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DIABETES MELLITUS Y HÁBITO TABÁQUICO COMO FACTORES PRONÓSTICOS DEL TRATAMIENTO ENDODÓNTICO:

REVISIÓN SISTEMÁTICA Y METAANÁLISIS

DIABETES MELLITUS AND SMOKING AS PROGNOSTIC FACTORS OF ENDODONTIC TREATMENT:

SYSTEMATIC REVIEW AND METAANALYSIS

Tesis Doctoral

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CERTIFICAN:

Que D. DANIEL CABANILLAS BALSEA, Graduado en Odontología por la Universidad de Sevilla e inscrito en el programa de Doctorado de Ciencias de la Salud de la Universidad de Sevilla, ha realizado bajo su tutela y dirección el trabajo titulado ***Diabetes mellitus y hábito tabáquico como factores pronósticos del tratamiento endodóntico: revisión sistemática y metaanálisis / Diabetes mellitus and smoking as prognostic factors of endodontic treatment: systematic review and metaanalysis***, que consideramos satisfactorio para optar al título de Doctor en Odontología.

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INTRODUCCIÓN

Las implicaciones de las enfermedades sistémicas en la salud o patología de los tejidos periapicales es un tema de gran interés en la investigación en los últimos años. En este sentido, surge el concepto de “Medicina Endodóntica” (Segura-Egea *et al.* 2015), que se desarrolla para buscar y analizar posibles implicaciones de enfermedades y/o hábitos sistémicos en la pulpa y los tejidos periapicales, así como de las consecuencias sistémicas que puedan tener la pulpitis y la periodontitis apical (Segura-Egea *et al.* 2015, Cintra *et al.* 2018).

PERIODONTITIS APICAL

La periodontitis apical es un proceso de inflamación y destrucción de los tejidos perirradiculares causado por una infección microbiana del sistema de conductos radiculares del diente afectado (Nair 2004, Al-Nazhan *et al.* 2017). Las bacterias causantes de la infección endodóntica presentes en el espacio pulpar, junto con las toxinas, antígenos y moléculas con efectos biológicos liberadas por las mismas, avanzan a través del foramen apical hacia los tejidos periapicales, desencadenando una defensa del hospedador (Figura 1 y Figura 2). Esto va a generar una reacción inmuno-inflamatoria local, junto con un daño tisular en la estructura ósea periapical, resultando en una reabsorción identificada radiográficamente como una lesión radiolúcida periapical (LRP) (Nair *et al.* 1999, Estrela *et al.* 2008, Van der Veken *et al.* 2017).

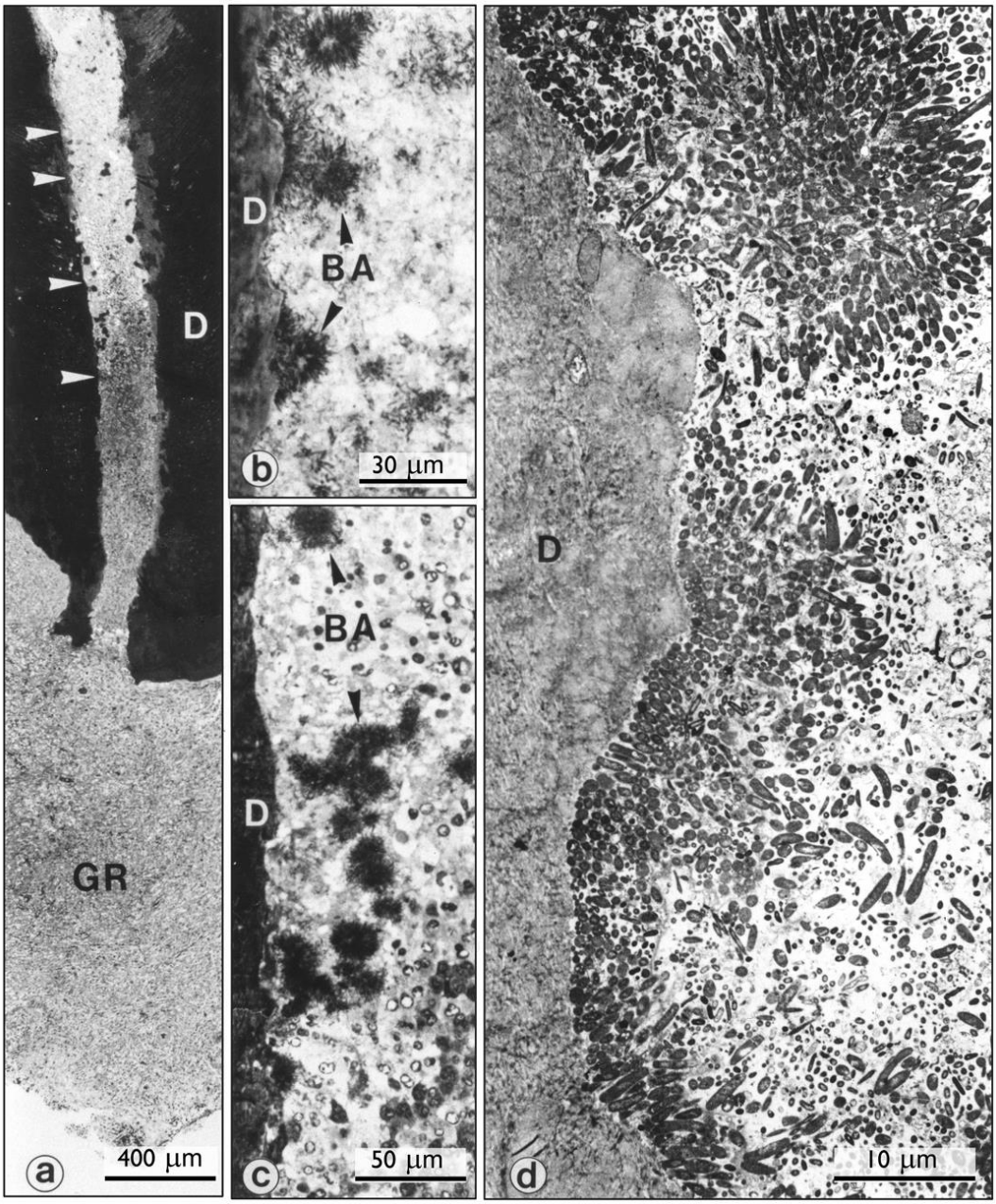

Figura 1. *Microflora endodóntica de un diente humano con periodontitis apical (GR). (a) Las áreas entre las dos puntas de flecha superiores e inferiores se amplían en (b) y (c), respectivamente. (b) Se observan densos agregados bacterianos (BA) que se adhieren a la pared dentinaria (D). (c) Los agregados bacterianos (BA) también permanecen suspendidos entre los granulocitos neutrófilos en el fluido del conducto radicular. (d) Vista de microscopio electrónico de transmisión de la interfase dentino-pulpar que muestra condensación bacteriana en la superficie de la pared dentinaria, formando un grueso biofilms en capas. Ampliaciones: (a) 46x; (b) 600x; (c) 370x; y (d) 2350x.* (Nair 2004).

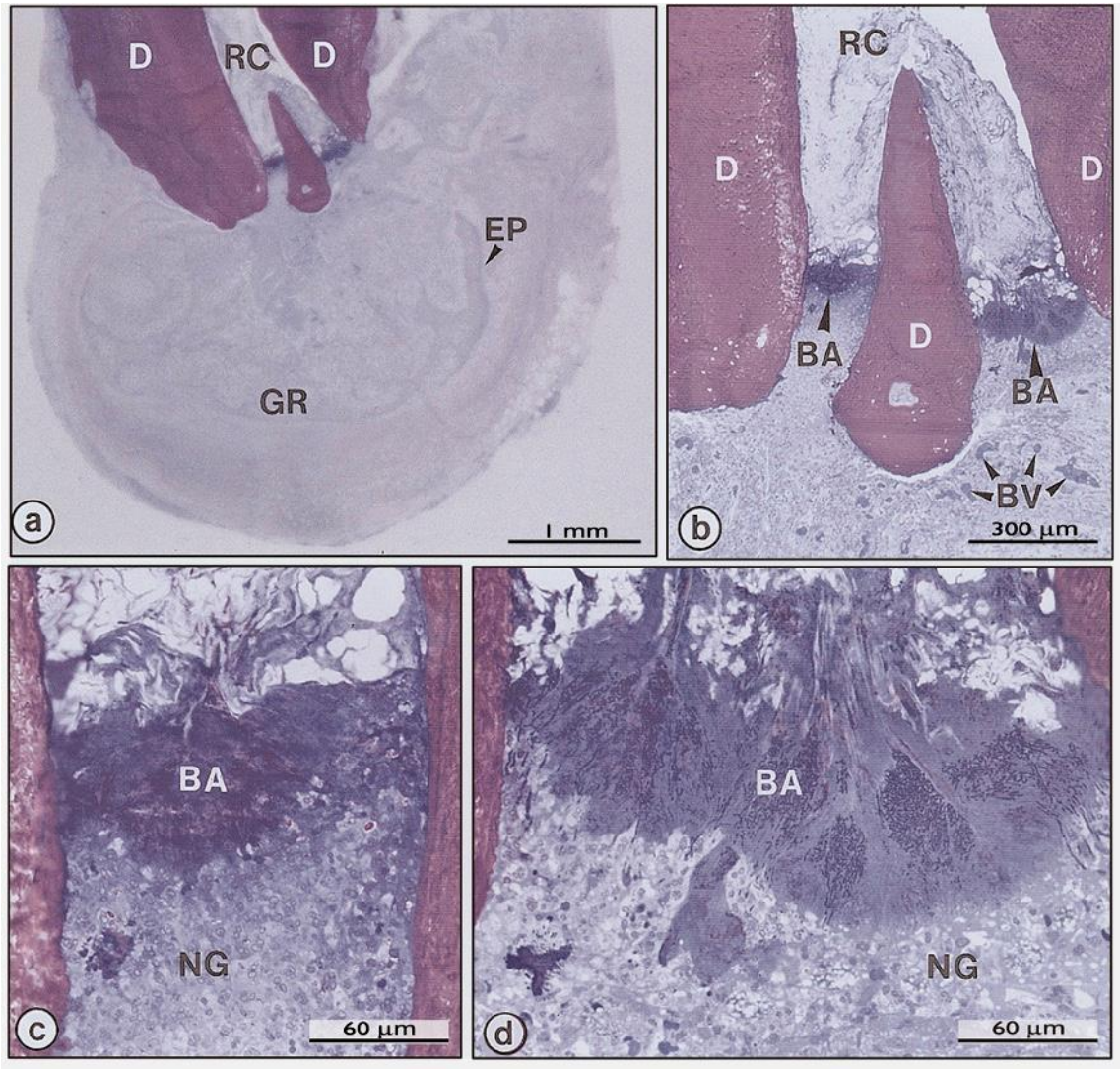

Figura 2. (a) Biofilm bien establecido en el foramen apical de un diente afectado con periodontitis apical (GR). (b) Delta apical ampliado. (c y d) Ampliaciones de las ramificaciones del canal radicular a la izquierda y a la derecha, respectivamente. Se observa la ubicación estratégica de los grupos bacterianos (BA) en el foramen apical, que parecen estar retenidos por una pared de granulocitos neutrófilos (NG). EP, epitelio. Ampliaciones: (a) 20x, (b) 65x y (c y d) 350x (Nair 2004).

La prevalencia de la periodontitis apical se ha estimado en numerosos estudios con unas cifras que oscilan entre el 0,6% (Eriksen *et al.* 1995) y el 15,1% (Mukhaimer *et al.* 2012) del total de dientes. Una reciente revisión sistemática y metaanálisis determina una prevalencia global de periodontitis apical del 52% de los cerca de 35.000 individuos, y del 5% de los cerca de 640.000 dientes analizados (Tibúrcio-Machado *et al.* 2021). Similar prevalencia de periodontitis apical, aunque ligeramente superior, ha sido estimada por otra revisión sistemática y metaanálisis que analiza los estudios transversales publicados en los últimos años (entre 2012 y 2020), estableciéndola en el 6,3% de los más de 200.000 dientes analizados (Jakovljevic et al. 2020). Esto lo convierte en una patología muy prevalente en la actualidad entre los pacientes odontológicos (Figdor 2002).

TRATAMIENTO DE CONDUCTOS. PRONÓSTICO EN ENDODONCIA.

Aquellos dientes que presentan periodontitis apical requieren de un tratamiento de conductos radicular que erradique la contaminación endodóntica causante (Ricucci *et al.* 2009). La prevalencia de dientes con tratamiento endodóntico no quirúrgico se sitúa entorno al 7,4% (Jakovljevic *et al.* 2020). Una vez eliminados los tejidos infectados del conducto radicular se restituyen los tejidos periapicales, produciéndose la regeneración ósea, caracterizada por la reducción del tamaño y desaparición de la radiolucidez radiográfica periapical (Danesh *et al.* 2019). La tasa de éxito del tratamiento endodóntico se sitúa entre el 53-95% (Jokinen *et al.* 1978, Ingle 1985, Ng *et al.* 2011*a*), en función de las poblaciones analizadas, así como de los parámetros clínicos y radiológicos establecidos en los diferentes estudios.

Cuando el tratamiento endodóntico fracasa, persiste la periodontitis apical y, por tanto, la lesión de los tejidos perirradiculares no se resuelve. Esta patología, denominada periodontitis apical persistente, se considera un problema microbiológico, incluso en dientes con tratamientos de conductos que parecen adecuados en las radiografías, que se extiende desde el espacio pulpar hacia los tejidos perirradiculares (Siqueira & Rôças 2014), y se caracteriza radiográficamente por presentarse como una lesión radiolúcida periapical

asociada a un diente endodonciado (Danesh *et al.* 2019). Diversos estudios muestran una alta prevalencia de periodontitis apical asociada a dientes endodonciados, oscilando entre el 15,8% (Ureyen Kaya *et al.* 2013) y el 59,5% (Mukhaimer *et al.* 2012), con una media del 39% (Tibúrcio-Machado *et al.* 2021) o del 41,3% en los artículos publicados desde 2012 (Jakovljevic *et al.* 2020), empleando criterios de evaluación clínicos y radiográficos.

