduction of BoP% (67% vs. 45%) and less buccal REC (0.1 mm vs. 0.7 mm) within the control group, when compared to the results reported by Derks et al. (2022; test group). The reasons for the more favourable outcomes in terms of reduction of soft tissue inflammation and reduced recession are not fully understood but may be related to patient selection, surgical experience and level of patient-performed infection control.

The primary outcome of the present study was a composite outcome including threshold values for PPD and buccal REC as well as the absence of any BoP at 12 months. Although shallow PPD and the absence of BoP are associated with long-term bone level stability, the inclusion of REC may be relevant as a surrogate for aesthetic outcomes (Berglundh et al., 2021; Carcuac et al., 2020; Derks, Ichioka, et al., 2022; Derks, Ortiz-Vigón, et al., 2022). Disease resolution using this definition was observed in 45% and 37% of implant sites in the control and test groups, respectively. These proportions are somewhat higher than what has been previously observed in corresponding evaluations (Derks, Ortiz-Vigón, et al., 2022; Jepsen et al., 2016; Renvert et al., 2018). The differences are most likely explained by the effective reduction of BoP in the present patient sample.

The results from this study also revealed no statistically significant differences in PROs between test and control groups at 12 months. Indeed, while self-perceived aesthetics and satisfaction with therapy were high, self-reported pain and bad smell/taste values were extremely low both at baseline and at the 12-month examination, which agrees with previous studies reporting scarce patient perception of peri-implant diseases before and after treatment (Derks, Ortiz-Vigón, et al., 2022; Romandini, Lima, Pedrinaci, Araoz, Soldini, & Sanz, 2021). Furthermore, the additional use of the resorbable

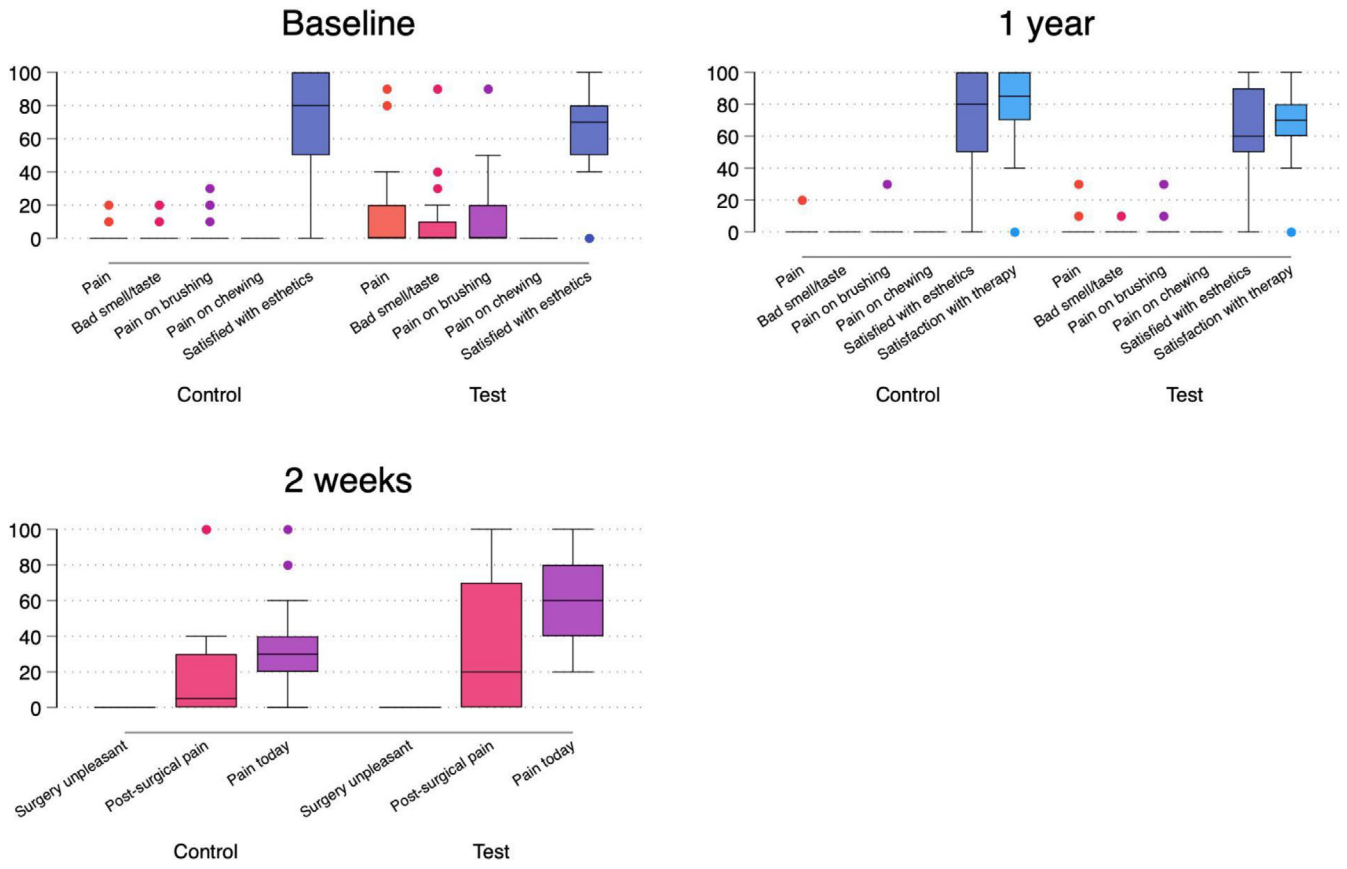

FIGURE 6 Patient-reported outcomes at baseline, 2 weeks and 12 months.

membrane resulted in a longer surgical time. This difference of 10 min is longer than the one previously described in corresponding RCTs on periodontal regenerative interventions (~5 min; Cortellini et al., 2001). This discrepancy may be related to the differences in defect configuration observed in peri-implantitis lesions (e.g., Monje et al., 2019) but also to difficulties in accessing the surgical site. It should be noted that the implant-supported prostheses could not be removed prior to the surgical intervention in 25.6% of cases (27.3% in the control group and 23.8% in the test group).

Data from the 2-week follow-up visit also indicated a high rate of complications associated with the use of barrier membranes, associated with significantly higher scores of post-surgical pain. The occurrence of post-surgical complications following the use of barrier membranes at peri-implantitis-associated bony defects has been previously described. Khoury and Buchmann (2001), for instance, treated 25 patients with peri-implantitis using different surgical approaches. The authors reported early post-therapy complications at >50% of sites in which barrier membranes were employed. It should, however, also be noted that other studies applying similar surgical techniques observed fewer complications (e.g., de Tapia et al., 2019; Renvert et al., 2021).

Although the results from the present trial are supported by a solid study design (e.g., randomization procedures, blinding, allocation concealment), some limitations should be highlighted. These include the relatively small study population and the consequent limited statistical power, since the sample size was calculated based on a secondary outcome (gain of MBL), which was not part of the composite outcome (primary endpoint of the study). Furthermore, we observed an imbalance in the distribution of defect types at baseline (i.e., more non-contained defects in the test group), which may have influenced the results, despite our efforts at randomization. It is therefore possible that the use of a membrane may provide added benefits at non-contained defects. Future studies are therefore needed to verify whether any specific peri-implant defect geometry or implants with a specific macro- (e.g., tissue or bone level) or micro-design (e.g., surface) may benefit from the application of a resorbable membrane. It should also be noted that we evaluated the combination of a resorbable membrane with one particular bone substitute material following a non-submerged protocol. Future studies are needed to verify whether the use of a resorbable membrane may provide added benefits with different surgical approaches (e.g., submerged healing) or bone substitute materials (e.g., xenograft in particles). Finally, the mono-centre setting may limit the external validity of the present findings.

5 | CONCLUSIONS

Within its limitations and considering the outcomes evaluated, this study failed to demonstrate any added clinical or radiographic benefits

of the use of a resorbable membrane covering a bone substitute material as part of reconstructive surgical therapy of peri-implantitis associated with intra-bony defects. A higher rate of post-operative complications and post-surgical pain, as well as longer surgical times, were observed when a membrane was employed.

AUTHOR CONTRIBUTIONS

Erik Regidor contributed to study conception and design, data acquisition, interpretation and manuscript drafting. Alberto Ortiz-Vigón contributed to study conception and design, data acquisition and critical revision of the manuscript. Mario Romandini contributed to data analysis and interpretation as well as manuscript drafting. Carlotta Dionigi contributed to data acquisition and manuscript drafting. Jan Derks contributed to data analysis and interpretation and critical revision of the manuscript. Mariano Sanz contributed to study conception and critical revision of the manuscript. All the authors gave their final approval of the version to be published and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Erik Regidor reports speakers honoraria from Electro Medical Systems, Straumann Group and Arrow Development research, and financial support from Thinking Perio Research. Alberto Ortiz-Vigón reports speakers honoraria from Straumann Group and Arrow Development research, and financial support from Thinking Perio Research. Mario Romandini reports research grants from Osteology Foundation, International Team for Implantology (ITI), Eklund Foundation, Proclinic and SEPA Foundation. Jan Derks reports grants and personal fees from Osteology Foundation and Dentsply Sirona Implants, grants and non-financial support from Electro Medical Systems, grants from Eklund Foundation, non-financial support from Geistlich Biomaterials as well as personal fees from Straumann Implants.

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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Apéndice

APPENDIX A

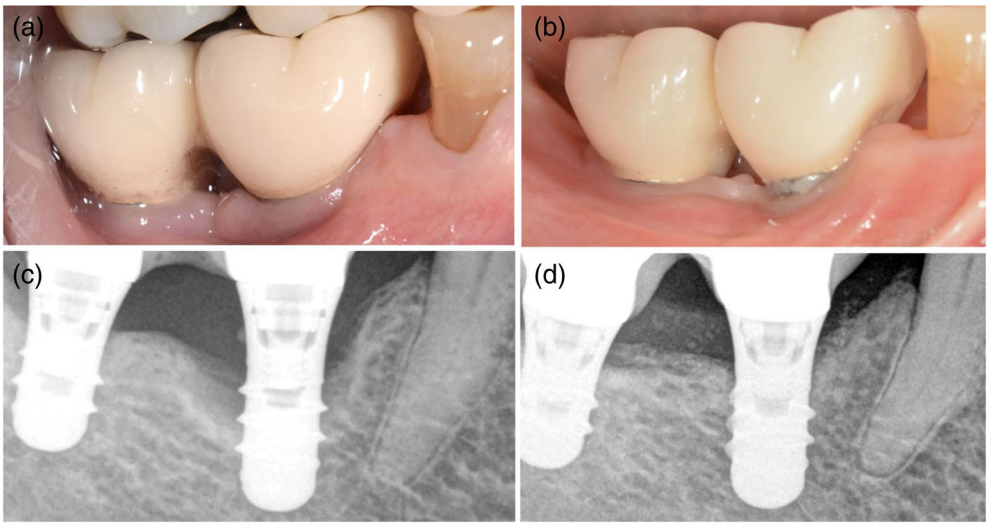


FIGURE A1 Images illustrating one patient in the control group. (a) Baseline clinical examination. (b) Clinical situation at 12 months. (c) Baseline radiographic examination (d) Radiographic situation at 12 months.