Cuando se presenta una periodontitis apical persistente, estaría indicada la realización de un retratamiento no quirúrgico, una cirugía periapical o una extracción del diente afectado (Lazarski *et al.* 2001). En este sentido, la cuantificación de una indicación y/o realización de estos procedimientos posteriores al tratamiento endodóntico también nos permite analizar el resultado o éxito del mismo.

Un primer estudio con seguimiento de al menos 2 años de más de 44.000 dientes, determina una incidencia global de estos eventos adversos después del tratamiento de conductos del 9,4%, siendo el 5,6% de todos los casos extraídos, el 2,5% retratado de manera no quirúrgica y el 1,4% sometido a cirugía periapical (Lazarski *et al.* 2001). Otro estudio que analiza el seguimiento tras 5 años de más de 1,5 millones de dientes endodonciados muestra una necesidad de tratamiento en el 12,1% del total de dientes, realizando la extracción del 7,5%, un retratamiento no quirúrgico del 4,4% y una cirugía periapical del 0,3% del total de dientes analizados (Chen *et al.* 2008).

La supervivencia funcional sin dolor de un diente endodonciado puede suponer una definición más indulgente del éxito del tratamiento frente a criterios de análisis radiológicos. Sin embargo, una variable dicotómica como retención/extracción del diente con tratamiento de conductos supone una medida de resultado que evita la subjetividad e interpretación de las pruebas radiográficas (Friedman & Mor 2004, Bartols *et al.* 2020).

La prevalencia de dientes endodonciados extraídos se estima en un reciente estudio en el 17,5% de cerca de 10.000 tratamientos endodónticos incluidos durante un período medio de observación de 3,9 años (rango: 0,0 – 17,6 años) (Bartols *et al.* 2020). Resultados similares, aunque ligeramente más favorables,

encontramos en estudios previos, donde un metaanálisis estima unas probabilidades combinadas de supervivencia que oscilan entre el 86% y el 93% de los dientes entre 2 y 10 años después del tratamiento de conductos (Ng *et al.* 2010).

El fracaso del tratamiento de conductos habitualmente se relaciona con factores intra-operatorios, propios de una técnica endodóntica incorrecta, como puede ser una instrumentación inadecuada, una perforación radicular, una irrigación deficiente, un conducto omitido, una separación de instrumentos o un defecto en el sellado y obturación tridimensional; o factores posoperatorios, como una fractura coronaria y/o radicular o una restauración coronal inadecuada que no garantice un correcto sellado frente a una reinfección del conducto radicular (Vire 1991, Ng *et al.* 2011*a*, Costa *et al.* 2019).

MEDICINA ENDODÓNTICA

Las investigaciones de la “medicina endodóntica” ponen de manifiesto que el resultado del tratamiento endodóntico también puede estar ampliamente influenciado con factores generales del paciente, como pueden ser condiciones médicas sistémicas como la diabetes mellitus, las enfermedades cardiacas o el tratamiento con corticoides, así como hábitos nocivos como el consumo de tabaco o alcohol (Marending *et al.* 2005, Mindiola *et al.* 2006, Ng *et al.* 2010, 2011*b*, *a*, Aminoshariae *et al.* 2017).

Asimismo, la presencia de patología periapical podría influir negativamente en el estado de salud sistémico del paciente, induciendo o perpetuando una respuesta inflamatoria crónica general, que pudiera llegar a ocasionar daños o desregulaciones en la salud general del paciente (Caplan *et al.* 2006, Zhang *et al.* 2016).

No obstante, los estudios que determinan asociaciones entre las patologías periapical y sistémica deben analizarse de forma crítica para determinar si se cumplen los criterios de causalidad descritos por Bradford Hill (Hill 1965), identificando de esta manera si un factor realmente influye en la aparición y desarrollo de una enfermedad. En caso contrario, podría existir relación o

asociación, pero no causalidad entre ambas variables (Tjäderhane 2015, Segura-Egea *et al.* 2019).

POSIBLES VÍAS DE CONEXIÓN ENTRE LA PERIODONTITIS APICAL Y LAS ENFERMEDADES SISTÉMICAS

La presencia de mecanismos biológicos bidireccionales es necesaria para que exista una conexión entre la periodontitis apical y las enfermedades sistémicas (Figura 3) (Segura-Egea *et al.* 2021).

1. Influencia de la patología periapical en la salud sistémica

La patología periapical es una enfermedad que representa una interacción entre un desafío microbiano, antígenos y toxinas de las bacterias endodoncias, y una respuesta inmune innata y adaptativa, dando como resultado una producción de citoquinas y, en última instancia, una reabsorción ósea (Morsani *et al.* 2011).

Las toxinas y enzimas liberadas por las bacterias provenientes del espacio pulpar invaden el área periapical mediante su paso a través del foramen apical, provocando un daño tisular directo. El lipopolisacárido capsular (LPS) de las bacterias gram negativas implicadas en la etiología de la periodontitis apical interacciona con receptores específicos TLR4 (toll-like receptor 4) localizados en monocitos, macrófagos, polimorfonucleares y células endoteliales, activando el factor transcripcional NF-κB (factor nuclear potenciador de las cadenas ligeras kappa de las células B activadas), que a su vez, activa la transcripción de genes implicados en la respuesta inflamatoria, induciendo la producción de interleucinas pro-inflamatorias, como las IL-1, IL-6, IL-8, IL-12 y TNFα, además de estimular la liberación de PGE2. Los efectos locales de estas citoquinas van a estimular la reabsorción ósea periapical (Figura 3) (Nair 2004, Rôças *et al.* 2014).

Sin embargo, los procesos inflamatorios periapicales también pueden tener repercusión a nivel sistémico mediante tres vías de comunicación diferentes:

a) Propagación de bacterias endodónticas

Pueden existir dos formas de propagación de las bacterias de la inflamación periapical: a.1) por contigüidad, mediante la propagación y extensión de la infección localizada en el periápice a los tejidos adyacentes, provocando celulitis cervicofacial, y pudiendo comprometer sistémicamente al paciente mediante un cuadro febril e inflamatorio generalizado si no se instaura el tratamiento adecuado; y a.2.) por bacteriemia, mediante el paso de bacterias endodónticas a la sangre, gracias a la existencia un tejido periapical inflamatorio granulomatoso muy rico en capilares, lo cual posibilita la invasión del torrente sanguíneo por parte de las bacterias presentes en el periápice, así como su propagación metastásica por vía hematógena (Marton & Bergenholtz 2005, Gomes *et al.* 2013).

b) Paso de moléculas liberadas en el tejido periapical a la sangre

Las bacterias causantes de la infección endodóntica también liberan moléculas con efectos biológicos. Asimismo, las citoquinas liberadas en la región periapical inflamada pueden pasar al torrente sanguíneo, produciendo efectos en zonas alejadas del organismo (Marton 2004).

Los patrones moleculares asociados a patógenos LPS y LTA (ácido lipoteicoico, antígeno de la pared celular de bacterias gram positivas), potentes estimulantes de la inmunidad innata, interaccionan con sus receptores LPS/TLR4 y LTA/TLR2 activando el factor transcripcional NF-$\kappa\beta$, potenciando la síntesis de las citoquinas pro-inflamatorias IL-1, IL-6, IL-8, IL-12 y TNFα (Ao *et al.* 2015). Esto conllevaría a una estimulación de la síntesis y liberación en el hígado de los reactantes de la fase aguda, como la proteína C reactiva (PCR), y el fibrinógeno, que favorecen la trombogénesis y podrían provocar lesiones en órganos alejados de la lesión endodóntica (Garrido *et al.* 2019, Georgiou *et al.* 2019). Además, las citoquinas pro-inflamatorias y los reactantes de la fase aguda, junto con los tromboxanos, las prostaglandinas (PGE2) y los leucotrienos que se acumulan en la región periapical inflamada durante el proceso de reabsorción ósea (Stashenko *et al.* 1998), pueden pasar al torrente sanguíneo

(Li *et al.* 2000) e inducir un estado sistémico pro-inflamatorio crónico (Caplan *et al.* 2006, Gomes *et al.* 2013).

Por otro lado, el mimetismo molecular por el que secuencias de péptidos bacterianos son confundidas con tejidos humanos, provocaría una reacción autoimmune por reactividad cruzada, pudiendo constituir otra vía de conexión entre la inflamación periapical y la patología sistémica (Marton 2004).

c) Presencia de factores de riesgo comunes a la patología endodóntica y sistémica y el polimorfismo genético

Determinados factores de riesgo, extrínsecos e intrínsecos, como por ejemplo la edad, el tabaco, el estilo de vida o el estado socioeconómico pueden estar implicados con la etiología tanto de la patología pulpo-periapical, como de numerosas enfermedades sistémicas. Estos factores comunes deben considerarse como posibles variables de confusión en estudios epidemiológicos que analicen la asociación entre ambas patologías. Ejemplo de ello es el tabaco, factor etiológico clave en la patología cardiovascular, y a la vez, asociado con una mayor prevalencia de periodontitis apical (Segura-Egea *et al.* 2015, Cintra *et al.* 2018).

Por otro lado, determinados polimorfismos genéticos, existencia de más de un alelo para el locus de un gen, pueden predisponer a patologías tanto sistémicas como endodónticas, como por ejemplo, las variantes polimórficas en genes relacionados con interleuquinas, enzimas, factores transcripcionales o moléculas implicadas en la respuesta inmune y reparativa (Morsani *et al.* 2011). Así tenemos el polimorfismo de un solo nucleótido en el gen KCNK3, que predispone a la hipertensión y, a la vez, se asocia a mayor prevalencia de periodontitis apical (Messing *et al.* 2019), o el polimorfismo en el gen IL-1β, que se asocia a mayor prevalencia de periodontitis apical (Salles *et al.* 2018) y a mayor riesgo de infarto de miocardio y de ictus (Bis *et al.* 2008).

2. Influencia de los factores sistémicos en la patología periapical

El proceso reparativo periapical tras la realización del tratamiento de conductos también puede verse afectado por determinadas condiciones sistémicas que afecten a la respuesta inmune innata, alterando la activación macrofágica y la función fagocítica de los neutrófilos, estimulando un estado pro-inflamatorio que altera la proliferación celular, y retrasando o impidiendo la reparación tisular periapical pos-endodóntica. Por tanto, determinadas patologías como son la diabetes mellitus, la arteriosclerosis, la hipertensión, la osteoporosis, el hábito tabáquico, problemas hereditarios de la coagulación, o algunos trastornos digestivos pueden disminuir la respuesta reparativa pulpar y periapical, lo que puede manifestarse como un incremento de la probabilidad de sufrir periodontitis apical y tratamiento de conductos, así como un aumento de la prevalencia de periodontitis apical persistente tras el tratamiento endodóntico (Ng *et al.* 2011*a*, Segura-Egea *et al.* 2015).

Otras patologías sistémicas producen una fuerte reacción inflamatoria que activa el factor NF-κB en los macrófagos e incrementa el estrés oxidativo, produciendo una alteración del recambio óseo, con incremento de la actividad osteoclástica y la reabsorción ósea, y disfunción de los osteoblastos y fibroblastos con alteración de la síntesis de colágeno. Estas enfermedades, que presentan altos niveles serológicos de PCR, colagenasas, citoquinas pro-inflamatorias (IL-1b, IL-6, IL-8, IL-10, TNF-α) e incremento de radicales libres, suelen generar lesiones periapicales de mayor progresión, a la vez que el proceso de cicatrización periapical se enlentece o detiene (Taylor *et al.* 2013, Peddis *et al.* 2019).

Por último, alteraciones en la vascularización con reducción del flujo sanguíneo y disminución del aporte de nutrientes y oxígeno a los tejidos, como las descritas en los fumadores crónicos, también pueden retrasar o detener la curación de la periodontitis apical, llevando incluso al fracaso del tratamiento endodóntico (Kinane & Chestnutt 2000, Duncan & Pitt Ford 2006, Segura-Egea *et al.* 2015).

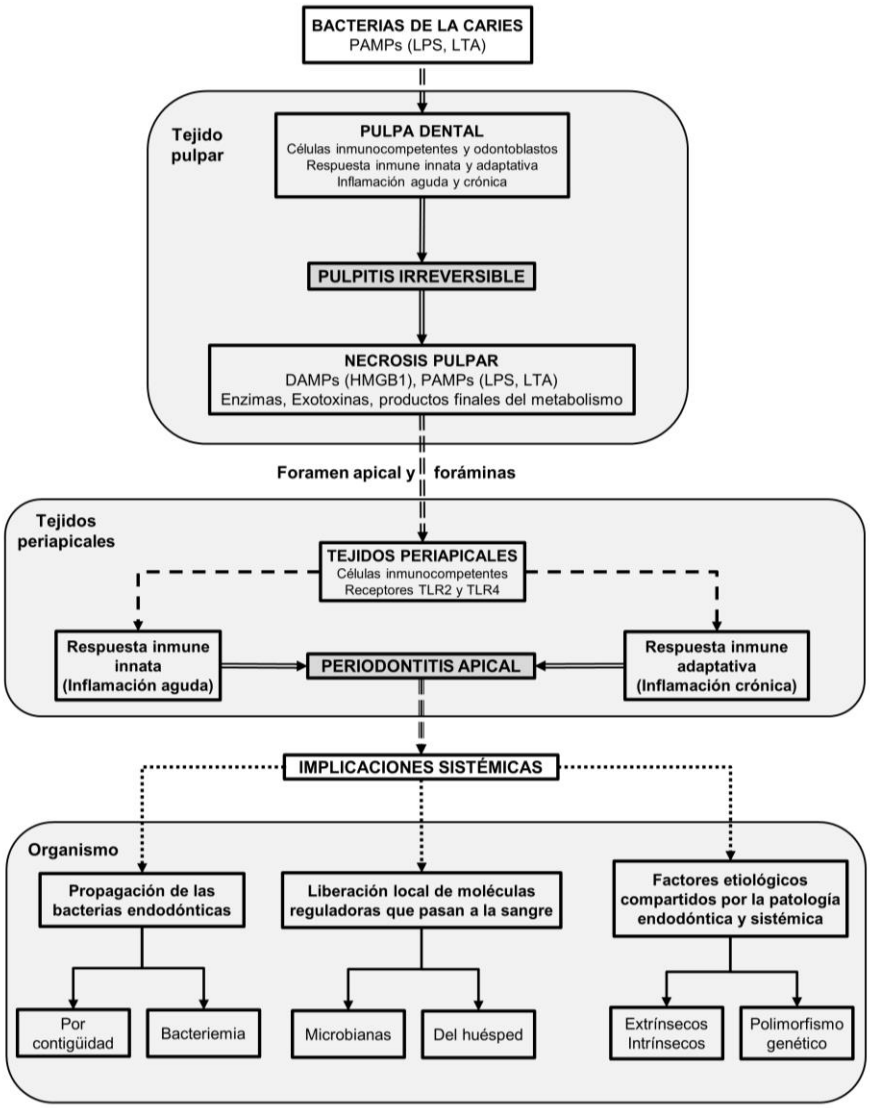

Figura 3. Los patrones moleculares asociados a patógenos (PAMP), como el lipopolisacárido capsular (LPS) de las bacterias gram-negativas o el ácido lipoteicoico (LTA) de la pared celular de las bacterias gram-positivas, junto con moléculas resultantes de la necrosis celular, denominadas patrones moleculares asociados a daño tisular (DAMP), como la proteína de alta movilidad del grupo 1 (HMGB1), invaden los tejidos periapicales y estimulan los receptores TLR2 y TLR4 de las células inmunes, provocando la reacción inmune e inflamatoria característica de la periodontitis apical. Las posibles interrelaciones de la patología endodóntica y sistémica pueden producirse a través de tres vías: la propagación de las bacterias endodónticas, el paso a la sangre de moléculas que se están liberando en el tejido periapical y la presencia de factores de riesgo comunes a la patología endodóntica y sistémica o el polimorfismo genético (Segura-Egea et al. 2021).

PATOLOGÍAS SISTÉMICAS ASOCIADAS A LA PATOLOGÍA ENDODÓNTICA

Las patologías sistémicas cuya posible relación con la periodontitis apical se han investigado son numerosas (Segura-Egea et al. 2015) (Figura 4). En la mayoría de los casos se ha encontrado asociación significativa, lo que no implica que exista relación causal (Segura-Egea et al. 2019).

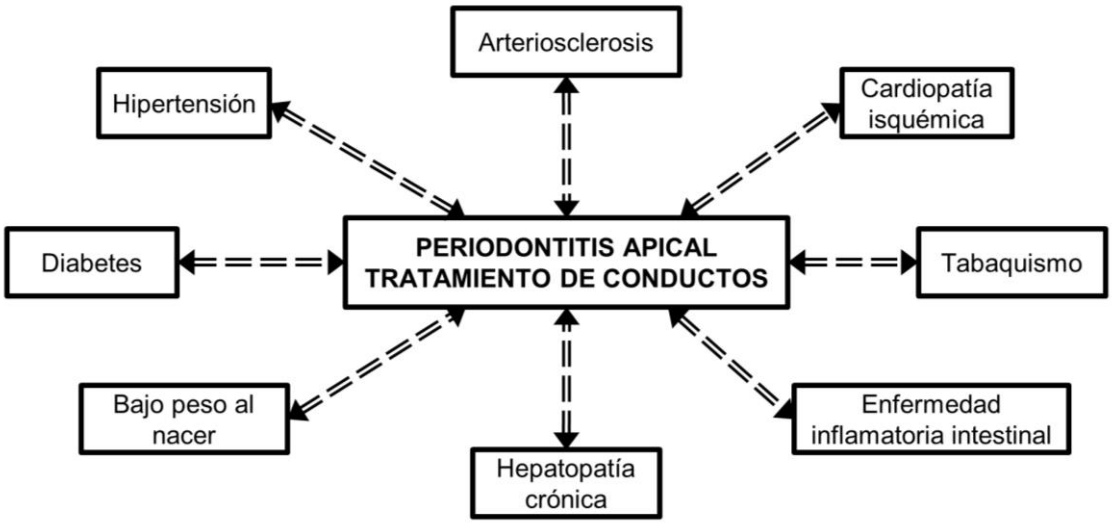

Figura 4. Patologías sistémicas que han sido asociadas a la patología endodóntica y al tratamiento de conductos (Segura-Egea et al. 2021).

Diabetes mellitus

La diabetes mellitus, enfermedad metabólica caracterizada por niveles elevados crónicos de glucosa en sangre como resultado de la incapacidad de las células beta del páncreas para producir la insulina adecuada o la utilización ineficaz de la insulina por las células del cuerpo (Alberti & Zimmet 1998), tiene una prevalencia estimada del 9,3% (463 millones) de la población global mundial, y se prevé su aumento al 10,2% (578 millones) para el 2030 y al 10,9% (700 millones) para 2045. Además, su prevalencia es mayor en zonas urbanas (10,8%) que en zonas rurales (7,2%) y en zonas de ingresos altos (10,4%) que en países de ingresos bajos (4,0%) (Saeedi *et al.* 2019) (Figura 5). Estos datos convierten a la diabetes mellitus en uno de los desafíos más importantes de la salud pública del siglo XXI (Zimmet *et al.* 2016).

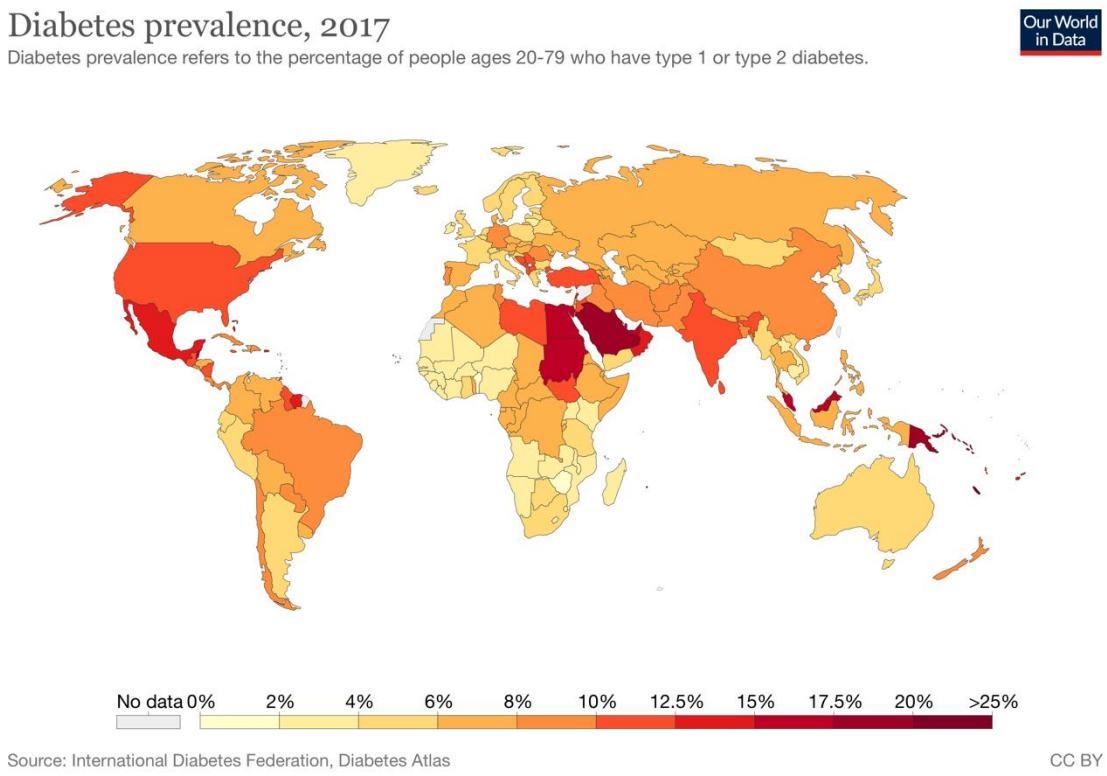

Figura 5. Mapa de la prevalencia mundial de diabetes mellitus (Our World in Data 2017).

Desde hace décadas, la diabetes mellitus se considera un factor de riesgo para determinadas patologías orales, como los problemas periodontales (Löe 1993) o el desarrollo de infecciones periapicales de mayor tamaño en pacientes con diabetes mellitus mal controlados (Bender *et al.* 1963). Desde entonces, se han llevado a cabo numerosas investigaciones buscando asociaciones entre la patología periapical y la diabetes mellitus (Riós-Osorio *et al.* 2020), encontrando entre sus resultados un aumento de la prevalencia de periodontitis apical en pacientes diabéticos comparado con sanos (Segura-Egea *et al.* 2005, López-López *et al.* 2011), un aumento de la frecuencia de lesiones perirradiculares en pacientes diabéticos de larga duración frente a corta duración (Mesgarani *et al.* 2014) o una asociación entre la infección periapical y el grado de control metabólico de la diabetes mellitus (Sánchez-Domínguez *et al.* 2015, Smadi 2017). Además, un estudio reciente indica que los pacientes con diabetes mellitus tipo 2 tienen cambios de dimensión fractal, una medida de la complejidad estructural de la región ósea evaluada, significativamente menores en el área de

la lesión apical de dientes tras el tratamiento de conductos en comparación con los individuos sanos, indicando una menor complejidad trabecular de forma cuantitativa, así como una menor curación de las lesiones periapicales tras el tratamiento endodóntico (Uğur Aydın *et al.* 2021).

En los pacientes con diabetes mellitus, el deterioro de la inmunidad innata, la hiperglucemia, y el incremento del nivel sérico de productos avanzados de la glicosilación (AGEs), podrían ser los mecanismos biológicos implicados en la mayor prevalencia y el retraso de la curación de la periodontitis apical (Segura-Egea *et al.* 2012, 2015) (Figura 6). Además, el polimorfismo genético también podría jugar un papel importante, habiéndose encontrado que el polimorfismo de los genes RANK y RANKL se asocia tanto a mayor prevalencia de periodontitis apical persistente (Petean *et al.* 2019) como a mayor prevalencia de diabetes tipo 2 (Duan *et al.* 2016).

Por otro lado, el posible efecto de la inflamación periapical sobre el control de la diabetes podría explicarse por el incremento de interleuquinas pro-inflamatorias que la periodontitis apical crónica induciría en el paciente diabético, contribuyendo al desarrollo de resistencia periférica a la insulina y al descontrol metabólico de la diabetes (Segura-Egea *et al.* 2019) (Figura 6).

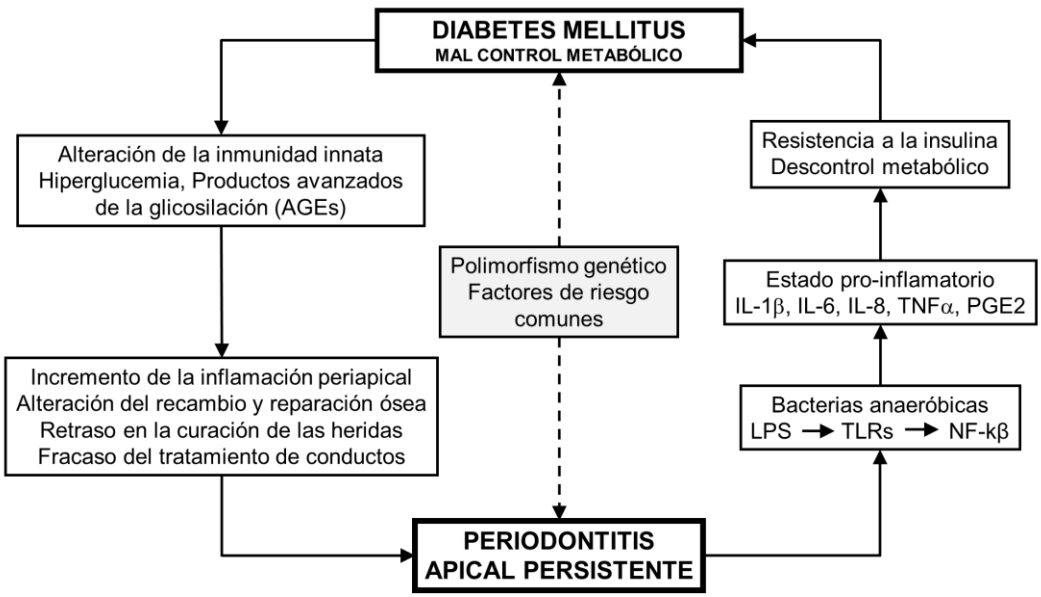

Figura 6. Posibles mecanismos biológicos que conectan la periodontitis apical con la diabetes tipo 2 (Segura-Egea et al. 2019).

Hábito tabáquico

El hábito tabáquico, factor de riesgo ampliamente reconocido de influencia negativa para la salud general y de morbilidad y mortalidad prematuras, presenta una prevalencia de fumadores diarios en mayores de 15 años de entre un 25.0-31,1% en hombres y del 5,4-6,2% en mujeres, lo que supone una tasa de número de fumadores mundial de alrededor de mil millones de personas (Ng *et al.* 2014, Reitsma *et al.* 2017) (Figura 7). Sin embargo, la distribución entre los diferentes países es muy heterogénea, lo que hace encontrar países con tasas del 40% de fumadores, como ocurre en Chile o Grecia (World Health Organization 2020). Además, aunque se espera una tendencia de disminución en la prevalencia del hábito tabáquico, en la actualidad supone una importante amenaza para la salud pública mundial, y en especial en los países de ingresos medios y bajo, puesto que el crecimiento y envejecimiento de la población general se traduce en un aumento de las complicaciones, enfermedades y número total de muertes relacionados con el tabaco (Ritchie & Roser 2013, Chung-Hall *et al.* 2019).