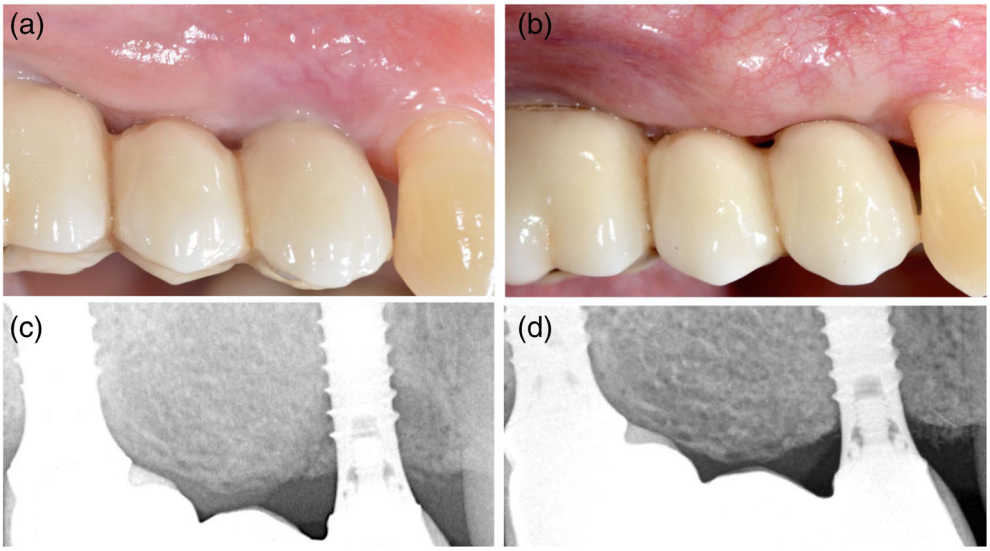


FIGURE A2 Images illustrating a patient in the test group. (a) Baseline clinical examination. (b) Clinical situation at 12 months. (c) Baseline radiographic examination (d) Radiographic situation at 12 months.

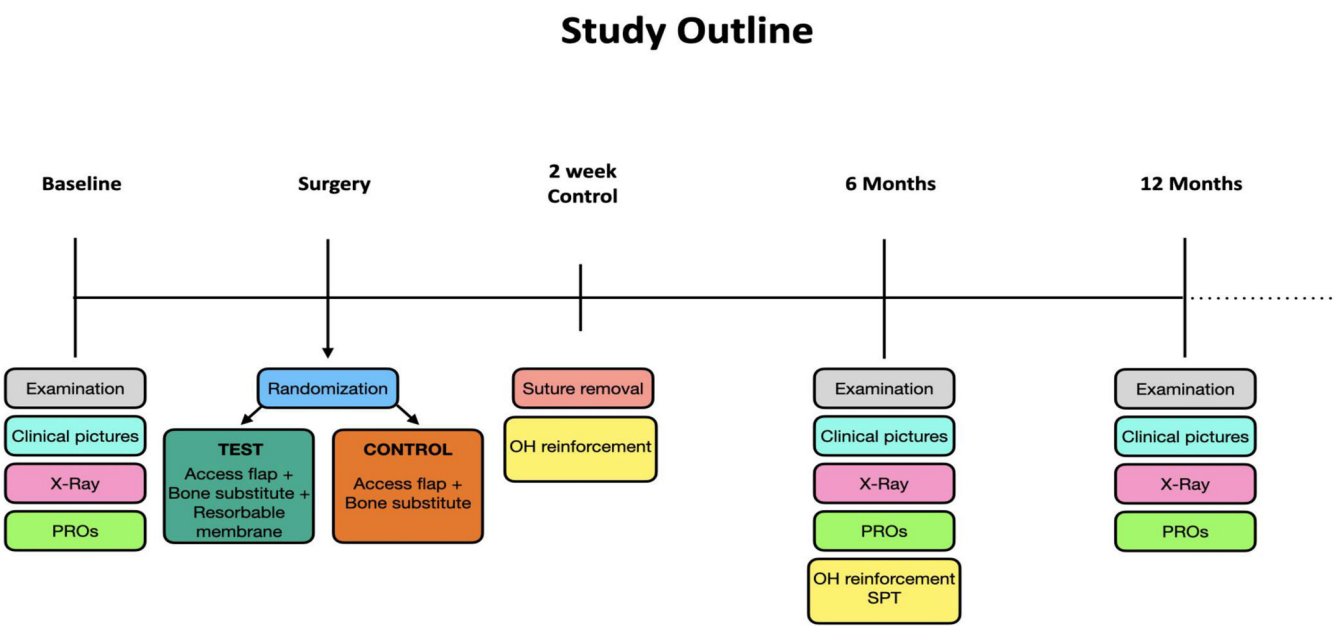
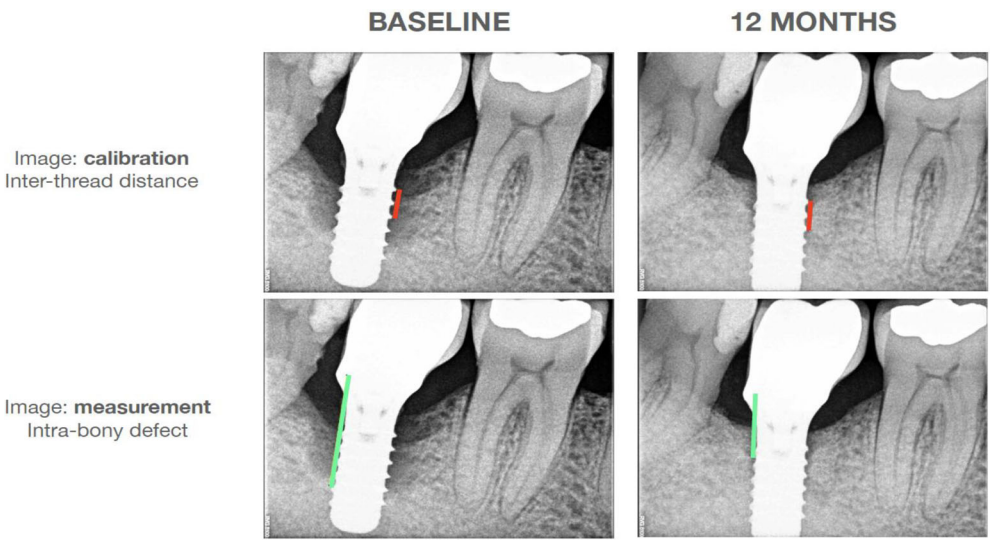


FIGURE A3 Flowchart illustrating the study outline.

FIGURE A4 Illustration of radiographic evaluation of marginal bone levels at baseline and at 1 year. Images were calibrated by known distances.



Questionnaire
Baseline (prior to surgery)

1. Are you experiencing any discomfort or pain from the implant(s) scheduled for surgery?

0 No pain/discomfort — 100 Substantial pain/discomfort

2. Are you experiencing any bad taste or smell from the implant(s) scheduled for surgery?

0 No bad taste/smell — 100 Substantial bad taste/smell

3. Are you experiencing any discomfort or pain when brushing the implant(s) scheduled for surgery?

0 None — 100 Substantial pain/discomfort

4. Are you experiencing any discomfort or pain when chewing with the implant(s) scheduled for surgery?

0 No pain/discomfort — 100 Substantial pain/discomfort

5. Are you satisfied with the esthetic appearance of the implant(s) scheduled for surgery?

0 Not at all satisfied — 100 Fully satisfied

Questionnaire
2 weeks after surgery

1. How would you describe the surgery?

0 Not unpleasant at all — 100 Very unpleasant

2. Did you experience discomfort/pain following the surgery?

0 No discomfort/pain — 100 Substantial discomfort/pain

3. Are you still experiencing discomfort/pain?

0 No discomfort/pain — 100 Substantial discomfort/pain

4. Comment (Eg "adverse events"):

Questionnaire
1 year after surgery

1. Are you experiencing any discomfort or pain from the implant(s) that were treated surgically?

0 No pain/discomfort — 100 Substantial pain/discomfort

2. Are you experiencing any bad taste or smell from the implant(s) that were treated surgically?

0 No bad taste/smell — 100 Substantial bad taste/smell

3. Are you experiencing any discomfort or pain when brushing the implant(s) that were treated surgically?

0 No pain/discomfort — 100 Substantial pain/discomfort

4. Are you experiencing any discomfort or pain when chewing with the implant(s) that were treated surgically?

0 No pain/discomfort — 100 Substantial pain/discomfort

5. Are you satisfied with the esthetic appearance of the implant(s) that were treated surgically?

0 Not at all satisfied — 100 Fully satisfied

6. How do you judge the outcome of therapy?

0 Failure — 100 Complete success

FIGURE A5 Questionnaires provided to study participants at baseline, at 2 weeks and at 12 months.

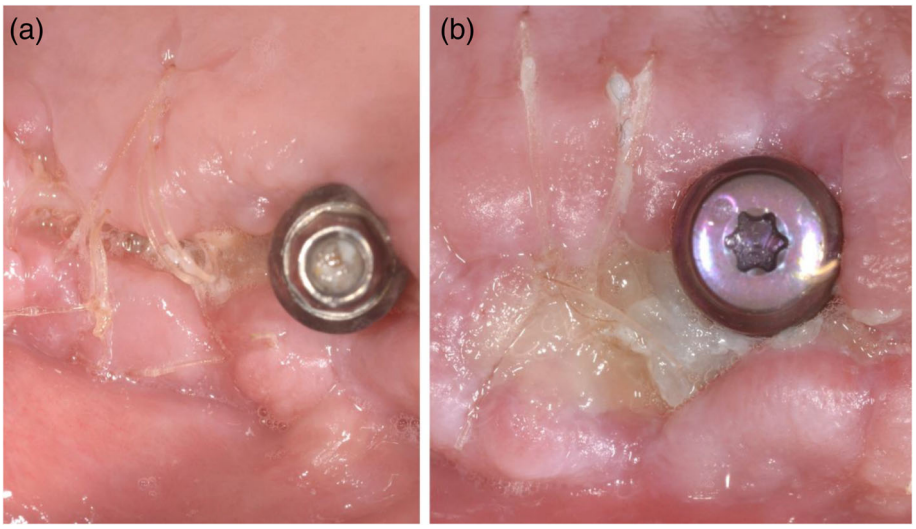


FIGURE A6 Images illustrating post-operative complications 2 weeks after surgical intervention. (a) Soft tissue dehiscence and exposure of particulate bone graft. (b) Soft tissue dehiscence and exposure of resorbable membrane.

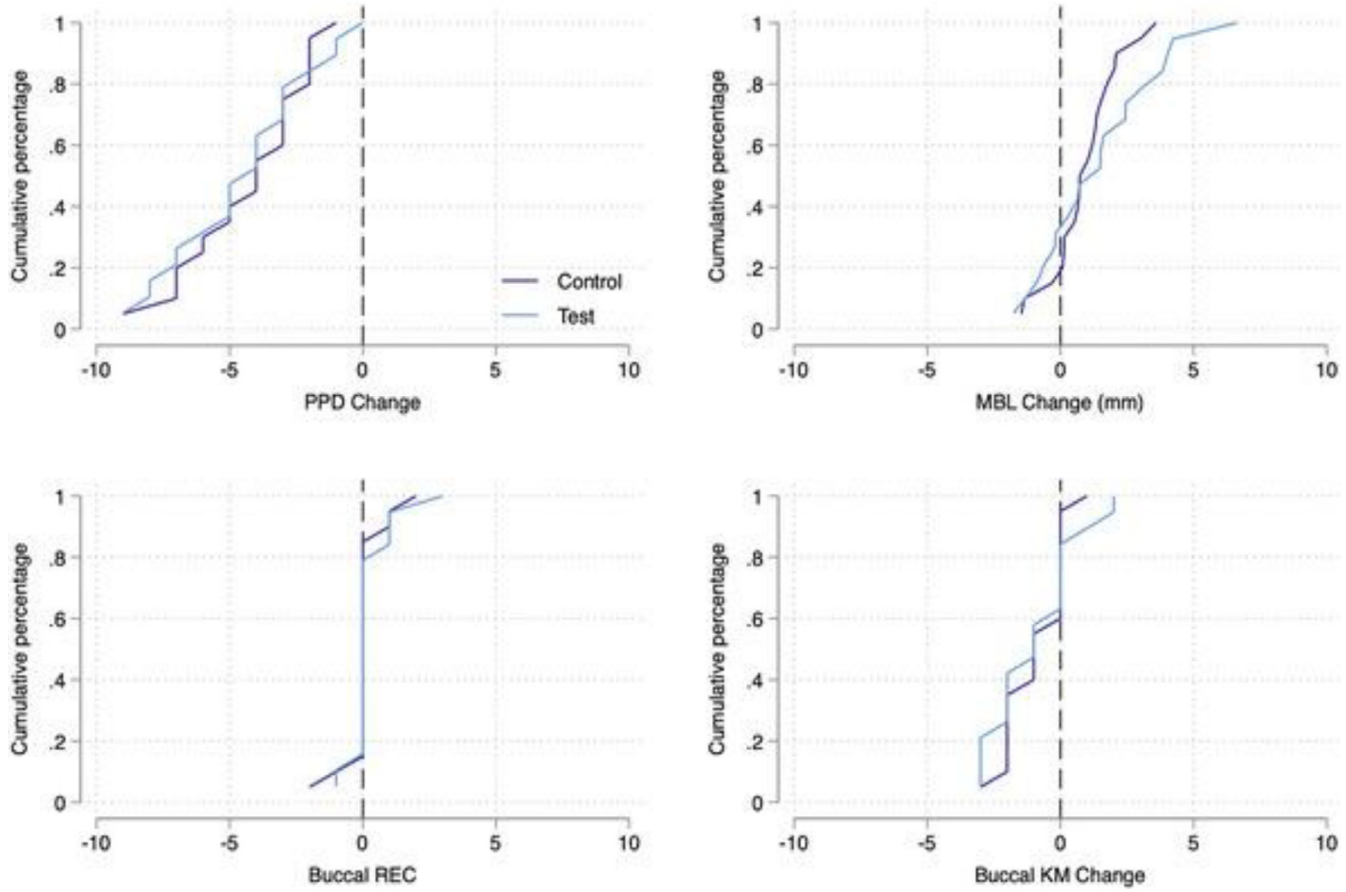


FIGURE A7 Cumulative curves of continuous outcomes at 12 months by group. KM, keratinized mucosa; MBL, marginal bone level; PPD, probing pocket depth; REC, recession.

TABLE A1 Characteristics of peri-implant defects assessed intra-surgically by group. $n = 43$ implants.

Surgery															
	Control					Test					Total				
	n	% /mean	SD	Min.	Max.	*n*	% /mean	SD	Min.	Max.	*n*	% /mean	SD	Min.	Max.
Bone crest to bottom of defect (mm)	22	5.2	(1.6)	3	9	21	6.4	(2.5)	3	12	43	5.8	(2.2)	3	12
Implant shoulder to bottom of defect (mm)	22	6.7	(2.1)	3	11	21	7.9	(2.8)	5	14	43	7.3	(2.5)	3	14
Defect width (mm)	22	2.6	(1.6)	1	9	21	3.1	(2.2)	1	12	43	2.9	(1.9)	1	12
Defect configuration															
Open at buccal and/or lingual aspect	12	54.5%				17	81.0%				29	67.4%			
Contained	10	45.5%				4	19.0%				14	32.6%			
Buccal bone wall															
Intact	5	22.7%				7	33.3%				12	27.9%			
Partially missing	7	31.8%				9	42.9%				16	37.2%			
Missing	10	45.5%				5	23.8%				15	34.9%			
Prosthesis removed															
No	6	27.3%				5	23.8%				11	25.6%			
Yes	16	72.7%				16	76.2%				32	74.4%			
Treatment time (min)	22	38.3	(10.3)	17	62	21	48.3	(14.4)	27	82	43	43.2	(13.3)	17	82

Note: Defect configuration: "Open" is defined as implant exposure >2 mm (implant shoulder to bottom of defect - Crest to bottom of defect >2 mm). Buccal bone wall: "Partially missing" is defined as buccal implant exposure >2 and ≤4 mm. "Missing" is defined as buccal implant exposure >4 mm.

TABLE A2 Threshold and composite outcomes at 12 months by group. $n = 43$ implants.

Threshold outcomes						
	Control		Test		Total	
	n	%	*n*	%	*n*	%
BoP						
No	11	(55.0)	11	(57.9)	22	(56.4)
Yes	9	(45.0)	8	(42.1)	17	(43.6)
SoP						
No	19	(95.0)	19	(100.0)	38	(97.4)
Yes	1	(5.0)	0	(0.0)	1	(2.6)
PPD						
≤5 mm	15	(75.0)	13	(68.4)	28	(71.8)
>5 mm	5	(25.0)	6	(31.6)	11	(28.2)
Buccal REC						
≤1 mm	14	(70.0)	12	(63.2)	26	(66.7)
>1 mm	6	(30.0)	7	(36.8)	13	(33.3)
Composite outcome						
Complete	9	(45.0)	7	(36.8)	16	(41.0)
Incomplete	11	(55.0)	12	(63.2)	23	(59.0)
MBL change ≥0 mm						
No	3	(13.6)	6	(28.6)	9	(20.9)
Yes	19	(86.4)	15	(71.4)	34	(79.1)
MBL gain >1 mm						
No	10	(45.5)	9	(42.9)	19	(44.2)
Yes	12	(54.5)	12	(57.1)	24	(55.8)
MBL gain >2 mm						
No	16	(72.7)	12	(57.1)	28	(65.1)
Yes	6	(27.3)	9	(42.9)	15	(34.9)
MBL loss >1 mm						
No	20	(90.9)	19	(90.5)	39	(90.7)
Yes	2	(9.1)	2	(9.5)	4	(9.3)

Test composite outcome									
	BoP+	SoP +	PPD >5 mm	Buccal REC >1 mm	MBL gain >0 mm	MBL gain >1 mm	MBL gain >2 mm	MBL loss >1 mm	Composite outcome
Coefficient	0.89	1.00	1.38	1.36	0.39	1.11	2.00	1.05	0.71
95% CI	0.25 3.16		0.34 5.62	0.36 5.17	0.08 1.85	0.33 3.71	0.56 7.16	0.13 8.24	0.20 2.57
p-value	.86		.65	.65	.24	.86	.29	.96	.61

Note: #Complete defined as: implant not lost; no BoP, no SoP, PPD ≤5 mm and buccal REC ≤1 mm.

Abbreviations: BoP, bleeding on probing; MBL, marginal bone level; PPD, probing pocket depth; REC, recession; SoP, suppuration on probing.

TABLE A3 Continuous outcomes at 12 months. The four implants lost during follow-up are not considered.

Continuous outcomes															
	Control					Test					Total				
	n	Mean	SD	Min.	Max.	*n*	Mean	SD	Min.	Max.	*n*	Mean	SD	Min.	Max.
PPD change	20	−4.2	(2.2)	−9.0	−1.0	19	−4.5	(2.6)	−9.0	0.0	39	−4.4	(2.3)	−9.0	0.0
BoP % change	20	−66.2	(40.0)	−100.0	0.0	19	−68.4	(39.8)	−100.0	0.0	39	−67.3	(39.4)	−100.0	0.0
Buccal REC change	20	0.1	(0.8)	−2.0	2.0	19	0.2	(0.9)	−1.0	3.0	39	0.1	(0.8)	−2.0	3.0
Buccal KM change	20	−0.9	(1.1)	−3.0	1.0	19	−0.9	(1.6)	−3.0	2.0	39	−0.9	(1.3)	−3.0	2.0
MBL change (mm)	20	0.9	(1.3)	−1.5	3.6	19	1.5	(2.2)	−1.8	6.6	39	1.2	(1.8)	−1.8	6.6

Test continuous outcomes					
	PPD change	BoP % change	Buccal REC change	Buccal KM change	MBL change
Coefficient	−0.22	−2.17	0.16	−0.47	0.54
95% CI	−1.39 0.94	−21.18 16.83	−0.24 0.57	−0.74 0.64	−0.24 1.32
p-value	.70	.82	.44	.89	.17

TABLE A4 Patient-reported outcomes at baseline, 2 weeks and 12 months. $n = 43$ patients.