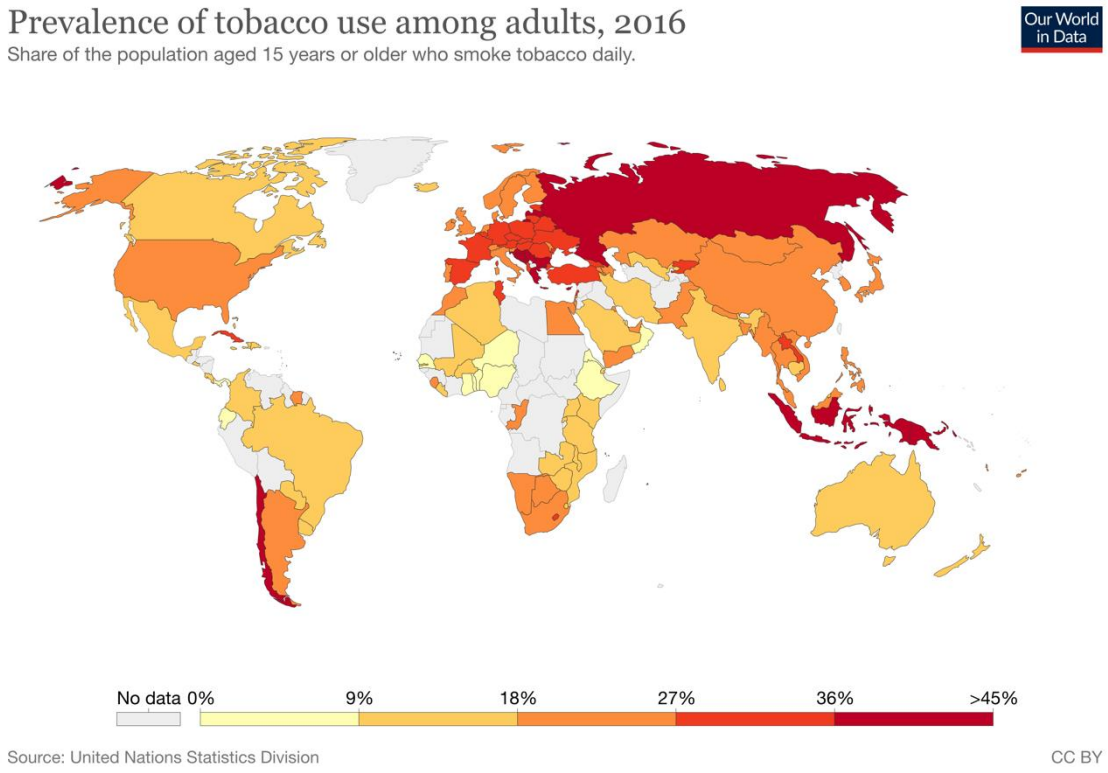

Figura 7. Mapa de la prevalencia mundial de fumadores (Our World in Data 2016).

El hábito tabáquico supone un riesgo bien definido para la salud sistémica y oral, incrementando el riesgo de caries (Fure 2004), de enfermedad periodontal (Walter et al. 2012a) y de patología endodóntica, encontrándose un aumento de la prevalencia de lesiones periapicales (Oginni *et al.* 2015) y de tratamientos de conductos (Segura-Egea *et al.* 2008, 2011).

Los posibles mecanismos por los cuales el tabaco puede alterar la respuesta inmune y reparadora, influyendo en la inflamación periapical, podrían ser diversos (Segura-Egea et al. 2015). El tabaco induce una fuerte respuesta inflamatoria crónica sistémica, con aumento de IL-1β, TNF-α o proteína C-reactiva, que junto con una disfunción de leucocitos polimorfonucleares, macrófagos y linfocitos T y una reducción de los niveles de anticuerpos (IgA, IgM, IgG), va a generar una alteración de la respuesta inmune frente a la infección pulpo-periapical (Tappia *et al.* 1995, Fröhlich *et al.* 2003) (Figura 8).

Por otro lado, el tabaco también provoca alteraciones morfológicas y funcionales en la microcirculación, con disminución del suministro de oxígeno y daño a células endoteliales por aumento de radicales libres (Ijzerman *et al.* 2003). Esto, junto con una disfunción de los fibroblastos y disminución de la síntesis de colágeno, se traduce en un aumento de la destrucción ósea y una alteración de la reparación tisular periapical (Wong *et al.* 2004, Balto *et al.* 2019) (Figura 8).

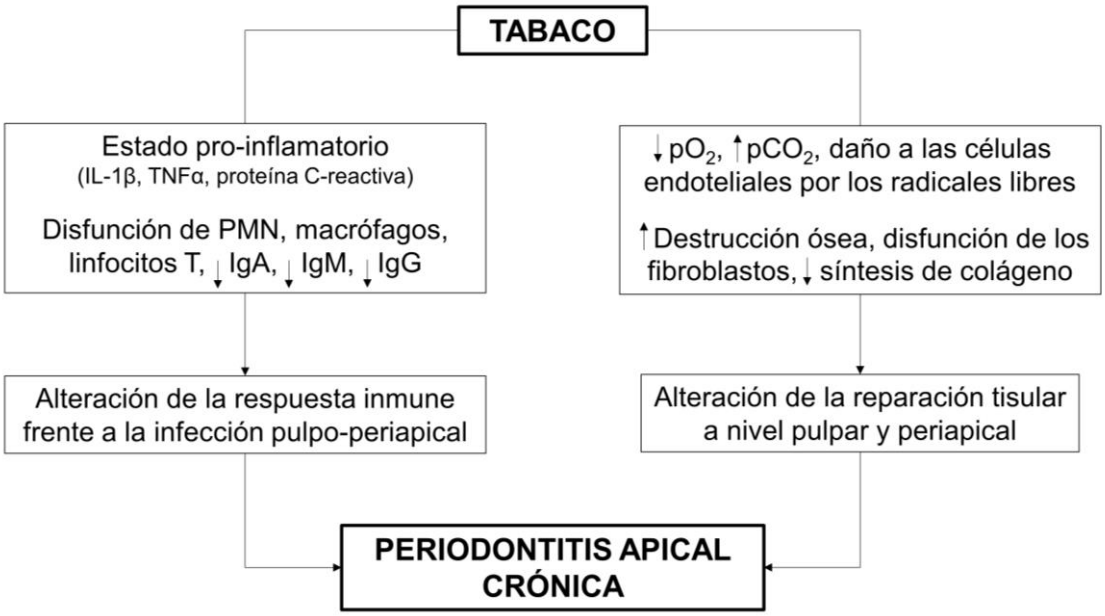

Figura 8. Posibles vías de conexión entre el tabaquismo y la periodontitis apical (Segura-Egea et al. 2015).

Otras patologías

Las enfermedades cardiovasculares (ECV), trastornos relativos al corazón y los vasos sanguíneos que tienen como factor etiológico común la aterosclerosis, suponen la principal causa de muerte mundial en la actualidad (Margaix-Muñoz *et al.* 2008). La cardiopatía coronaria o isquémica (producida por una oclusión parcial o total de las arterias coronarias, que resulta en un aporte sanguíneo insuficiente al miocardio, apareciendo hipoxia y acúmulo de metabolitos en una región del músculo cardíaco, y manifestándose como un angor pectoris, un infarto agudo de miocardio o una muerte súbita) y la hipertensión arterial (trastorno consistente en una elevación de los niveles de presión que el corazón ejerce sobre las arterias de forma continua o sostenida) son las ECVs que presentan mayor prevalencia.

Pioneros estudios epidemiológicos publicados hace más de 30 años relacionan las ECVs y las infecciones orales como la periodontitis apical (Mattila *et al.* 1989, 1995, Mattila 1993). Desde entonces se ha descrito mayor prevalencia de infarto de miocardio en pacientes con infecciones periodontales

y endodónticas (Oikarinen *et al.* 2009, Willershausen *et al.* 2009), asociación significativa entre ECVs y la prevalencia de periodontitis apical (Virtanen *et al.* 2017, Messing *et al.* 2019), mayor probabilidad de tener cardiopatía isquémica en pacientes con amplia historia de tratamientos endodónticos (Joshipura *et al.* 2006, Caplan *et al.* 2009), asociación entre periodontitis apical crónica y aterosclerosis aórtica (Glodny *et al.* 2013, Petersen *et al.* 2014) o relación entre hipertensión y un mayor riesgo de pérdida de dientes endodonciados (Mindiola *et al.* 2006, Wang *et al.* 2011).

Sin embargo, la evidencia científica respecto a la relación de la periodontitis apical con las ECVs es moderada-baja (Berlin-Broner *et al.* 2017*b*), con estudios que, por otro lado, no encuentran diferencias significativas en la prevalencia de periodontitis apical entre los enfermos con ECVs y los pacientes sanos (Aleksejuniene *et al.* 2000, Frisk *et al.* 2003, Segura-Egea *et al.* 2010, de Oliveira *et al.* 2017), o asocian la presencia de dientes endodonciados con menor probabilidad de padecer cardiopatía isquémica y menor riesgo de mortalidad cardiovascular (Meurman *et al.* 2017).

Las posibles conexiones biológicas entre las ECVs y la periodontitis apical podrían ser, por un lado, el paso de bacterias a la sangre con posterior colonización de la placa aterosclerótica (Berlin-Broner *et al.* 2017*a*) y, por otro lado, el estado pro-inflamatorio sistémico asociado a la periodontitis apical, que aumentaría la carga inflamatoria asociada al desarrollo de la aterosclerosis (Cotti & Mercuro 2015) (Figura 9).

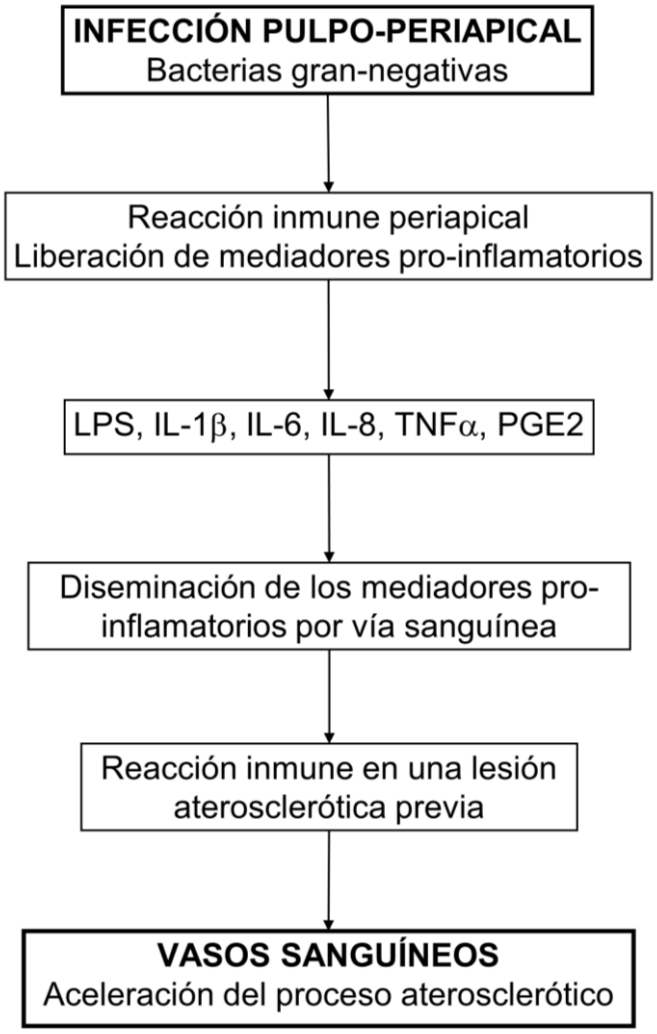

Figura 9. Posibles mecanismos biológicos que enlazan la infección endodóntica con la aterosclerosis (Segura-Egea et al. 2021).

Por otro lado, la periodontitis apical y las ECVs comparten factores de riesgo, como la diabetes mellitus o el hábito tabáquico, que pueden predisponer a que los estudios epidemiológicos encuentren asociación significativa entre ambas patologías (Jiménez-Sánchez *et al.* 2020). De igual forma, factores genéticos o determinados polimorfismos, como del gen IL-1B (Salles *et al.* 2018) o del gen KCNK3 (Messing *et al.* 2019), también se asocian tanto a la periodontitis apical como a las ECVs.

Además de la diabetes mellitus, el tabaco y las enfermedades cardiovasculares, la patología endodóntica se ha relacionado con otras enfermedades sistémicas (Figura 4), encontrándose asociación entre una mayor prevalencia de periodontitis apical y pacientes con coagulopatías hereditarias (Castellanos-Cosano *et al.* 2013*a*), mujeres postmenopáusicas con osteoporosis (López-López *et al.* 2015), mujeres embarazadas con hijos de bajo peso al nacer (Leal *et al.* 2015), pacientes con enfermedad inflamatoria intestinal (colitis ulcerosa y enfermedad de Crohn) (Poyato-Borrego *et al.* 2020), enfermos hepáticos crónicos terminales (Castellanos-Cosano *et al.* 2013*b*) o complicaciones relacionadas con la cirrosis (Grønkjær *et al.* 2016).