PROMs	Control							Test							Total						
	n	Med	IQR	Mean	SD	Min.	Max.	*n*	Med	IQR	Mean	SD	Min.	Max.	*n*	Med	IQR	Mean	SD	Min.	Max.
Baseline																					
Pain	22	0.0	0.0	1.8	5.0	0	20	21	0.0	20.0	14.8	26.4	0	90	43	0.0	10.0	8.1	19.7	0	90
Bad smell/taste	22	0.0	0.0	2.7	6.3	0	20	21	0.0	10.0	10.5	21.6	0	90	43	0.0	10.0	6.5	16.0	0	90
Pain on brushing	22	0.0	0.0	3.6	8.5	0	30	21	0.0	20.0	14.3	23.6	0	90	43	0.0	10.0	8.8	18.2	0	90
Pain on chewing	22	0.0	0.0	0.0	0.0	0	0	21	0.0	0.0	0.0	0.0	0	0	43	0.0	0.0	0.0	0.0	0	0
Satisfied with aesthetics	22	80.0	50.0	73.6	28.7	0	100	21	70.0	30.0	67.6	25.5	0	100	43	70.0	50.0	70.7	27.0	0	100
1 year																					
Pain	22	0.0	0.0	0.9	4.3	0	20	21	0.0	0.0	1.9	6.8	0	30	43	0.0	0.0	1.4	5.6	0	30
Bad smell/taste	22	0.0	0.0	0.0	0.0	0	0	21	0.0	0.0	0.5	2.2	0	10	43	0.0	0.0	0.2	1.5	0	10
Pain on brushing	22	0.0	0.0	1.4	6.4	0	30	21	0.0	0.0	1.9	6.8	0	30	43	0.0	0.0	1.6	6.5	0	30
Pain on chewing	22	0.0	0.0	0.0	0.0	0	0	21	0.0	0.0	0.0	0.0	0	0	43	0.0	0.0	0.0	0.0	0	0
Satisfied with aesthetics	22	80.0	50.0	67.3	35.9	0	100	21	60.0	40.0	61.9	32.0	0	100	43	70.0	50.0	64.7	33.8	0	100
Satisfied with therapy	22	85.0	30.0	78.2	30.0	0	100	21	70.0	20.0	69.5	27.8	0	100	43	80.0	30.0	74.0	29.0	0	100
2 weeks																					
Surgery unpleasant	22	0.0	0.0	0.0	0.0	0	0	21	0.0	0.0	0.0	0.0	0	0	43	0.0	0.0	0.0	0.0	0	0
Post-surgical pain	22	5.0	30.0	23.6	34.2	0	100	21	20.0	70.0	34.3	34.6	0	100	43	20.0	50.0	28.8	34.4	0	100
Pain today	22	30.0	20.0	35.0	26.0	0	100	21	60.0	40.0	56.7	22.9	20	100	43	40.0	50.0	45.6	26.6	0	100

Note: Pain at 2 weeks significantly different between groups, $p = .0045$ (Mann–Whitney).

TABLE A5 Complications. $n = 43$ implants.

Complications						
	Control		Test		Total	
Soft tissue dehiscence						
No	22	100.0%	17	81.0%	39	90.7%
Yes	0	0.0%	4	19.0%	4	9.3%
Exposure of barrier material						
No	22	100.0%	19	90.5%	41	95.3%
Yes	0	0.0%	2	9.5%	2	4.7%
Exposure of particulate bone graft						
No	22	100.0%	20	95.2%	42	97.7%
Yes	0	0.0%	1	4.8%	1	2.3%
Post-operative infection						
No	22	100.0%	21	100.0%	43	100.0%
Sensory disturbance						
No	22	100.0%	21	100.0%	43	100.0%

DISCUSIÓN:

El objetivo principal del presente trabajo fue evaluar la eficacia clínica de los procedimientos quirúrgicos reconstructivos de los defectos óseos alrededor de implantes provocados por la progresión de la periimplantitis.

La hipótesis general que se planteó fue que la utilización de injertos óseos en procedimientos de reconstrucción de defectos periimplantarios podría obtener resultados clínicos superiores a la cirugía de acceso. Además, también se planteó que la utilización de una membrana reabsorbible cubriendo dicho injerto óseo aportaría un beneficio adicional frente a la utilización del injerto óseo solamente.

Los resultados obtenidos en la revisión sistemática (Tomasi, et al. 2019) y en los dos ensayos clínicos (Derks, et al. 2022 y Regidor, et al. 2023) desmienten la hipótesis planteada.

En primer lugar, la utilización de sustitutos óseos no demostró una eficacia clínica superior frente a la cirugía de acceso. Además, la ganancia analizada a nivel radiográfico es discutible y debe ser interpretada con precaución, debido a la dificultad de distinguir el injerto óseo del hueso nuevo formado. Solamente se puede destacar la presencia de una mayor recesión apical de los tejidos blandos tras la cirugía de acceso.

Con respecto a la utilización de membranas reabsorbibles cubriendo los injertos óseos, no solamente no se reportó un beneficio clínico adicional frente a la utilización de injertos óseos solamente, sino que además se reportó un índice de complicaciones clínicas mayores y una peor satisfacción por parte de los pacientes.

EFICACIA DEL TRATAMIENTO QUIRÚRGICO RECONSTRUCTIVO DE LA PERIIMPLANTITIS

1. Cambios a nivel clínico y radiográfico:

A fin de analizar la eficacia del tratamiento quirúrgico reconstructivo de la periimplantitis, se realizaron 3 estudios, 1 revisión sistemática y 2 ensayos clínicos aleatorizados.

En la revisión sistemática (**#Estudio 1**) se incluyeron un 25 publicaciones derivadas de 16 estudios clínicos que cumplían con los criterios de inclusión marcados a tal fin, incluyendo un total de 116 implantes. Los resultados de la revisión sistemática indican que existe un escaso número de estudios controlados y una gran heterogeneidad entre ellos. Además existe una gran variabilidad de los resultados a 12 meses de seguimiento.

Los principales hallazgos obtenidos tras el metaanálisis muestran un mayor incremento de los niveles óseos marginales (WMD= 1.7mm) y mayor relleno óseo radiográfico (WMD=57%) para los procedimientos test, pero no se encontraron diferencias en las variables clínicas (reducción de profundidades de sondaje y de sangrado al sondaje). Adicionalmente, no se consideraron el nivel de inserción clínica, los niveles de los tejidos blandos periimplantarios y la satisfacción de los pacientes.

Estos resultados concuerdan con otros publicados en otras revisiones sistemáticas (Chan et al. 2014; Khoshkam et al. 2013; Khoshkam et al. 2016; Sahrmann et al. 2011; Donos et al. 2023; Li et al. 2023). Los resultados sugieren que la terapia reconstructiva de los defectos óseos alrededor de implantes afectados por periimplantitis es posible, pero cabe destacar que la evidencia disponible es limitada. La mayoría de los estudios incluidos en la presente revisión son observacionales y series de casos. Solo 3 estudios eran ensayos clínicos aleatorizados que tuvieran como objetivo analizar el beneficio que podría tener la terapia reconstructiva frente al desbridamiento con colgajo solamente.

Además, es necesario mencionar que existe una gran variabilidad entre las muestras atribuible a las diferentes técnicas y materiales empleados. Con respecto a los materiales de injerto el material más utilizado en los estudios no controlados fue el hueso bovino mineral, mientras que ninguno de los estudios controlados evaluó este material.

En relación con el mantenimiento de los resultados en el tiempo sucede algo similar. Si bien es cierto que la supervivencia podría considerarse elevada, no sucede lo mismo con el éxito del tratamiento (Roccuzzo et al. 2018; Hwang et al. 2023). Hasta la fecha, los procedimientos no reconstructivos (desbridamiento con colgajo y cirugía resectiva) han demostrado ser efectivos, sin embargo, la tasa de recurrencia de la enfermedad es elevada (Karlsson et al. 2022). En lo que respecta a la terapia reconstructiva, la variabilidad en el éxito es considerable y no ha demostrado superioridad frente a procedimientos quirúrgicos sin aumento óseo. Mercado y colaboradores en el año 2018 y Rocuzzo y colaboradores en el año 2017 reportaron una tasa de éxito de 56% y 41% a 3 y 7 años respectivamente mediante terapias reconstructivas, mientras que Heitz-Mayfield y colaboradores en el año 2018 reportaron una tasa de éxito de 71% a 5 años de seguimiento mediante desbridamiento con colgajo (Mercado et al. 2018; Roccuzzo et al. 2017; Heitz-Mayfield et al. 2018). Una revisión sistemática reciente reporta que la tasa de éxito varía entre 11 y 38.5% dependiendo de los criterios empleados para definir la variable (Ramanauskaite et al. 2019). En cualquiera de los casos se trata de una tasa de éxito baja. Estos resultados, están estrechamente relacionados con aquellos reportados acerca de la reducción de las profundidades de sondaje y del sangrado al sondaje. La presente revisión sistemática no reportó beneficios en estas dos variables con respecto a los grupos control. Jepsen y colaboradores reportaron una reducción de 45% y 56% en los grupos control y test respectivamente, mientras que la proporción de implantes sin sangrado en ninguno de los aspectos analizados fue del 30% para ambos grupos a 12 meses de seguimiento (Jepsen et al. 2016). Estos resultados no son superiores a los de los estudios de eliminación de bolsas alrededor de implantes. Carcuac y colaboradores en el año 2017 y Heitz-

Mayfield y colaboradores en 2018, reportaron una proporción del 40% de los implantes libres de sangrado a 3 y 5 años respectivamente (Carcuac et al. 2017; Heitz-Mayfield et al. 2018).

Para poder esclarecer el impacto de la utilización de un injerto óseo en el tratamiento quirúrgico de la periimplantitis, se realizó un ensayo clínico aleatorizado multicéntrico (**#Estudio 2**). Este fue el primer proyecto en analizar una muestra de pacientes tan amplia sometidos a tratamiento quirúrgico reconstructivo de defectos óseos periimplantarios. Este hecho permite dar validez externa a los resultados y de esta manera poder entender mejor el impacto de la utilización de un xenoinjerto colágeno en la terapia reconstructiva de defectos óseos asociados a la periimplantitis. Se trata de un ensayo clínico aleatorizado multicéntrico en el que se incluyeron 138 pacientes, portadores de 147 implantes. La variable primaria de este estudio era una variable compuesta por (I) supervivencia de implante, (II) ausencia de sangrado / supuración al sondaje en todos los puntos analizados, (III) profundidades de sondaje ≤5 mm en todos los puntos y (IV) ≤1mm de recesión o migración apical de la mucosa en el aspecto vestibular del implante. Cabe destacar que, en este estudio, se reportaron resultados relacionados con los cambios en los tejidos blandos y con la satisfacción de los pacientes.

Tras 12 meses de seguimiento, solamente 16.4% y 13.5% de los implantes de los grupos test y control respectivamente cumplían con los criterios predefinidos para el éxito.

Al analizar las variables individualmente, la reducción de las profundidades de sondaje fue de alrededor de 3.7mm para ambos grupos. Esta reducción es mayor que la reportada en otros estudios de terapia reconstructiva periimplantaria (Wohlfahrt et al. 2012; Jepsen et al. 2016; Renvert et al. 2021; Isehed et al. 2016; Isehed et al. 2018). La obtención de unos resultados mayores en la reducción de la profundidad de sondaje podría ser plausible debido a que la profundidad de sondaje media en este estudio era mayor que en los mencionados anteriormente (8.6mm). Precisamente, De Tapia y colaboradores también obtuvieron una reducción marcada de

las profundidades de sondaje partiendo de una situación basal similar (PPD: 8.5mm) (De Tapia et al. 2019).

En relación al sangrado al sondaje, es necesario destacar que, a pesar de obtener una reducción significativa tras el tratamiento quirúrgico en ambos grupos, la ausencia completa de sangrado en todos los puntos analizados por implante fue reducida en ambos grupos. Esto concuerda con los resultados obtenidos en otros estudios (Carcuac et al. 2016; Carcuac et al. 2017; Carcuac et al. 2020; Heitz-Mayfield et al. 2012; Heitz-Mayfield et al. 2018).

Por otra parte, en torno a la regeneración ósea guiada siempre se ha discutido el valor adicional que podría llegar a aportar la utilización de una membrana. La hipótesis de poder emplear membranas en la reconstrucción de defectos óseos alrededor de implantes deriva de aquella literatura científica que defiende su utilización para la reconstrucción ósea tridimensional para la colocación de implantes en hueso prístino (simultánea o diferida) (Dahlin et al. 1988; Omar et al. 2019; Benic et al. 2014; Sanz-Sanchez et al. 2015; Sanz-Sanchez et al. 2018; Thoma et al. 2019; Naenni et al. 2019b). En estos estudios se defiende que la utilización de una membrana, siempre y cuando no se exponga durante la cicatrización, ofrece un beneficio adicional en términos de ganancia ósea. Adicionalmente, existen estudios que defienden que detalles como la fijación de la membrana puede ofrecer una mayor estabilidad del coágulo y aporte aún mejores resultados (Naenni et al. 2019b; Mir-Mari et al. 2016; An et al. 2022). No obstante, la literatura en torno a su utilización en la reconstrucción de defectos óseos asociados a la progresión de la periimplantitis es escasa y contradictoria. En consecuencia, se propuso la realización de otro ensayo clínico aleatorizado que dilucidase el beneficio adicional de la utilización de una membrana barrera cubriendo un injerto óseo en el tratamiento quirúrgico reconstructivo de la periimplantitis **(#Estudio 3)**.

Se trata de un ensayo clínico aleatorizado en el que se incluyeron 43 pacientes, portadores de 43 implantes y en el que se utilizó la misma variable respuesta primaria que en el estudio anterior.

12 meses después del procedimiento quirúrgico se observó un éxito de 36.8% y 45% en los implantes en los grupos test (Xenoinjerto colágeno + membrana reabsorbible) *versus* control (Xenoinjerto colágeno) respectivamente. Por otra parte, no se encontraron diferencias estadísticamente significativas entre ambos grupos en términos de reducción de las profundidades de sondaje, reducción de sangrado/supuración al sondaje, cambios en mucosa queratinizada, niveles óseos marginales o recesión vestibular. Solamente se observaron complicaciones postquirúrgicas en el grupo de la membrana (dehiscencia de tejido blando, exposición del injerto óseo y/o membrana). Además, se reportaron tiempos de intervención mayores así como más dolor a las 2 semanas en el grupo de membrana.

Si bien es cierto que algunos estudios observacionales reportan resultados positivos mediante la utilización coadyuvante de una membrana sobre un injerto óseo, hasta la fecha, el beneficio adicional de una membrana no ha sido ampliamente evaluado en ensayos clínicos (Matarasso et al. 2014; Nart et al. 2018; Galarraga-Vinueza et al. 2020; La Monaca et al. 2018; Monje et al. 2020). Los pocos estudios que hasta la fecha han analizado el beneficio potencial de una membrana en este tipo de situaciones clínicas no reportan resultados superiores frente a la utilización únicamente de un injerto óseo (Roos-Jansaker et al. 2007; Roos-Jansaker et al. 2011; Roos-Jansaker et al. 2014). En esta misma línea un ensayo clínico aleatorizado reciente que analizaba el beneficio adicional de una membrana junto a un injerto óseo alogénico reportó que los resultados clínicos y radiográficos no fueron superiores a aquellos del grupo control donde solamente utilizaban el aloinjerto (Monje et al. 2022). A pesar de que en el estudio de Monje colaboradores obtuvieron resultados similares en términos de reducción de las profundidades de sondaje y cambios a nivel óseo, la tasa de éxito fue superior. No obstante, esto podría deberse a los diferentes métodos de descontaminación (Baima et al. 2022) e incluso al hecho de tener una variable primaria compuesta más permisiva o laxa.

Más allá de la membrana reabsorbible, el abordaje quirúrgico, el método de descontaminación y el injerto óseo empleado en este estudio es idéntico al descrito por Derks y colaboradores en el estudio anterior (Estudio #2) (Derks et al. 2022). Ambos estudios reportan cifras similares en

términos de reducción de la profundidad de sondaje media (alrededor de 4mm) y ganancia ósea marginal (1mm). Sin embargo, en el presente estudio, en el grupo control (solamente injerto óseo) se observó una mayor reducción del sangrado al sondaje (67% Vs 45%) y una menor recesión (0.1 Vs 0.7mm) que las reportadas por Derks y colaboradores (2022) en su respectivo grupo test (solamente injerto óseo) (Derks et al. 2022). Hasta la fecha no se ha podido justificar la diferencia de estos resultados, sin embargo, la selección del paciente, la experiencia quirúrgica de los operadores y el control de la infección llevado a cabo por los propios pacientes intervenidos podría llegar a influir en los resultados finales. Además, este estudio reporta una mayor tasa de éxito que otros (Derks et al. 2022; Jepsen et al. 2016; Renvert et al. 2018). Esto podría deberse a una mayor eficacia en la reducción del sangrado al sondaje en el presente estudio como se ha descrito con antelación.

A nivel radiográfico, la revisión sistemática sí reportó un beneficio en las variables radiográficas analizadas. Sin embargo, es importante mencionar que 2 de los 3 estudios controlados incluidos utilizaron gránulos de titanio poroso como sustituto óseo en sus respectivos grupos test (Jepsen et al. 2016; Wohlfahrt et al. 2012). En consecuencia, no se pudo realizar el cegamiento de los examinadores. En este sentido, la radio-opacidad de los injertos óseos puede alterar las mediciones debido a la complejidad de distinguir las partículas del injerto óseo del hueso nuevo formado. Isehed y colaboradores emplearon proteínas derivadas de la matriz del esmalte en el grupo test y el beneficio a nivel radiográfico fue más modesto (0.5mm) que el reportado en los demás estudios (Isehed et al. 2016). En esta misma línea, es importante detenerse a analizar los resultados radiográficos descritos en el primer ensayo (#Estudio 2). En este estudio, la ganancia fue de 1mm en ambos grupos. Este resultado es inferior a los publicados por otros estudios que además sí que encontraron diferencias entre test y control. Jepsen y colaboradores (2016) y Renvert y colaboradores (2021) reportaron 2.7 - 3.5mm de ganancia en los respectivos grupos test, mientras que para los grupos control la ganancia fue de 0.9-1.4mm. En el presente estudio se utilizó un xenoinjerto colágeno en bloque en el grupo test. No obstante, otros estudios utilizan

injertos de otros orígenes e incluso en otros formatos como partículas (Aghazadeh et al. 2022; Polymeri et al 2020). Aghazadeh y colaboradores en el año 2022, reportaron resultados a 3 y 5 años de seguimiento de un ensayo clínico que comparaba la utilización de un injerto óseo autólogo frente a otro xenogénico para reconstruir el defecto óseo periimplantario (Aghazadeh et al. 2022). A nivel radiográfico, a 5 años de seguimiento se pudo observar una ganancia de 1.6mm en el grupo del xenoinjerto, mientras que en el grupo del injerto autólogo el cambio fue de -0.7mm. Además, cabe destacar que, en este estudio, una de las variables incluidas dentro del éxito era la ausencia de pérdida ósea, de manera que estos resultados tuvieron un impacto negativo directo en el porcentaje de implantes con éxito en el grupo de injerto autólogo. Como ya se ha mencionado con antelación a lo largo de este trabajo, la radio-opacidad de algunos injertos óseos como los xenogénicos o los aloplásticos puede alterar las mediciones radiográficas, debido a la dificultad de distinguir el injerto óseo del hueso nuevo formado (Jepsen et al. 2016).

2. <u>Comportamiento de los tejidos blandos periimplantarios tras procedimientos quirúrgicos reconstructivos de la periimplantitis:</u>

En relación a las variables clínicas mencionadas en el apartado anterior es importante destacar que ninguno de los estudios controlados incluidos en la revisión sistemática **(#Estudio 1)** reportó resultados acerca de los cambios en los tejidos blandos tras la terapia reconstructiva periimplantaria. Una revisión sistemática reciente, reporta que la recesión o migración apical de la mucosa periimplantaria es menor al compararla con los resultados del desbridamiento con colgajo (Sanz-Martin et al. 2022). En consecuencia, en ambos ensayos clínicos aleatorizados (**#Estudios 2 y 3**), una de las variables a analizar fue el comportamiento de los tejidos blandos tras las diferentes modalidades de tratamiento quirúrgico de la periimplantitis. Si bien es cierto que estudios como los de Renvert y colaboradores no reportaron diferencias estadísticamente significativas entre los grupos test y control en los niveles de los tejidos blandos, el primer ensayo (#Estudio 2) sí que reportó una migración apical de los tejidos blandos mayor en el grupo control (Renvert et al. 2018;

Renvert et al. 2021) coincidiendo con Sanz-Martin y colaboradores (2022). Aunque por el momento la justificación de estos resultados permanece sin esclarecerse por completo, la utilización de un biomaterial podría minimizar el riesgo de migración apical de los tejidos blandos, mientras que al abordaje resectivo y/o desbridamiento con colgajo se le podría atribuir un mayor riesgo de colapso volumétrico de los tejidos blandos (Schwarz et al. 2021). De hecho, solamente 2 estudios de terapia reconstructiva han reportado una recesión considerable y esto podría deberse a dos motivos. El primero podría ser que en ambos casos el grado de avance de la periimplantitis era severo, de hecho, ambos estudios reportan una reducción media de la profundidad de sondaje superior a la de otros estudios (superior a 4mm). El segundo motivo podría deberse a que la terapia quirúrgica no era reconstructiva *per se*, sino combinada, resectiva en la porción supra-ósea y reconstructiva en la porción infra-ósea (Matarasso et al. 2014; Monje et al 2020).

De manera que podría decirse que cualquier procedimiento quirúrgico lleva inherente el riesgo de sufrir recesión de los tejidos blandos, sea resectivo, reconstructivo o combinado. Por eso, no es de extrañar que la literatura científica haya llegado a proponer la realización de injertos de tejido blando simultáneo al tratamiento quirúrgico de la periimplantitis (Schwarz et al. 2014; Roccuzzo et al. 2016), fundamentalmente en áreas de compromiso estético (Sanz-Martin et al. 2020; Sanz-Martin et al. 2021; Sanz-Martin et al. 2022; Monje & Mesquita 2023).