A pesar de que la asociación entre la salud sistémica y la patología endodóntica ha sido ampliamente estudiada, la relación entre el estado sistémico del paciente y la respuesta reparadora periapical y el resultado del tratamiento endodóntico sigue siendo una controversia en la actualidad (Segura-Egea *et al.* 2015, Cintra *et al.* 2018). Este trabajo de tesis doctoral pretende analizar y esclarecer la evidencia científica disponible acerca de la diabetes mellitus y el hábito tabáquico como factores pronósticos del tratamiento de conductos.

OBJETIVOS

El objetivo de esta tesis doctoral es investigar la posible asociación entre el estado sistémico del paciente enfermo con diabetes mellitus o con hábito tabáquico, y el pronóstico del tratamiento de conductos mediante la realización de revisiones sistemáticas y metaanálisis para los siguientes objetivos específicos:

1. Determinar la posible asociación entre la diabetes mellitus y el fracaso del tratamiento endodóntico evaluando:

    - La prevalencia de lesiones radiolúcidas periapicales en dientes endodonciados en pacientes diabéticos y en sujetos controles sanos.
      En: CAPÍTULO I. *Association between diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth: systematic review and meta-analysis.*

    - La prevalencia de dientes endodonciados extraídos en pacientes diabéticos y en sujetos controles sanos.
      En: CAPÍTULO II. *Association between diabetes and nonretention of root filled teeth: a systematic review and meta-analysis.*

    - El tipo de asociación, causal o no, existente entre la enfermedad endodóntica y la diabetes mellitus, de acuerdo con los criterios de Bradford-Hill.
      En: CAPÍTULO III. *Endodontics and diabetes: association versus causation.*

2. Determinar la posible asociación entre el hábito de fumar y el fracaso del tratamiento endodóntico evaluando:

    - La prevalencia de lesiones radiolúcidas periapicales en dientes endodonciados en pacientes fumadores y en sujetos controles no fumadores.
      En: CAPÍTULO IV. *Smoking and Radiolucent Periapical Lesions in Root Filled Teeth: Systematic Review and Meta-Analysis.*

- La prevalencia de dientes endodonciados extraídos en pacientes fumadores y en sujetos controles no fumadores.
  En: CAPÍTULO V. *Cigarette Smoking and Root Filled Teeth Extraction: Systematic Review and Meta-Analysis.*

OBJECTIVES

The objective of this doctoral thesis is to investigate the possible association between the systemic state of the patient with diabetes mellitus or smoking, and the prognosis of root canal treatment by conducting systematic reviews and metaanalyses for the following specific objectives:

1. Determine the possible association between diabetes mellitus and endodontic treatment failure by evaluating:

    - The prevalence of radiolucent periapical lesions in root-filled teeth in diabetic patients and in healthy control subjects.
      In: CHAPTER I. *Association between diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth: systematic review and meta-analysis.*

    - The prevalence of extracted root-filled teeth in diabetic patients and in healthy control subjects.
      In: CHAPTER II. *Association between diabetes and nonretention of root filled teeth: a systematic review and meta-analysis.*

    - The type of association, causal or not, existing between endodontic disease and diabetes mellitus, according to the Bradford-Hill criteria.
      In: CHAPTER III. *Endodontics and diabetes: association versus causation.*

2. Determine the possible association between smoking and endodontic treatment failure by evaluating:

    - The prevalence of radiolucent periapical lesions in root-filled teeth in smoking patients and in non-smoking control subjects.
      In: CHAPTER IV. *Smoking and Radiolucent Periapical Lesions in Root Filled Teeth: Systematic Review and Meta-Analysis.*

- The prevalence of extracted root-filled teeth in smoking patients and non-smoking control subjects.
  In: CHAPTER V. *Cigarette Smoking and Root Filled Teeth Extraction: Systematic Review and Meta-Analysis.*

MATERIAL Y MÉTODOS

La metodología empleada para llevar a cabo los objetivos de la presente tesis doctoral incluye la realización de una revisión sistemática y metaanálisis para cada una de las posibles variables de asociación, permitiendo la combinación y el análisis de datos de diferentes estudios realizados sobre temas de investigación similares.

REVISIÓN SISTEMÁTICA

Una revisión sistemática es una revisión de la literatura planificada y ejecutada de manera meticulosa, incluyendo un plan detallado y completo, y una estrategia de búsqueda bien definida, con el objetivo de reducir el sesgo al identificar, evaluar y sintetizar todos los estudios relevantes sobre un tema en particular (Uman 2011, Nagendrababu *et al.* 2020*b*).

Habitualmente, las revisiones sistemáticas incluyen un componente de metaanálisis que implica el uso de técnicas estadísticas para analizar y sintetizar los datos de varios estudios, combinándolos en una sola estimación cuantitativa o tamaño del efecto global (Uman 2011).

Tradicionalmente, la pirámide de la evidencia establece una jerarquía otorgando un nivel estático para los distintos diseños de estudios, posicionando aquellos con metodología más débil en la parte inferior (informes y series de casos), seguidos de estudios de casos y controles y estudios de cohortes en el centro, posteriormente ensayos controlados aleatorios y, en la parte superior, revisiones sistemáticas y metaanálisis (Figura 10) (Murad *et al.* 2016).

Sin embargo, esta pirámide de la evidencia se cuestiona al considerar que la certeza de la evidencia se basa en la combinación del diseño del estudio junto con otros factores, como la imprecisión, incoherencia o resultados indirectos. De esta manera, en el modelo actual, las revisiones sistemáticas y metaanálisis dejan de ocupar la parte superior de la pirámide, pasando a considerarse los mismos como una “lupa” a través de la cual se ve y se aplica un análisis de la

evidencia, siendo la certeza de la evidencia variable y dinámica para distintos estudios con un mismo diseño (Figura 10) (Murad *et al.* 2016).

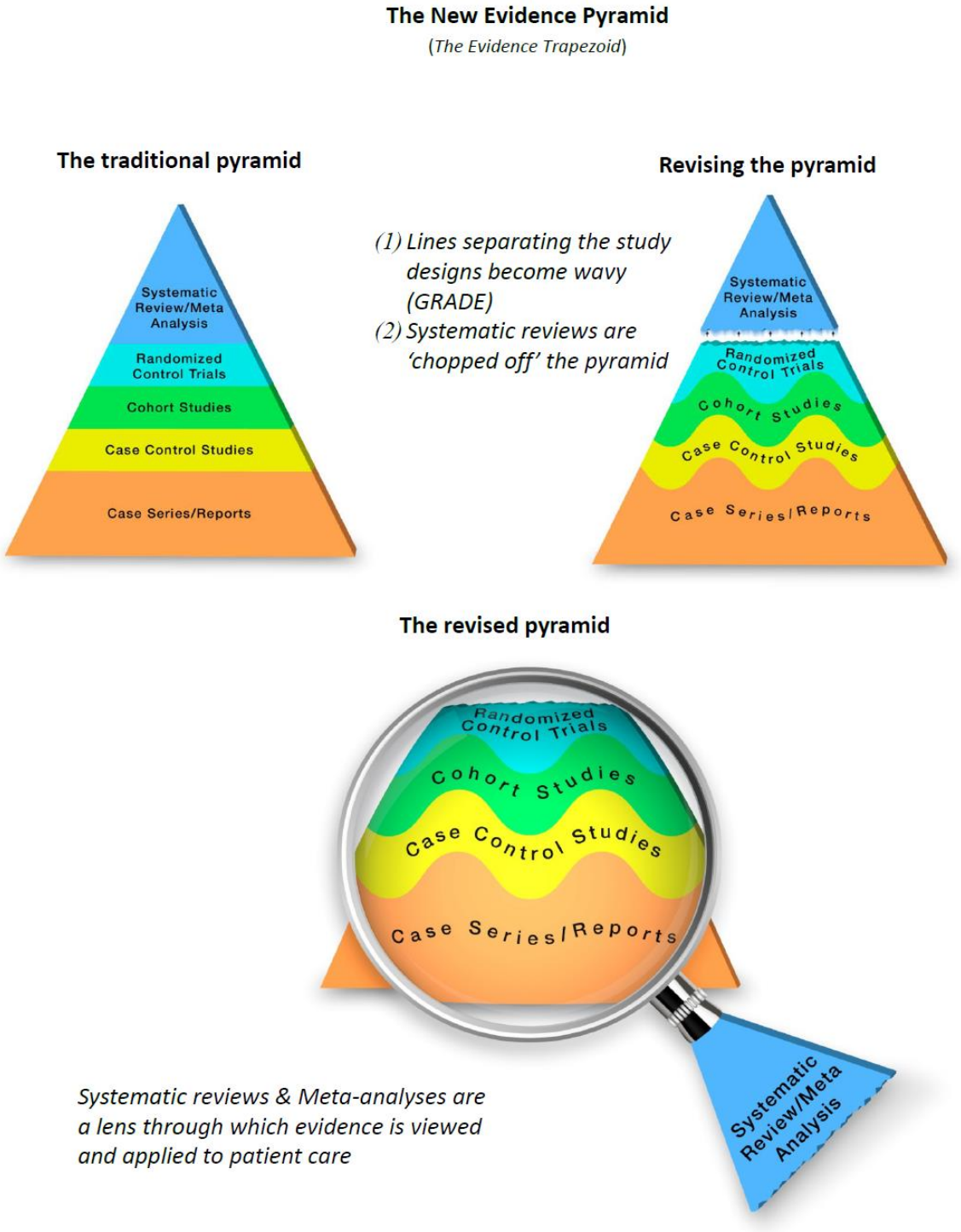

Figura 10. *Nueva pirámide de la evidencia propuesta por Murad et al.* (Murad et al. 2016).

Una revisión sistemática debe considerar el análisis de los siguientes factores (Uman 2011, Ahn & Kang 2018, Higgins *et al.* 2019, Nagendrababu *et al.* 2020*b*):

Pregunta PICO

El primer paso de una revisión sistemática es definir la pregunta de revisión con metodología *PICO: population, intervention, comparison, outcome.* La formulación de esta pregunta permite establecer los diferentes componentes claves que se van a tener en cuenta antes de comenzar la revisión, definiendo la población (P): problema o pacientes con una condición en particular; intervención (I): actuación o tratamiento que queremos analizar; comparación (C): intervención alternativa con la cual comparar; y resultado (O, de *outcome*): desenlace esperado de la intervención.

Criterios de inclusión y exclusión

Los investigadores deben definir a priori las características de los estudios que se van a incluir, precisando el tipo de estudios (ensayos controlados aleatorios, estudios de cohortes, de casos y controles…), el período de investigación, el tamaño muestral mínimo de cada grupo, el rango de edad de la población, las condiciones, resultados y tipos de intervenciones y grupos de control, o las restricciones de idioma o acceso de los trabajos (Uman 2011). Asimismo, también es necesario determinar los criterios o características de los estudios que conllevarán a su exclusión de la revisión sistemática.

Estrategia de búsqueda

Esta etapa es esencial para garantizar una búsqueda que incluya todos los estudios que reporten información acerca de la pregunta planteada.

Para ello, es conveniente elaborar una lista completa de palabras clave o términos MeSH relacionados con cada componente de la pregunta PICO, desarrollando una estrategia de búsqueda óptima y equilibrada entre sensibilidad (identificar una alta proporción de estudios relevantes) y especificidad (identificar una baja proporción de estudios irrelevantes) (Ahn & Kang 2018).

Las búsquedas deben realizarse incluyendo varias bases de datos electrónicas relevantes, así como, búsquedas manuales en las principales revistas de investigación y referencias de artículos y revisiones destacados sobre el tema abordado. Además, también puede considerarse la denominada literatura gris, incluyendo búsquedas en actas de congresos, tesis doctorales, artículos no publicados o informes o registros de investigaciones (Kang 2016).

Selección de los estudios y extracción de datos

Una vez identificados todos los estudios de las búsquedas, los investigadores deben eliminar los artículos duplicados y seleccionar los estudios que cumplen con los criterios de inclusión / exclusión según su título y resumen. Posteriormente, se lleva a cabo la selección final de los estudios mediante la revisión del texto completo de los mismos.

Para mantener la objetividad y eliminar posibles sesgos en la selección de los estudios, este proceso debe realizarse de forma independiente por al menos dos investigadores, recurriendo a la intervención de un revisor adicional en caso de inconsistencia entre las opiniones.

A continuación, se lleva a cabo la extracción de datos de los diferentes estudios seleccionados, siendo interesante la sintetización de la información aportada en los mismos en una tabla resumen. Esta tabla puede incluir los autores, año de publicación, diseño del estudio, número de participantes, variables de evaluación o principales resultados (Ahn & Kang 2018).

Calidad de la evidencia

Finalmente, la evaluación de la calidad o certeza de la evidencia permite determinar la solidez de las conclusiones o recomendaciones de una revisión sistemática y/o metaanálisis, basada en la evaluación de los artículos que se incluyen.

Existen multitud de métodos que describen un procedimiento para evaluar la calidad de la evidencia. Entre ellos encontramos los niveles de evidencia propuestos por el Centro de Medicina Basada en Evidencia (CEBM) de Oxford. Se trata de una escala o jerarquía para estratificar la evidencia de la más fuerte a la más débil sobre la base de la susceptibilidad al sesgo y la calidad del diseño del estudio, esto es, dependiendo de las características metodológicas propias de la investigación. De esta manera, los ensayos clínicos aleatorizados reciben el nivel más alto porque están diseñados para ser imparciales y tienen menos riesgo de errores sistemáticos, mientras que una serie de casos o la opinión de un experto a menudo está sesgada por la experiencia u opiniones del autor y no hay control de los factores de confusión (Tabla 1). Además, en base a estos niveles de evidencia se emite un grado de recomendación o clasificación del juicio de la sugerencia de llevar a cabo la intervención según rigor científico (Tabla 2) (‘Oxford Centre for Evidence-based Medicine - Levels of Evidence - CEBM’ 2009).

Tabla 1. Niveles de evidencia propuestos por el Centro de Medicina Basada en la Evidencia (CEBM) de Oxford (‘Oxford Centre for Evidence-based Medicine - Levels of Evidence - CEBM’ 2009).

Level	Type of evidence
1a	Systematic review with homogeneity of randomized control trials
1b	Individual randomized control trials with narrow confidence interval

1c	All or none related outcome
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study (including low quality randomized control trials; e.g., <80% follow-up)
2c	"Outcomes" Research; Ecological studies
3a	Systematic review with homogeneity of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Tabla 2. Grados de recomendación propuestos por el Centro de Medicina Basada en la Evidencia (CEBM) de Oxford ('Oxford Centre for Evidence-based Medicine - Levels of Evidence - CEBM' 2009).

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies *or* extrapolations from level 1 studies
C	Level 4 studies *or* extrapolations from level 2 or 3 studies
D	Level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level

Otro procedimiento para la evaluación de la certeza de la evidencia es la metodología GRADE (Grading of Recommendations Assessment, Development and Evaluation), que ofrece un proceso estructurado para desarrollar y presentar

la síntesis de la evidencia, incluida su certeza, para la confección de tablas resumen de hallazgos en revisiones sistemáticas y formulación de recomendaciones en la atención médica (Kirmayr *et al.* 2021).

Según el diseño metodológico utilizado se define un nivel de certeza inicial que, posteriormente, puede variar dependiendo de diferentes factores o dominios, para concluir en un nivel de certeza final. Habitualmente, los resultados derivados de ensayos aleatorizados sin limitaciones importantes proveen un alto nivel de certeza de evidencia inicial, mientras que aquellos derivados de los estudios observacionales sin fortalezas especiales, un nivel bajo.

El análisis de los dominios que disminuyen la certeza puede resultar en “no serio”, “serio” o “muy serio” en función del impacto que presente, manteniendo o disminuyendo en 1 o 2 niveles la certeza de evidencia, respectivamente. Estos dominios son los siguientes:

- Riesgo de sesgo (limitaciones del estudio). Las limitaciones en el diseño y ejecución del estudio pueden sesgar los estimativos del efecto de la intervención. Una falta de ocultación de la asignación, falta de cegamiento, contabilidad incompleta de pacientes y de resultados de eventos, informes de resultados selectivos u otras limitaciones, dan lugar a un resultado sesgado.

- Inconsistencia de resultados. Si existe heterogeneidad o variabilidad inexplicable en los resultados de diferentes estudios, es probable que existan verdaderas diferencias en el efecto del tratamiento subyacente. Por ello, es importante el análisis de las posibles causas que generan heterogeneidad con el objetivo de identificar una explicación plausible.

- Evidencia indirecta. La evidencia directa en investigaciones compara directamente las intervenciones en las cuales se está interesado, aplicadas en la población de interés, y mide los resultados importantes

para los pacientes. Diferencias en la población, en la intervención, en las medidas de resultado o comparaciones indirectas son fuentes de evidencia indirecta.

- Imprecisión. Los resultados son imprecisos cuando los estudios incluyen relativamente pocos pacientes y pocos eventos y, por lo tanto, tienen un intervalo de confianza amplio alrededor de la estimación del efecto, generando de esta manera incertidumbre acerca de los resultados.

- Sesgo de publicación. El sesgo de publicación es una subestimación o sobreestimación sistemática del efecto beneficioso o perjudicial subyacente debido a la publicación selectiva de estudios.

Por otro lado, además de los dominios anteriores que disminuyen la certeza de la evidencia, también existen factores que pueden aumentar dicho nivel:

- Gran magnitud del efecto. Cuando el análisis de los resultados de los estudios arroja estimaciones grandes o muy grandes de la magnitud del efecto de una intervención podemos tener más confianza en los resultados. Además de considerarse la estimación puntual del efecto, también debe tenerse en cuenta la precisión o amplitud del intervalo de confianza en torno a dicho efecto.

- Gradiente dosis respuesta. La presencia de un gradiente dosis-respuesta es un criterio importante de una posible relación de causalidad (causa-efecto), pudiendo aumentar la confianza en los hallazgos y, por tanto, la calidad de la evidencia.

- Efecto de los potenciales factores de confusión residual. En ocasiones, los potenciales factores de confusión residual de los estudios pueden estar actuando para disminuir o incrementar el efecto demostrado. En estos casos, es necesario realizar una medición con precisión de los

factores pronósticos asociados al desenlace de interés y se conducirá un análisis ajustado que demuestre las diferencias en la distribución de estos factores entre los grupos de intervención y control. Cuando el resultado obtenido no se ve afectado por estos factores, es posible aumentar la certeza en un nivel.

Finalmente, se obtiene la calidad global de la evidencia, resultado de la calificación combinada de la calidad de la evidencia a lo largo de los desenlaces considerados en los dominios anteriores (Figura 11). Esta calidad de la evidencia, clasificada en cuatro grados, refleja hasta qué punto estamos seguros de que una estimación del efecto es correcta (Tabla 3). Además, todo lo anterior se recopila en una tabla resumen de hallazgos (Schünemann *et al.* 2013, Kirmayr *et al.* 2021).

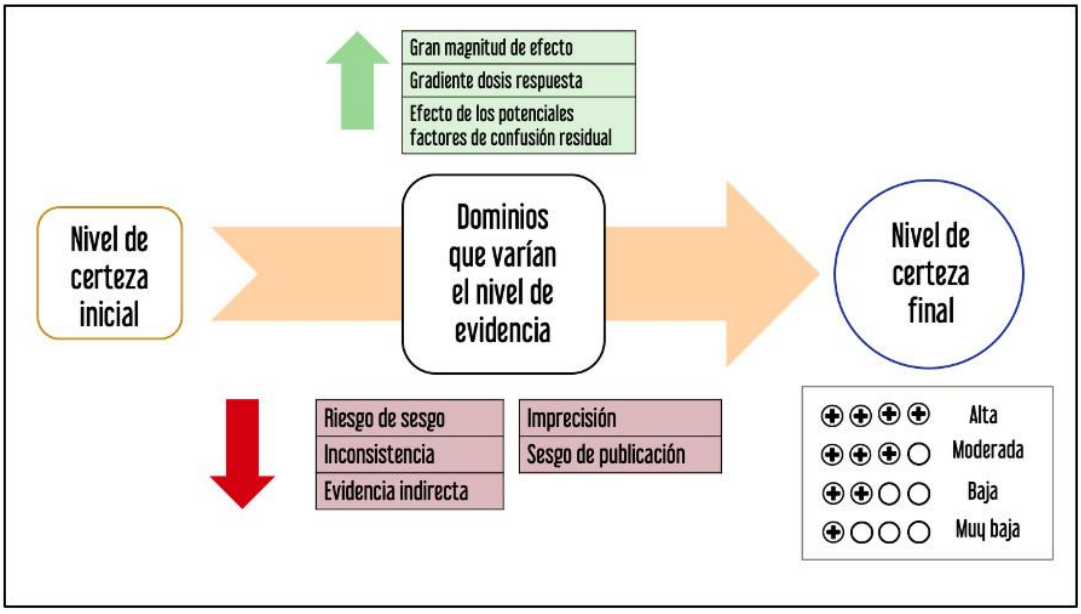

Figura 11. Procedimiento GRADE para determinación del nivel de certeza (Kirmayr et al. 2021).

Tabla 3. Grados de calidad de la evidencia propuestos por GRADE (Schünemann et al. 2013).

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

METAANÁLISIS

Una vez obtenidos los datos de los estudios incluidos en la revisión sistemática, es necesario llevar a cabo una revisión y análisis de los mismos cualitativa y cuantitativamente. Si los diferentes resultados de la investigación no se pueden combinar, los datos obtenidos de los estudios individuales se recopilan en una tabla o se muestran de forma descriptiva, realizándose una revisión cualitativa. Sin embargo, si los resultados se pueden combinar, es conveniente llevar a cabo una revisión cuantitativa evaluando la estimación global ponderada de las intervenciones obtenida por metaanálisis.

Por tanto, un metaanálisis, que a menudo acompaña a una revisión sistemática, es un procedimiento estadístico que combina o agrupa los resultados de varios estudios y proporciona una estimación más exacta y precisa del efecto de un tratamiento, intervención o fármaco, la validez de una hipótesis

o un factor de riesgo de enfermedad, en comparación con lo que puede lograr un estudio individual tomado de forma aislada (Haidich 2010).

A la hora de realizar un metaanálisis, es necesario tener en cuenta una serie de aspectos fundamentales (Ahn & Kang 2018, Higgins *et al.* 2019, Nagendrababu *et al.* 2020*b*):

Forest plot

La estimación agrupada obtenida del metaanálisis se representa mediante un *forest plot* o diagrama de bosque (Figura 12) (Lewis & Clarke 2001). En el eje de abscisas se representa la medida del efecto investigado que, en el caso de los estudios analizados en esta tesis, es la razón de probabilidades u *odds ratio* (OR). Una línea continua vertical (línea de efecto nulo) representa la falta total de asociación, es decir, la OR = 1, dejando a un lado el grupo control y en otro el grupo experimental. Los resultados obtenidos por cada uno de los estudios incluidos en el metaanálisis (las OR) se representan mediante cuadrados en el *forest plot*. Las líneas horizontales marcan los intervalos de confianza del 95% de la OR de cada estudio. El área o tamaño de cada cuadrado es proporcional al peso (%) que ese estudio tiene en el metaanálisis, lo que depende del tamaño de la muestra que tenga. El resultado total del metaanálisis viene representado por un rombo, que es la OR, con su intervalo de confianza del 95% estimados para la combinación de todos los estudios incluidos. A nivel del rombo, suele pintarse una línea vertical discontinua para que se pueda apreciar mejor el valor de la OR total obtenida y la relación de las OR de cada uno de los estudios con el resultado total del metaanálisis. Dado que la línea vertical continua representa la ausencia de efecto o asociación (OR = 1), si el intervalo de confianza dibujado sobre el rombo contacta con esta línea, significa que no se encuentra diferencia estadísticamente significativa entre los grupos experimental y control.

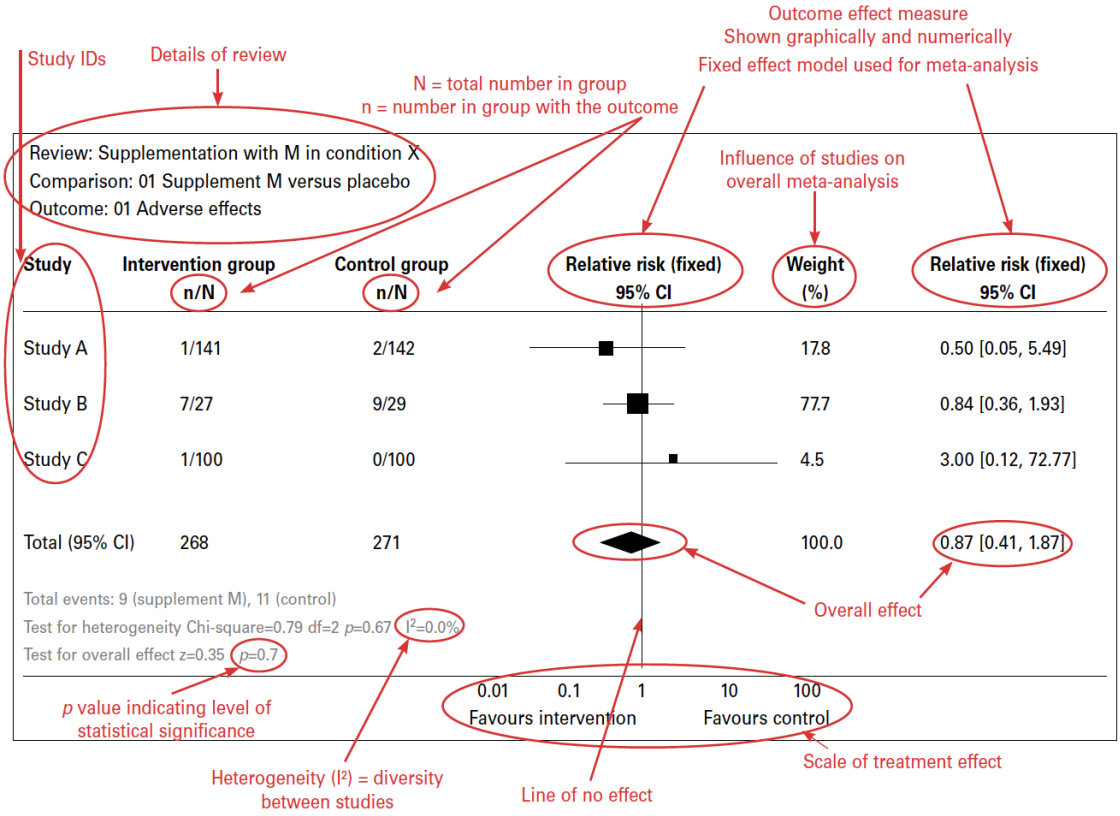

Figura 12. Interpretación de forest plot o diagrama de bosque (Ried 2006).

Variables dicotómicas y variables continuas

En el análisis de datos, las variables de resultado se pueden considerar en términos de variables dicotómicas y variables continuas.

Cuando se analizan estudios que utilizan variables continuas, en el eje de abscisas del *forest plot* se representa la diferencia de medias (DM), diferencia absoluta en los valores medios entre los grupos; o la diferencia de medias estandarizada (DME), diferencia media entre los grupos dividida por la desviación estándar. En estos casos, un valor "0" para DM o DME marcará la línea de efecto nulo. Un valor menor que "0" significa que la intervención estudiada en el grupo experimental es menos efectiva que la del grupo control, y un valor mayor que "0" significa que la intervención experimental es más efectiva que la control.

Como antes se ha explicado, cuando se combinan datos para variables dicotómicas se puede utilizar la odds ratio (OR), la razón de riesgo o riesgo relativo (RR) o la diferencia de riesgo (DR). La RR y la DR se deben emplear en la evaluación en estudios de cohortes prospectivos, mientras que la OR se utiliza para estudios retrospectivos, casos-control, o transversales (Ranganathan *et al.* 2015).