Cabe destacar que, en ambos ensayos (#Estudios 2 y 3), se empleó un injerto óseo xenogénico con colágeno en bloque, que ha demostrado tener una menor contracción volumétrica en el tiempo que el mismo injerto en forma de partículas (Mir-Mari et al. 2017).

3. Influencia del defecto óseo periimplantario inicial en los resultados del tratamiento quirúrgico reconstructivo de la periimplantitis:

La literatura existente hasta la fecha en el ámbito del tratamiento quirúrgico reconstructivo de la periimplantitis, posicionan las características tridimensionales del defecto óseo como uno de los factores más relevantes o con mayor implicación en el resultado final. A la hora de realizar estudios de investigación, la flexibilidad para incluir diferentes tipos de defecto podría llegar a comprometer los resultados, mientras que unos criterios de inclusión más estrictos con relación a las características del defecto (anchura y profundidad) y número de paredes remanentes, podría dar lugar a resultados más favorables. En el primer ensayo (#Estudio 2), los defectos se clasificaron pudiendo ser contenidos o abiertos en ausencia de la cara vestibular y/o lingual. La proporción de defectos abiertos en este estudio fue de 40%. Sin embargo, en estudios como el de Roccuzzo y colaboradores (Roccuzzo et al. 2016) la proporción de defectos abiertos fue solamente del 18%. En referencia a los defectos de perfil contenido, Renvert y colaboradores (2021) reportaron una proporción de 62%, mientras que en el presente estudio solamente fue del 24%.

La primera cuestión a analizar es el número de paredes remanentes. Al igual que Monje y colaboradores (Monje et al. 2020), ambos ensayos (#Estudios 2 y 3) no excluían implantes que no presentasen el aspecto óseo vestibular y lingual (mínimo 2 paredes). Por el contrario, estudios como el de Renvert y colaboradores en los estudios de 2018 y 2021 solamente incluían defectos de 3 o 4 paredes (Renvert et al. 2018; Renvert et al. 2021), mientras que Roccuzo y colaboradores, por su parte, exclusivamente incluían defectos de carácter contenido o tipo cráter (Roccuzzo et al. 2021).

Adicionalmente, en el segundo ensayo (#Estudio 3), cabe destacar que el grupo en el que se empleaba una membrana (grupo test) tenía unas características menos favorables debido a que se trataba de defectos más extensos. La presencia de defectos completamente contenidos en el

grupo control fue de 45%, mientras que en el grupo test solamente del 19%. En consecuencia, el 81% de los implantes en el grupo test carecían de la pared vestibular y/o lingual, mientras que en el grupo control esto sucedía en el 54% de las ocasiones. Además, la distancia desde el pico óseo al fondo del defecto, la distancia desde el cuello del implante al fondo del defecto y la anchura del defecto eran mayores en el grupo test que en el control (6.4mm Vs 5.2mm ; 7.9mm Vs 6.7mm; 3.1mm Vs 2.6mm).

La siguiente característica a analizar es la profundidad del defecto óseo. Aghazadeh y colaboradores (2020) reportaron que el pronóstico es más favorable a más profundo sea el defecto (Aghazadeh et al. 2020). En este sentido, el primer ensayo (#Estudio 2) e Isehed y colaboradores (2016) reportaron una profundidad del defecto inicial de unos 6mm, mientras que estudios como los de Wohlfahrt y colaboradores (2012) y el de Jepsen y colaboradores reportaron profundidades de defecto iniciales inferiores a 5mm (Wohlfahrt et al. 2012; Jepsen et al. 2016). En esta misma línea, en el segundo ensayo (#Estudio 3) la distancia desde el pico óseo al fondo del defecto y la distancia desde el cuello del implante al fondo del defecto eran mayores en el grupo test que en el control (6.4mm Vs 5.2mm ; 7.9mm Vs 6.7mm respectivamente).

Asimismo, la anchura del defecto periimplantario en el segundo ensayo (#Estudio 3) también era mayor en el grupo test que en el control (3.1mm Vs 2.6mm). Este concepto, podría asociarse a literatura emergente que sugiere que el ángulo del defecto óseo también puede ser un factor predictor del resultado en el tratamiento quirúrgico reconstructivo de este tipo de defectos, afectando negativamente a los resultados cuanto mayor sea la anchura del defecto (Monje et al. 2023).

4. Satisfacción de los pacientes con el tratamiento quirúrgico reconstructivo de la periimplantitis:

La revisión sistemática (#Estudio 1) deja en evidencia que hasta el momento de su realización, los estudios existentes no han incluido resultados relacionados con la satisfacción de los pacientes (morbilidad post-quirúrgica y percepción estética).

En el primer ensayo (#Estudio 2) no se observaron diferencias estadísticamente significativas entre los pacientes de ambos grupos en cuanto a su satisfacción con el tratamiento recibido. Solamente existe otro estudio hasta la fecha que compare la utilización de injertos óseos frente al desbridamiento con colgajo o cirugía de acceso y analice los resultados relacionados con la satisfacción de los pacientes (Renvert et al. 2021). En el caso de Renvert y colaboradores (2021), utilizaron un injerto óseo y una membrana de colágeno en el grupo test y tampoco encontraron diferencias estadísticamente significativas entre grupos (Renvert et al. 2021).

Por el contrario, en el segundo ensayo (#Estudio 3), la satisfacción de los pacientes fue inferior en el grupo test o en el grupo que se utilizaba la membrana. Esto podría deberse precisamente a una mayor prevalencia de complicaciones post-quirúrgicas en este grupo. Precisamente, la morbilidad reportada en este estudio a 2 semanas era mayor en el grupo en el que se empleaba la membrana. Además, también se reportó un mayor tiempo de intervención en el grupo test (10 minutos más de media). Si bien es cierto que el porcentaje de pacientes en los que no se pudo retirar la corona era similar en ambos grupos (27% control Vs 23% test), la dificultad de adaptar una membrana a las características del defecto periimplantario es mayor que la de simplemente rellenar el defecto intra-óseo con un injerto óseo.

5. Otros factores que podrían influir en el resultado final:

En primer lugar, es importante reseñar el carácter multi-céntrico del estudio y la muestra de pacientes tan amplia incluida en el mismo proporciona una mayor validez externa a los resultados obtenidos. Más si cabe, teniendo en cuenta que entre la marca del implante o diseño de superficie no era excluyente en este caso, tratándose así todo tipo de implantes y superficies. Por el contrario, estudios como el de Roccuzzo y colaboradores (2021) solamente trataban implantes colocados por los propios autores y de una marca y diseño concretos (Roccuzzo et al. 2016; Roccuzzo et al. 2021).

Por otra parte, el método de descontaminación empleado en ambos ensayos (#Estudios 2 y 3) fue un cepillo de titanio. Lamentablemente, hoy en día sigue sin existir un consenso sobre cuál es el método `gold standard´ en descontaminación de la superficie de un implante contaminado. Por ende, son numerosos y variados los protocolos de descontaminación empleados en los diferentes estudios. Sin embargo, no cabe duda de que una adecuada descontaminación de la superficie del implante es esencial para optar a recuperar la inserción perdida alrededor de un implante afectado por periimplantitis (Sanz-Martin et al. 2021; Derks et al. 2023; Herrera et al. 2023; Ichioka et al. 2023).

Por último, en relación a la implicación que podría tener la utilización de una membrana, resulta llamativa la diferencia en la eficacia de una membrana entre procedimientos reconstructivos para la colocación de implantes frente a aquellos de tratamiento reconstructivo de la periimplantitis. Por el momento, se desconoce el motivo pero podría deberse a que en el tratamiento de la periimplantitis se está abordando una situación infecciosa, por lo que el riesgo de complicaciones postoperatorias puede ser mayor, condicionando así los resultados. Precisamente, estudios de regeneración ósea guiada describen una ganancia ósea menor en aquellas situaciones en las que la membrana se exponga tras una dehiscencia de los tejidos blandos (Machtei et al 2001; Sanz-Sanchez et al. 2015; Urban et al. 2023).

Otro de los motivos por los que el riesgo de complicaciones es mayor en periimplantitis podría ser el tipo de cicatrización. En procedimientos de regeneración ósea guiada para la colocación de implantes, la cicatrización acostumbra a ser sumergida. Por el contrario, en estudios como el segundo ensayo (#Estudio 3) la cicatrización de los implantes tras el tratamiento quirúrgico reconstructivo de la periimplantitis fue sin sumergir. De esta manera el riesgo de dehiscencia de los tejidos blandos y por ende exposición del injerto óseo y/o membrana es mayor. Acorde a los resultados del segundo ensayo (#Estudio 3), un estudio de investigación de Roos-Jansaker y colaboradores (2007) con cicatrización no sumergida, reporta que no obtiene ningún beneficio adicional tras la utilización de una membrana (Roos-Jansaker et al. 2007a). Sin embargo, otro estudio del mismo grupo de investigación reportó mejores resultados mediante la utilización de una cicatrización sumergida (Roos-Jansaker et al. 2007b). Estos resultados concuerdan con los de un estudio experimental que comparaba la cicatrización sumergida frente a la no sumergida en periimplantitis y reportó mejores resultados para el grupo de la cicatrización sumergida (Schwarz et al. 2006). En cuanto a estudios clínicos, también coincide con los resultados reportados por Monje y colaboradores (2020) y Wen y colaboradores (2021) que emplearon una cicatrización sumergida tras la terapia reconstructiva con membranas reabsorbibles y no reabsorbibles respectivamente (Monje et al. 2020; Wen et al. 2021).

LIMITACIONES:

Estudio 1:

Al analizar los resultados se deben tener en consideración las limitaciones de la revisión sistemática. A nivel metodológico cabe destacar es la ausencia de consenso a la hora de estandarizar los métodos de medición de los diferentes estudios. Además, no solo se incluyeron ensayos clínicos que comparasen un método reconstructivo frente a la cirugía de acceso, sino que además se incluyeron series de casos. La inclusión de este tipo de estudios representa un sesgo debido a la presencia de una única opción de tratamiento.

Por otra parte, los estudios analizados en la revisión sistemática se centran más en la reducción de las profundidades de sondaje y del sangrado al sondaje, que en el re-establecimiento de la salud periimplantaria en todos los aspectos afectados de los implantes. Idealmente, debería utilizarse una variable compuesta como variable primaria que incluyera la ausencia de sangrado/supuración al sondaje en todos los aspectos del implante, profundidades de sondaje ≤5mm y reducción del nivel de la mucosa periimplantaria ≤1 mm.

Además, a nivel radiográfico la radio-opacidad de los injertos óseos empleados dificulta considerablemente las mediciones a realizar debido a la complejidad de distinguir el injerto óseo del hueso nuevo formado.