Modelos de efectos fijos y modelos de efectos aleatorios

Para analizar el tamaño del efecto se pueden emplear modelos de efectos fijos o de efectos aleatorios. Un modelo de efectos fijos supone que el efecto del tratamiento es el mismo y que la variación entre los resultados en diferentes estudios se debe a un error aleatorio, por lo que se utiliza cuando se considera que los estudios tienen el mismo diseño y metodología, con escasa variabilidad en los diferentes resultados. Por tanto, los modelos fijos asumen homogeneidad del efecto en los diferentes estudios que se combinan, incluyendo como únicos determinantes en el peso ponderado en el metaanálisis el tamaño del estudio y su propia varianza.

El método de Mantel-Haenszel (MH) es uno de los más utilizados en la estimación ponderada con efectos fijos en medidas de resultado dicotómicas. El estimador global o combinado de Mantel-Haenszel es consistente incluso si los estudios individuales tienen pocos sujetos, siendo la media ponderada de los efectos de los estudios individuales con factores de ponderación peso MH.

Por otro lado, un modelo de efectos aleatorios supone heterogeneidad entre los estudios que se combinan y, en consecuencia, se utilizan cuando se considera que los estudios son diferentes, incluso si una prueba de heterogeneidad no muestra un resultado significativo. El modelo de efectos aleatorios supone que el tamaño del efecto del tratamiento difiere entre los estudios y, por tanto, se cree que las diferencias en la variación entre los estudios

se deben no solo al error aleatorio, sino también a la variabilidad de los resultados entre las investigaciones. Por ello, la ponderación de los estudios tiene en cuenta, además de la varianza o tamaño de los mismos, la varianza entre los diferentes estudios.

El modelo de efectos aleatorios de la varianza inversa es un método de agregar dos o más variables aleatorias para minimizar la varianza del promedio ponderado, de manera que cada variable aleatoria se pondera en proporción inversa a su varianza, es decir, proporcional a su precisión.

Una modificación del método de la varianza inversa es el modelo de efectos aleatorios DerSimonian y Laird (DerSimonian & Laird 1986), que incorpora la variabilidad interestudio en el estimador combinado, de manera que el peso de cada estudio se calcula como el inverso de la suma de la varianza del estudio individual más la varianza interestudio. En la práctica, el método de DerSimonian y Laird incorpora una prueba de heterogeneidad en la estimación de la varianza interestudio. Cuando el valor p de la prueba de heterogeneidad es no significativo, el resultado del modelo de efectos aleatorios es igual al de efectos fijos. Sin embargo, si la prueba de heterogeneidad es significativa, la varianza interestudio aumenta progresivamente cuanto menor es el valor p de dicha prueba, de forma que los pesos para cada estudio en el modelo de efectos aleatorios tienden a igualarse (Hasselblad *et al.* 1995).

Heterogeneidad

La heterogeneidad es una medida de la varianza entre los estudios, esto es, un método para determinar si el grado de heterogeneidad es mayor de lo que se esperaría que ocurriera naturalmente cuando el tamaño del efecto calculado a partir de varios estudios es mayor que el error de muestreo.

Una superposición deficiente de los intervalos de confianza para los resultados de los estudios individuales, representados gráficamente mediante

líneas horizontales en el *forest plot* (Lewis & Clarke 2001), generalmente indica la presencia de heterogeneidad estadística.

El gráfico *L'Abbé plot* (Figura 13) (L'Abbé *et al.* 1987) permite mostrar visualmente las variaciones en los resultados observados en los estudios individuales incluidos en el metaanálisis, esto es, permite explorar la heterogeneidad entre los estudios.

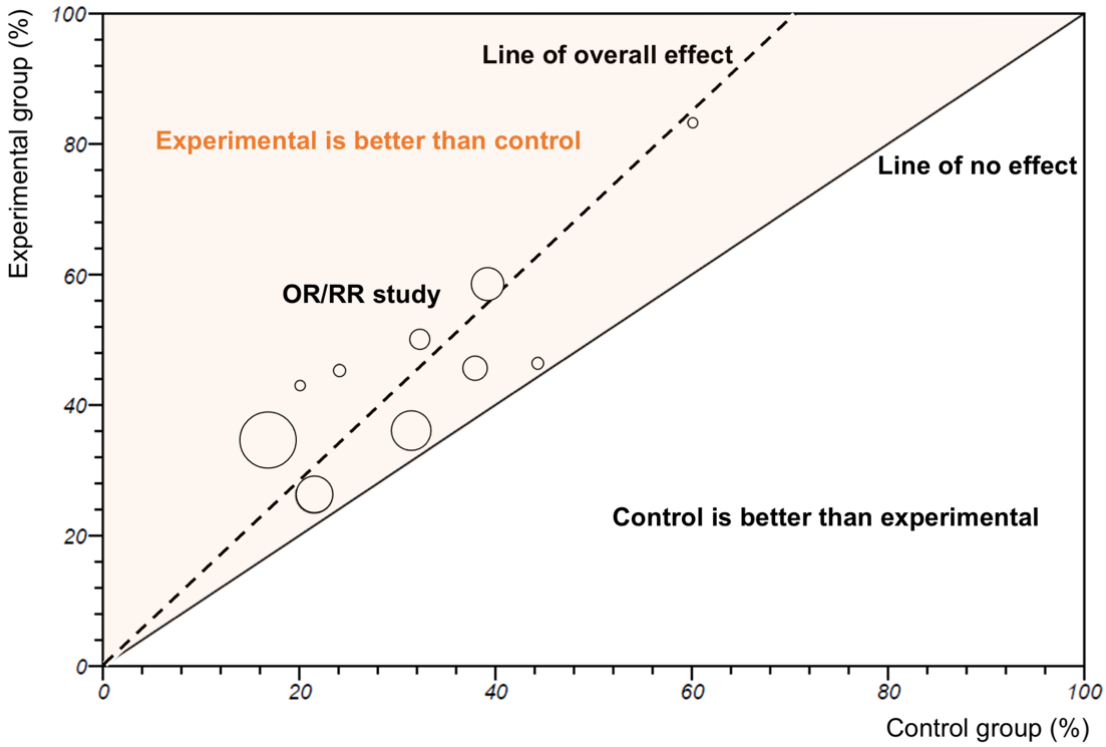

Figura 13. Gráfico de L'Abbé (L'Abbé et al. 1987). La línea continua representa la línea sin efecto. La línea discontinua representa el efecto combinado de todos estudios como OR o RR. Los círculos representan los resultados de estudios individuales, y su tamaño representa el peso del estudio.

Por otro lado, cuando el valor p de la prueba de chi^2 es bajo (inferior a 0.1) se considera que existe heterogeneidad estadística en los efectos de la intervención (variación en las estimaciones del efecto más allá del azar). Finalmente, el estadístico I^2 con un valor de entre 0 y 40% sugiere que no es importante la heterogeneidad, 30-60% indica heterogeneidad moderada, 50-

90% heterogeneidad sustancial, mientras que un valor 75-100% indica una heterogeneidad considerable (Deeks *et al.* 2019).

Sesgo de publicación

El sesgo de publicación es el tipo más común de sesgo en los metaanálisis, generando distorsión en el resultado debido a la mayor probabilidad de publicación de estudios estadísticamente significativos en lugar de estudios no significativos.

Un *funnel plot* o gráfico de embudo (Figura 14) permite probar la presencia o ausencia de sesgo de publicación. En él, los estudios se representan en un diagrama de dispersión con el tamaño del efecto en el eje x y la precisión o el tamaño total de la muestra en el eje y. Cuando los puntos forman un embudo invertido (base amplia que se estrecha hacia la parte superior de la gráfica), indica ausencia de un sesgo de publicación. Por otro lado, una forma asimétrica del gráfico (sin puntos en un lado del gráfico) hace sospechar un sesgo de publicación (Sterne *et al.* 2011).

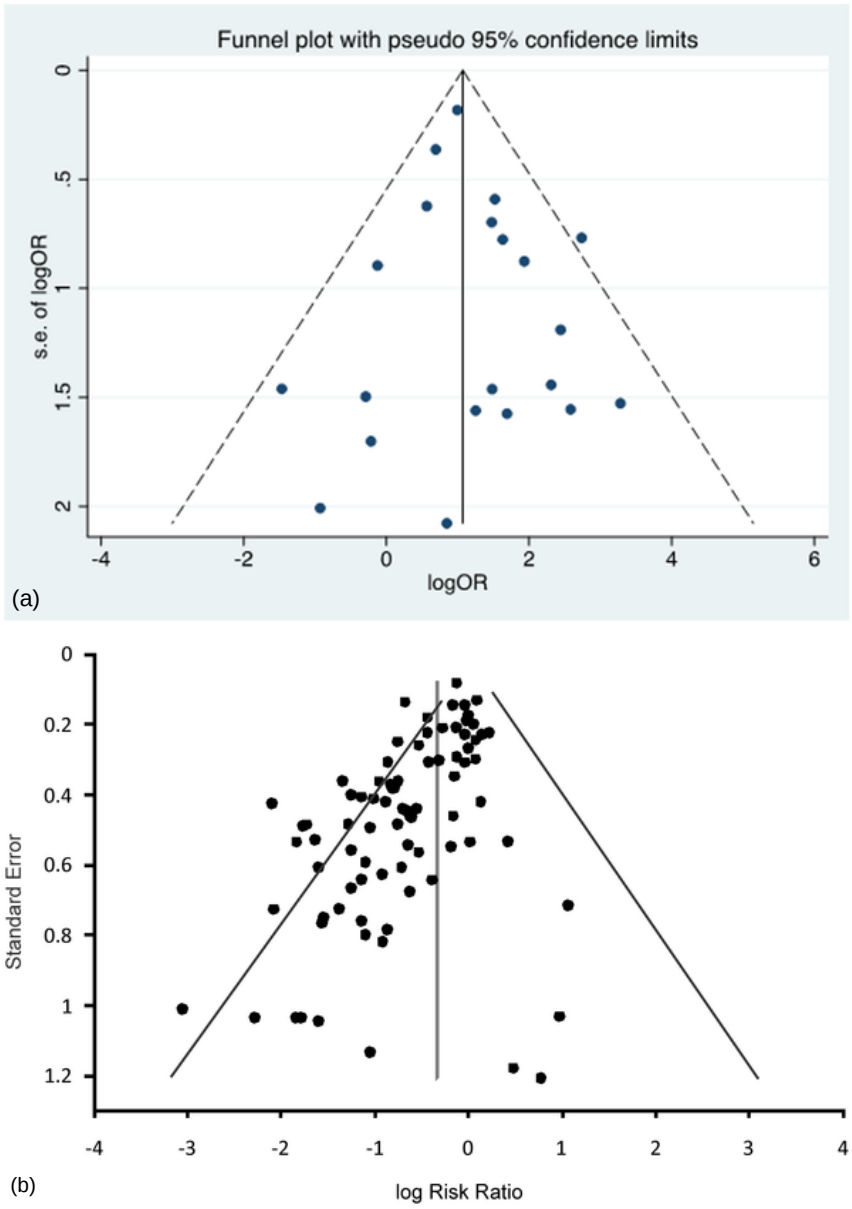

Figura 14. Ejemplo de gráfico de embudo simétrico (a), compatible con una menor probabilidad de sesgo de publicación; y asimétrico (b), que indica un posible sesgo de publicación (Rao et al. 2017).

Primera Parte

Diabetes Mellitus y Pronóstico del Tratamiento de Conductos

CAPÍTULO I

Association between diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth: systematic review and meta-analysis

Capítulo publicado en:

Segura-Egea JJ, Martín-González J, Cabanillas-Balsera D, Fouad AF, Velasco-Ortega E, López-López J (2016) Association between diabetes and the prevalence of radiolucent periapical lesions in root-filled teeth: systematic review and meta-analysis. *Clinical Oral Investigations* **20**, 1133–41.

ABSTRACT

Introduction. The question of whether diabetes mellitus can influence the outcome of root canal treatment (RCT) remains unclear. The aim of this systematic review and meta-analysis was to analyze scientific available evidence on the association between diabetes and the presence of radiolucent periapical lesions (RPLs) in root-filled teeth (RFT).

Methods. The review question was as follows: in adult patients who had endodontically treated teeth, does the absence or presence of diabetes result in an increase in the prevalence of RPL associated to RFT? A systematic MEDLINE/PubMed, Wiley Online Database, Web of Science, and Scopus search was conducted using the following MeSH and keywords: Diabetes Mellitus OR Diabetes OR Diabetic OR Hyperglycemia, AND Endodontics, Periapical Periodontitis, Periapical Diseases, Apical Periodontitis, Periradicular Lesion, Periapical Radiolucency, Radiolucent Periapical Lesion, Root Canal Treatment, Root Canal Preparation, Root Canal Therapy, Root Filled Teeth, Endodontically Treated Teeth. Seven studies reporting data on the prevalence of RPL associated to RFT both in diabetic and control subjects were included.

Results. After the study selection, seven epidemiological studies fulfilled the inclusion criteria, representing data from 1593 root canal treatments, 1011 in non-diabetic control subjects, and 582 in diabetic patients. The calculated pooled odds ratio (OR = 1.42; 95 % CL = 1.11–1.80; p = 0.0058) indicates that diabetic patients have higher prevalence of RFT with RPLs than controls.

Conclusion. Available scientific evidence indicates that diabetes is significantly associated to higher prevalence of periapical radiolucencies in endodontically treated teeth, being an important putative pre-operative prognostic factor in RCT.

Clinical relevance. Taking into account that diabetes is the third most prevalent chronic medical condition among dental patients, endodontic providers should be aware of the relationship between the outcome of endodontic treatment and diabetes.