Por último, es importante reseñar, que los estudios clínicos incluidos en la revisión sistemática carecen de resultados que hagan mención al resultado estético y a la percepción de los pacientes (morbilidad post-quirúrgica y satisfacción con el tratamiento recibido).

Estudio 2:

Una de las limitaciones más evidentes de este estudio es que la incapacidad para cegar al examinador y a los pacientes incrementa el riesgo de sesgo.

Por otra parte, al igual que se reportaba en la revisión sistemática, la utilización de injertos óseos radio-opacos puede provocar confusión en las mediciones por la dificultad de distinguir las partículas del injerto óseo del hueso formado nuevamente.

Por último, si bien es cierto que la variable primaria empleada fue una variable compuesta por ausencia de sangrado / supuración al sondaje en todos los aspectos del implante, profundidades de sondaje ≤5 mm en todos los aspectos y ≤1 de recesión de la mucosa, el cálculo del tamaño muestral se realizó en base a cambios en las profundidades de sondaje.

Estudio 3:

Al igual que en el estudio anterior, no se empleó la variable respuesta primaria para el cálculo del tamaño muestral. En este caso fue el cambio en los niveles óseos marginales el que determinó la población a incluir en el estudio.

Además, se pudo observar un desequilibrio considerable en el tipo de defectos óseos incluidos en el grupo test. La prevalencia de defectos no contenidos era mayor en el grupo en el que se empleaba la membrana reabsorbible, lo cual pudo tener una influencia remarcable en los resultados. Por último, cabe destacar la falta de validez externa al haberse realizado el estudio en un único centro.

IMPLICACIONES CLÍNICAS

Los resultados de la revisión sistemática indican que la heterogeneidad en los estudios clínicos existentes hasta la fecha dificulta la extracción de conclusiones solidas en cuanto al beneficio de utilizar injertos óseos en la reconstrucción de defectos periimplantarios. Solamente se apreciaron beneficios a nivel radiográfico, pero es necesario extremar la cautela debido a la complejidad de distinguir el hueso nuevo formado de la propia radio-opacidad de los injertos óseos empleados.

Los resultados del primer ensayo clínico evidencian que, aunque la utilización de un injerto óseo para reconstruir los defectos periimplantarios asociados a la periimplantitis no proporciona una mayor resolución de la patología, contribuye a una mayor estabilidad de los niveles de los tejidos blandos periimplantarios.

Los resultados del segundo ensayo clínico ponen en duda la justificación de utilizar una membrana en el tratamiento quirúrgico reconstructivo de los defectos óseos provocados por el desarrollo y avance de la periimplantitis. No solo no se obtuvieron mejores resultados con el uso coadyuvante de la membrana reabsorbible, sino que además fue un grupo asociado a mayores complicaciones post-quirúrgicas, mayor morbilidad y peor satisfacción de los pacientes.

RECOMENDACIONES Y PERSPECTIVAS DE FUTURO

De la revisión sistemática se puede inferior que hay una necesidad de estandarizar los métodos de medición para poder analizar de forma fiable y reproducible los cambios tras los procedimientos reconstructivos de los defectos óseos provocados por periimplantitis. Además, deja en evidencia la ausencia de datos en relación con las variables estéticas y de satisfacción de los pacientes.
Teniendo en cuenta que la utilización de un injerto óseo ayuda a preservar los niveles de la mucosa periimplantaria es un tipo de tratamiento a tener en consideración en implantes con defectos óseos ubicados en zona estética o frente anterior (Monje & Mesquita 2023).

La utilización de una membrana reabsorbible no solo no ofrece un beneficio a nivel clínico ni radiográfico sino que incrementa el riesgo de complicaciones (dehiscencia de la herida, exposición del injerto óseo y/o membrana) y empeora la percepción de los pacientes con respecto al tratamiento. Cabe destacar que, en este caso, todos los pacientes fueron intervenidos con un diseño de colgajo crestal convencional. La irrupción de nuevos diseños quirúrgicos como el acceso apical o lateral o incluso diseños mínimamente invasivos en el campo de la Periodoncia e Implantología van enfocados a reducir el riesgo de exposición de los materiales de injerto y membranas utilizados, alejando la incisión del área o defecto a tratar. Estos diseños quirúrgicos, que aún carecen del respaldo científico suficiente, empiezan a mostrar resultados prometedores en regeneración periodontal y cirugía mucogingival (Moreno-Rodriguez & Caffesse 2018; Moreno-Rodriguez et al. 2019; Bethaz et al. 2014; Calzavara et al. 2021; Aslan et al. 2017; Montero et al. 2023). En torno a la periimplantitis, hasta el momento apenas existe literatura con este tipo de diseños quirúrgicos (Iorio-Siciliano et al. 2019; Noelken & Al-Nawas 2020; Noelken & Al-Nawas 2023; Noelken et al. 2023; Montero et al 2023). Las futuras investigaciones deberían analizar el impacto del diseño quirúrgico en las complicaciones postquirúrgicas y en consecuencia en los resultados tanto clínicos como de satisfacción de los pacientes.

Por último, es necesario reseñar que los resultados del último estudio ponen en entredicho el beneficio adicional que proporciona la utilización de una membrana. Sin embargo, los estudios venideros deberían cumplir con unos criterios de inclusión más estrictos en cuanto a las características de los defectos óseos a incluir en cada grupo de tratamiento para poder dilucidar con mayor precisión el impacto de una membrana en este tipo de procedimientos.

CONCLUSIONES

1. Los resultados de la revisión sistemática dejaron en evidencia que la utilización de un injerto óseo para la terapia quirúrgica reconstructiva de defectos óseos periimplantarios muestra resultados heterogéneos

2. La mejoría a nivel radiográfico que conlleva la utilización de un injerto óseo ha de ser interpretada con cautela debido a la dificultad de distinguir las partículas del injerto óseo del hueso nuevo formado.

3. Los resultados del primer ensayo clínico sugieren que la utilización de un injerto óseo ofrece beneficios a nivel de estabilidad de los tejidos blandos periimplantarios, siendo mayor la recesión o migración apical de los tejidos blandos en ausencia del injerto óseo.

4. Los resultados del segundo ensayo clínico ponen en entredicho el beneficio adicional de una membrana de colágeno reabsorbible, al no poder demostrar superioridad a nivel clínico ni radiográfico.

5. La utilización de de membranas se asocia a tiempos de intervención mayores y mayor riesgo de complicaciones post-quirúrgicas (dehiscencia de la herida y exposición de partículas y/o membrana) pudiendo tener un impacto negativo en la morbilidad y satisfacción de los pacientes.

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Anexos

Autorizaciones

- Autorización del Comité Ético de Gotenburgo para el #Estudio 2.
- Autorización del Comité Ético de Investigación Clínica de Euskadi (CEIC-E) para el #Estudio 2.
- Autorización del Comité Ético de Investigación Clínica de Euskadi (CEIC-E) para el #Estudio 3.
- Certificaciones de los productos investigados.

Reconocimientos

- Diploma de presentación en el Congreso de la Sociedad Española de Periodoncia y Osteointegración (SEPA) en categoría video 2020: Segundo premio. (#Estudio 3).
- Diploma de presentación en el Congreso de la Sociedad Española de Periodoncia y Osteointegración (SEPA) en formato Comunicación Oral de Investigación 2021. (#Estudio 3).
- Diploma de presentación en el Congreso de la Sociedad Española de Periodoncia y Osteointegración (SEPA) en formato Comunicación Oral de Investigación 2022. (#Estudio 3).
- Diploma de presentación en el Congreso de la Sociedad Italiana de Periodoncia (SIDP) 2022. Premio: Prize for Best Research Poster. Osteology Research Prize. (#Estudio 3).
- Premio Fonseca Internacional 2023. Obtenido en el Congreso de la Sociedad Española de Periodoncia (SEPA) 2023. (#Estudio 2).

2017-02-24

UNIVERSITY OF GOTHENBURG

DEPARTMENT OF PERIODONTOLOGY

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Ethical approval

Enclosed please find a copy of the ethical approval granted for the study: **Reconstructive surgical therapy of peri-implantitis-related osseous defects. A multicenter randomized controlled clinical trial.**

The Regional Ethical Committee in Gothenburg, Sweden studied and approved the project. Approval was granted 2017-02-16 with the approval code: Dnr 1192-16.

Tord Berglundh

CEIC E
Euskadiko Ikerketa Klinikoetarako Batzorde Etikoa
Comité Ético de Investigación Clínica de Euskadi

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SALUD

DICTAMEN DEL COMITE ETICO DE INVESTIGACION CLINICA DE EUSKADI (CEIC-E)

Iciar Alfonso Farnós
Vicepresidenta del CEIC Comunidad Autónoma del País Vasco (CEIC-E)

CERTIFICA

Que este Comité, en cumplimiento de las exigencias de Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos, resto de principios éticos y legales actualmente exigidos, ha evaluado la propuesta del promotor: **Dr. Alberto Ortiz Vigón**, para que se realice el estudio de investigación de Título: **"TRATAMIENTO QUIRÚRGICO REGENERATIVO DE DEFECTOS ÓSEOS PERIIMPLANTARIOS. ENSAYO CLÍNICO CONTROLADO, ALEATORIZADO, PROSPECTIVO, MULTICÉNTRICO."**

Código Interno: 2017018 (PS)

Versión del Protocolo: Versión 2, 19 de junio de 2017
Versión Hoja Información al Paciente y Consentimiento Informado: GENERAL / Versión 2, 19 de Junio de 2017

Y que este Comité reunido el día 21/06/2017 (recogido en acta Nº 06/2017) ha decidido emitir Dictamen Favorable a que dicho ensayo sea realizado en PerioCentrum Bilbao por:

- Alberto Ortiz-Vigón Carnicero (responsable del estudio)
- Erik Regidor Correa

Lo que firmo en Vitoria, a 10 de julio de 2017

EUSKO JAURLARITZA
GOBIERNO VASCO
OSASUN SAILA
DEPARTAMENTO DE SALUD
2017 UZT. 10
Euskadiko Ikerketa Klinikoetarako Batzorde Etikoa
Comité Ético de Investigación Clínica de Euskadi (CEIC-E)

Iciar Alfonso Farnós
Vicepresidenta del CEIC Comunidad Autónoma del País Vasco (CEIC-E)

Nota: Una vez comenzado el estudio, se recuerda la obligación de enviar un **informe de seguimiento anual** y el **informe final** que incluya los resultados del estudio (si el estudio dura menos de un año, con el informe final será suficiente). Más información en la página web del CEIC-E:
http://www.osakidetza.euskadi.eus/informacion/comite-etico-de-investigacion-clinica-de-euskadi-presentacion/r85-pkfarm03/es/

CEIm
Euskadiko Medikamentuen gaineko Ikerkuntza Batzorde Etikoa
Comité de Ética de la Investigación con medicamentos de Euskadi
E

EUSKO JAURLARITZA
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DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS DE EUSKADI (CEIm-E)

Arantza Hernández Gil
Secretaria del CEIm de Euskadi (CEIm-E)

CERTIFICA

Que este Comité, en cumplimiento de las exigencias de Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos, resto de principios éticos y legales actualmente exigidos, ha evaluado la propuesta del promotor: **PERIOCENTRUM BILBAO**, para que se realice el estudio de investigación de Título: **"Tratamiento quirúrgico reconstructivo de defectos óseos periimplantarios: aplicación de un xenoinjerto bovino con o sin membrana reabsorbible: ensayo clínico aleatorizado multi-céntrico"**.

Código Interno: PS2019012

Versión del Protocolo: 2, 29 de Abril de 2019

Versión Hoja Información al Paciente y Consentimiento Informado: GENERAL / 2, 29 de Abril de 2019

Y que este Comité reunido el día 02/05/2019 (recogido en Acta 06/2019) ha decidido emitir **Dictamen Favorable** a que dicho estudio sea realizado por el siguiente personal investigador:

- Erik Regidor *(Estomatología) Consulta Médica Privada*
- Luis Antonio Aguirre Zorzano *Universidad del País Vasco UPV/EHU*
- Ana María García de la Fuente *Universidad del País Vasco UPV/EHU*
- Mariano Sanz *Universidad Complutense de Madrid*
- Alberto Ortiz-Vigón *(Estomatología) Consulta Médica Privada*

Que el CEIm-E, 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 CEIm-E 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 no habrá participado en la evaluación ni en el dictamen de la solicitud de autorización

Lo que firmo en Vitoria, a 15 de mayo de 2019

Arantza Hernández Gil
Secretaria del CEIm de Euskadi (CEIm-E)

Nota: Se recuerda la obligación de:
- Incluir en Osabide la alerta correspondiente a cada paciente, de que se encuentra bajo estudio o ensayo clínico
- Enviar un **informe de seguimiento anual** y el **informe final** que incluya los resultados del estudio (si el estudio dura menos de un año, con el informe final será suficiente). Más información en la página web del CEIm-E: http://www.euskadi.eus/comite-etico-investigacion-clinica/

ZERTIFIKAT ◆ CERTIFICATE ◆ 認証書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

Product Service

EC Certificate

Full Quality Assurance System

Directive 93/42/EEC on Medical Devices (MDD), Annex II excluding (4)
(Devices in Class IIa, IIb or III)

No. G1 15 08 39446 062

Manufacturer: **Geistlich Pharma AG**
Bahnhofstr. 40
6110 Wolhusen
SWITZERLAND

Facility(ies): Geistlich Pharma AG
Bahnhofstr. 40, 6110 Wolhusen, SWITZERLAND

Product Category(ies): **Natural Bone Mineral, Resorbable Collagen Implants**

The Certification Body of TÜV SÜD Product Service GmbH declares that the aforementioned manufacturer has implemented a quality assurance system for design, manufacture and final inspection of the respective devices / device categories in accordance with MDD Annex II. This quality assurance system conforms to the requirements of this Directive and is subject to periodical surveillance. For marketing of class III devices an additional Annex II (4) certificate is mandatory. See also notes overleaf.

Report No.: 713065321

Valid from: 2015-11-09
Valid until: 2020-11-08

Date, 2015-09-11

Hans-Heiner Junker

04052768730015

TÜV SÜD Product Service GmbH is Notified Body with identification no. 0123

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Product Service

EC Certificate

EC Design-Examination Certificate

Directive 93/42/EEC on Medical Devices (MDD), Annex II (4)
(Devices in Class III)

No. G7AO 14 09 39446 068

Manufacturer: **Geistlich Pharma AG**
Bahnhofstr. 40
6110 Wolhusen
SWITZERLAND

Product: **Non-Active Implants**
Bone Substitute

Model(s): **Geistlich Bio-Oss® Collagen**

Parameters:
Block 100 mg
Block 250 mg
Block 500 mg

The Certification Body of TÜV SÜD Product Service GmbH declares that a design examination has been carried out on the respective devices in accordance with the directive 93/42/EEC Annex II (4) and Regulation (EU) 722/2012 on medical devices manufactured utilizing tissues of animal origin. The design of the devices conforms to the requirements of the Directive and the Regulation. If a certificate of the European Directorate for the Quality of Medicines (EDQM) has been issued for the respective material of animal origin, the validity of our certificate is associated with the validity of the EDQM certificate. Any changes of the EDQM certificate need to be reported immediately to TÜV SÜD Product Service GmbH by a change notification. For marketing of these devices an additional Annex II without (4) certificate is mandatory. See also notes overleaf.

Report no.: 713041457

Valid from: 2014-09-29
Valid until: 2019-09-28

623099

Date, 2014-09-26

Hans-Heiner Junker

TÜV SÜD Product Service GmbH is Notified Body according to Council Directive 93/42/EEC concerning medical devices with identification no. 0123.

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Product Service

EC Design Examination Certificate

(Annex II, section 4 of the Directive 93/42/EEC on Medical Devices)

No. G7 10 09 39446 047

Manufacturer: **Geistlich Pharma AG**
Bahnhofstr. 40
6110 Wolhusen
SWITZERLAND

Product: **Non-Active Implants**

Model(s): **Geistlich Bio-Gide®**
Resorbable collagen membrane
for GBR und GTR treatment

Parameters:
16x22 mm
25x25 mm
30x40 mm

The Certification Body of TÜV SÜD Product Service GmbH declares that a design examination has been carried out on the aforementioned devices according to Annex II, section 4 of the Directive 93/42/EEC on Medical Devices. The design of the devices conforms to the provisions of this Directive. For marketing of these products an additional Annex II.3 certificate is mandatory. See also notes overleaf.

Report no.: 71372504

Valid until: 2015-11-08

Date, 2010-11-09

Hans-Heiner Junker

445100

TÜV SÜD Product Service GmbH is Notified Body according to Council Directive 93/42/EEC concerning medical devices with identification no. 0123.

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Sepa'20 OnAir

Un congreso para todos

SepaTV

C E R T I F I C A D O

La Sociedad Española de Periodoncia y Osteointegración
CERTIFICA QUE:

Erik Regidor Correa

Ha presentado la comunicación en formato
Comunicación en formato vídeo -Segundo premio en la categoría vídeo.

con el título

TRATAMIENTO QUIRÚRGICO RECONSTRUCTIVO DE LA PERIIMPLANTITIS MEDIANTE LA UTILIZACIÓN DE UN XENOINJERTO JUNTO CON MEMBRANA REABSORBIBLE.

Firmada por

Erik Regidor Correa; Alberto Ortiz-Vigón; Belen Iturre; Miren Gil; Ana Mª Garcia de la Fuente; Luis A. Aguirre; Mariano Sanz

en el congreso Sepa OnAir 2020 celebrado virtualmente entre el 11 septiembre y el 28 noviembre de 2020.

Antonio Bujaldón
Presidente de SEPA

Sepa.

SepaTV

25 – 27 Noviembre 2021
Sevilla

Sepa21

Sepa.
PERIO

CERTIFICADO DE COMUNICACIONES

La Sociedad Española de Periodoncia y Osteointegración certifica que

Erik Regidor Correa

ha presentado con el título

COMUNICACIÓN ORAL DE INVESTIGACIÓN

APLICACIÓN DE UN XENOINJERTO COLÁGENO CON MEMBRANA REABSORBIBLE PARA EL TRATAMIENTO QUIRÚRGICO RECONSTRUCTIVO DE DEFECTOS ÓSEOS PERIIMPLANTARIOS: ENSAYO CLÍNICO ALEATORIZADO

firmada por

Erik Regidor Correa; Alberto Ortiz-Vigón Carnicero; Idoia Ayllon; Daniel Rodrigo; Fabio Vignoletti; Mariano Sanz

En el congreso **SEPA Periodoncia** celebrado en Sevilla del 25 al 27 de Noviembre de 2021

Dr. Antonio Bujaldón
Presidente SEPA

SEPA
FUNDACIÓN SEPA DE PERIODONCIA E IMPLANTES DENTALES

Málaga
18 — 21 Mayo
2022

Sepa22

Sepa.
PERIO

CERTIFICADO DE COMUNICACIONES

La Sociedad Española de Periodoncia y Osteointegración certifica que

Erik Regidor Correa

ha presentado la comunicación en formato:

Research Oral communications

con el título

APLICACIÓN DE UN XENOINJERTO COLÁGENO CON MEMBRANA REABSORBIBLE PARA EL TRATAMIENTO QUIRÚRGICO RECONSTRUCTIVO DE DEFECTOS ÓSEOS PERIIMPLANTARIOS: ENSAYO CLÍNICO ALEATORIZADO

firmada por

Alberto Ortiz-Vigón Carnicero; Mario Romandini; Fabio Vignoletti; Jan Derks; Mariano Sanz

En el congreso Sepa Periodoncia celebrado
en Málaga del 18 al 21 de Mayo de 2022

Dr. Antonio Bujaldón
Presidente SEPA

Osteology Foundation

SIdP
Società Italiana di Parodontologia e Implantologia

OSTEOLOGY FOUNDATION & SIdP
JOINT MEETING

National Osteology Symposium Rome
THE "GREAT BEAUTY" OF REGENERATION
Innovation and personalization in treatment approaches

CERTIFICATE

Osteology Research Prize

Mario Romandini

The use of a resorbable membrane in the reconstructive surgical therapy of peri-implantitis - a randomized clinical trial

1. Prize for Best Research Poster

Click here and insert signature
(Insert / Picture)

Ronald E. Jung
Scientific Chairman

Raffaele Cavalcanti
Scientific Chairman

Rome, 05 November 2022
LINKING SCIENCE WITH

PRACTICE IN REGENERATION

Sepa.

SOCIEDAD ESPAÑOLA DE PERIODONCIA Y OSTEOINTEGRACIÓN

Dr. Francisco Vijande Díaz de Corcuera, en su calidad de Secretario General de la Sociedad Española de Periodoncia y Osteointegración

C E R T I F I C A

Que el **Dr. Jan Derks** ha resultado ganador de la edición 2023 del **Premio Fonseca Internacional**, otorgado por la Sociedad Española de Periodoncia y Osteointegración, con el artículo **Reconstructive surgical therapy of peri-implantitis: A multicenter randomized controlled clinical trial**, firmado por los doctores Jan Derks, Alberto Ortiz-Vigón, Adrián Guerrero, Mauro Donati, Eriberto Bressan, Paolo Ghensi, Dennis Schaller, Cristiano Tomasi, Karolina Karlsson, Ingemar Abrahamsson, Yuki Ichioka, Carlotta Dionigi, Erik Regidor y Tord Berglundh, y publicado en el Clinical Oral Implants Research. 2022;00:1-24.

Y para que así conste a los efectos oportunos, firma el presente Certificado, en Sevilla a tres de junio de dos mil veintitrés