Keywords. Diabetes mellitus. Meta-analysis. Periapical inflammation. Persistent apical periodontitis. Root canal treatment outcome. Root-filled teeth.

1. INTRODUCTION

Apical periodontitis (AP) is an inflammatory process around the apex of a tooth root, following the bacterial infection of the pulp space of the tooth [1]. The bone lesion associated with apical periodontitis is characterized radiographically by the presence of radiolucent periapical lesion (RPL), i.e., a radiolucent image surrounding the root apex of the affected tooth [2]. AP is an extraordinarily prevalent problem [3]. In the USA, radiographic signs of periapical disease are evident in 4.1–5.1 % of all teeth [4, 5]. The incidence of new cases of apical periodontitis over a 24-year period in the USA ranges from 27 to 41 % depending on age [6]. In Europe, the prevalence of AP is as high as 34–61 % of individuals and 2.8–4.2 % of the teeth [7, 8], increasing with patient's age [9]. The treatment for teeth with AP is root canal treatment (RCT) [10]. In the USA, 4.8–5.5 % of teeth have been endodontically treated [4, 5] and 10 % of young military recruits were shown to have existing RCT [11]. In Europe, the prevalence of endodontic treatment is estimated around 41–59 % of individuals and 2–6.4 % of teeth [7, 8].

When RCT fails, resolution of the periapical lesion and complete healing of periapical tissues do not occur, persisting AP [12, 13]. Persistent apical periodontitis (PAP) is characterized radiographically by a RPL associated with the root-filled tooth (RFT). The prevalence of radiographic evidence of persistent AP is 31–36 % in the USA [4, 5] and 24–65 % in European countries [7, 8, 14]. Periapical granulomas and cysts are the most common periapical lesions of endodontic origin associated with PAP. However, some of the RPL associated with RFT may not represent PAP, but incomplete healed lesions after root canal treatment, periapical connective scars [15], or non-endodontic pathosis [16].

Factors implicated in persistent AP are not only intra-operatives, such as inadequate aseptic control, missed canals, insufficient instrumentation, and leaking temporary or permanent restorations [17], but also systemic factors, such as pro-inflammatory status and impaired immune response associated with systemic diseases [14, 18].

One of the systemic diseases whose possible association with AP has been investigated is diabetes mellitus (DM) [14, 19], a heterogeneous group of

metabolic disorders, with hyperglycemia as the main feature [20]. DM is due to pancreatic β-cell dysfunction, with deficiency in insulin secretion and/or insulin resistance in liver and muscle [21]. Diabetic patients have impaired immune cell function. Pro-inflammatory cytokines from monocytes/polymorphonuclear leukocytes are upregulated, and growth factors from macrophages are downregulated, predisposing to chronic inflammation, progressive tissue breakdown, and diminished tissue repair capacity [22]. In addition, diabetic patients have increased levels of advanced glycation end-products (AGEs), which interact with cell surface receptors for them to increase oxidative stress in tissues and upregulate the inflammatory response [23]. In poor controlled diabetics, the immune response is further diminished, with decreased leukocyte function and delay of wound healing [22–25]. Consequently, an increased number and/or size of periapical lesions would be expected in root-filled teeth of diabetic patients.

Since the pioneer study of Bender et al. [26] in 1963, several epidemiological studies have investigated the impact of diabetes on periapical health and RCT outcome. Mostly, these studies were cross-sectional and employed only radiographic examination [14, 19, 27]. However, the question of whether diabetes mellitus can influence the outcome of RCT remains unclear [14].

2. AIM OF THE STUDY

The purpose of this study was to conduct a systematic review and meta-analysis of the possible association between diabetes and RCT failure, assessed as the prevalence of radiolucent periapical lesions in root-filled teeth. The clinical PICO question to be answered was as follows: in adult patients who had endodontically treated teeth (problem and intervention), does the absence or presence of diabetes mellitus (comparison) result in an increase in the prevalence of RPL associated to RFT (outcome)?

3. MATERIALS AND METHODS

Literature search strategy

According to the conventional procedures to develop systematic review and meta-analysis [28, 29], firstly the PICO question was formulated, for which the search strategy was constructed. Inclusion and exclusion criteria were defined, the studies located and selected, their quality assessed, and the data extracted and interpreted [30].

The literature search strategy was as follows. A MEDLINE/PubMed, Wiley Online Database, Web of Science, and Scopus search was performed using the following combination of Mesh terms and keywords: (Diabetes Mellitus OR Diabetes OR Diabetic OR Hyperglycemia) AND (Endodontics OR Periapical Periodontitis OR Periapical Diseases OR Apical Periodontitis OR Periradicular Lesion OR Periapical Radiolucency OR Radiolucent Periapical Lesion OR Root Canal Treatment OR Root Canal Preparation OR Root Canal Therapy OR Root Filled Teeth OR Endodontically Treated Teeth) (Table 1).

Table 1 Lists MeSH and key words combinations used for the search strategy

((“diabetes mellitus”[MeSH Terms] OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields]) OR (“diabetes mellitus”[MeSH Terms] OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields] OR “diabetes”[All Fields] OR “diabetes insipidus”[MeSH Terms] OR (“diabetes”[All Fields] AND “insipidus”[All Fields]) OR “diabetes insipidus”[All Fields]) OR Diabetic[All Fields] OR (“hyperglycaemia”[All Fields] OR “hyperglycemia”[MeSH Terms] OR “hyperglycemia”[All Fields])) AND ((“endodontics”[MeSH Terms] OR “endodontics”[All Fields]) OR (“periapical periodontitis”[MeSH Terms] OR (“periapical”[All Fields] AND “periodontitis”[All Fields]) OR “periapical periodontitis”[All Fields]) OR (“periapical diseases”[MeSH Terms] OR (“periapical”[All Fields] AND “diseases”[All Fields]) OR “periapical diseases”[All Fields]) OR (“periapical periodontitis”[MeSH Terms] OR (“periapical”[All Fields] AND “periodontitis”[All Fields]) OR “periapical periodontitis”[All Fields] OR (“apical”[All Fields] AND “periodontitis”[All Fields]) OR “apical periodontitis”[All Fields]) OR (Periradicular[All Fields] AND Lesion[All Fields]) OR (Periapical[All Fields] AND Radiolucency[All Fields]) OR (Radiolucent[All Fields] AND Periapical[All Fields] AND Lesion[All Fields]) OR ((“dental pulp cavity”[MeSH Terms] OR (“dental”[All Fields] AND “pulp”[All Fields] AND “cavity”[All Fields]) OR “dental pulp cavity”[All Fields] OR (“root”[All Fields] AND “canal”[All Fields]) OR “root canal”[All Fields]) AND (“therapy”[Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “therapeutics”[MeSH Terms] OR “therapeutics”[All Fields])) OR (“root canal preparation”[MeSH Terms] OR (“root”[All Fields] AND “canal”[All Fields] AND “preparation”[All Fields]) OR “root canal preparation”[All Fields]) OR (“root canal therapy”[MeSH Terms] OR (“root”[All Fields] AND “canal”[All Fields] AND “therapy”[All Fields]) OR “root canal therapy”[All Fields]) OR ((“plant roots”[MeSH Terms] OR (“plant”[All Fields] AND “roots”[All Fields]) OR “plant roots”[All Fields] OR “root”[All Fields]) AND Filled[All Fields] AND (“tooth”[MeSH Terms] OR “tooth”[All Fields] OR “teeth”[All Fields])) OR (“tooth, nonvital”[MeSH Terms] OR (“tooth”[All Fields] AND “nonvital”[All Fields]) OR “nonvital tooth”[All Fields] OR (“endodontically”[All Fields] AND “treated”[All Fields] AND “teeth”[All Fields]) OR “endodontically treated teeth”[All Fields]))

Several journals (Journal of Endodontics; International Endodontic Journal; Clinical Oral Investigations; Oral Diseases; Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology; Endodontics and Dental Traumatology; and Australian Endodontic Journal) and the bibliography of all relevant papers and review papers were hand-searched.

Study selection and inclusion and exclusion criteria

Three investigators (J.M-G., D.C-B., and J.J.S-E.) screened the titles and abstracts of all articles identified in the electronic and manual searches. Articles that did not meet the inclusion criteria were excluded. All remaining articles were obtained and full-text reviewed independently by four reviewers (J.M-G., D.C-B., E.V-O., and J.J.S-E) based on the following inclusion criteria: (1) the type of study: epidemiological studies published from January 1980 to March 2016, (2) studies comparing adult diabetic patients and non-diabetic controls, (3) studies involving RFT, and (4) studies establishing the periapical condition of RFT and reporting data on the prevalence of RPL associated with RFT both in diabetic and control subjects.

Exclusion criteria included the following: (1) the type of study: cell culture laboratory studies or animal studies, (2) studies that only examined diabetic patients, and (3) studies without radiographic assessment of periapical radiolucency.

Cases of disagreement between reviewers were discussed until a consensus was reached.

Quality assessment and data extraction

The texts of the potentially relevant studies were systematically evaluated. Data were extracted, synthesized, and analyzed, and the quality of the methodology was assessed. For each study, the following parameters recorded: authors' names, date of publication, study design, sample size and included subjects and RCTs, diagnosis of RPLs, main results on association between diabetes and RFT with RPLs, and evidence level, determined according to guidelines provided by The Centre for Evidence-Based Medicine at Oxford [31].

Outcome variables and statistical analysis

The odds ratio (OR) for the prevalence of RPL in RFT of control and diabetic subjects was established as primary outcome variable and measure of the effect. The pooled OR was calculated using the method of Mantel-Haenszel with fixed effects, and 95 % confidence intervals for the OR were calculated using the Robins, Breslow, and Greenland variance formula. To test for heterogeneity among the ORs calculated, the Breslow-Day test (BDT) and the I^2 test [32] were used. L'Abbé plots [33] were used to illustrate the homogeneity. A forest plot [34] was used to display the OR results, along with the Mantel-Haenszel (MH) pooled estimate. Significance level of $p < 0.05$ was considered, and the meta-analysis was carried out with the StatsDirect software [35].

4. RESULTS

The search strategy is presented in Fig. 1. The combinations of the initial electronic search terms and manual searches identified 545 titles. Duplicated references (349 items) and articles published before 1980 (16 items) were discarded. A subsequent search at the title and abstract level among the 180 remaining titles, taking into account the inclusion and exclusion criteria, revealed 16 articles for full-text reading. At this level, nine studies were excluded for the following reasons: one of them was referred to periodontal disease [36], six did

not provide data about the prevalence of RFT with RPLs in diabetics and controls [37–41], and two others only provide data regarding retention of RFT in diabetic and controls [42, 43].

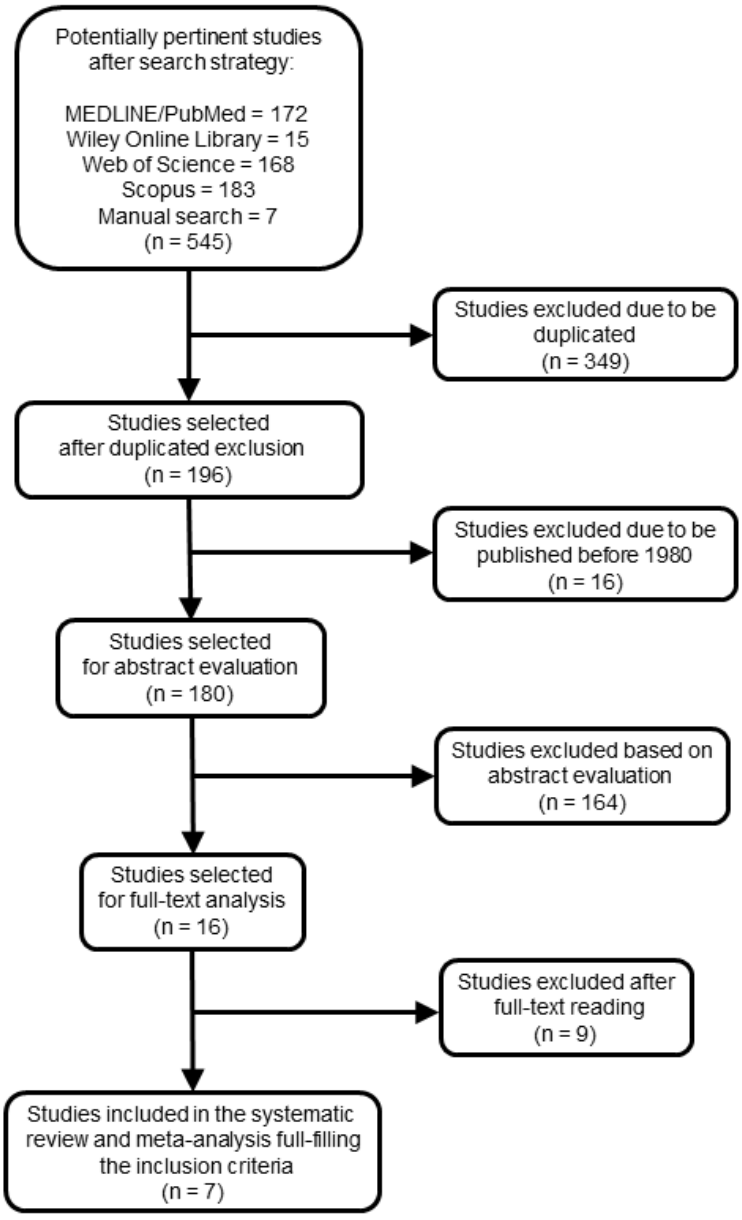

Fig. 1 Selection process of the studies included in the systematic review and meta-analysis

Study characteristics

In the final analysis, the following seven studies were included: (1) Falk et al. [44]) [44]; (2) Fouad and Burleson [45]) [45]; (3) Britto et al. [46]) [46]; (4) Segura-Egea et al. [47]) [47]; (5) López-López et al. [48]) [48]; (6) Marotta et al. [49]) [49]; and (7) Marques-Ferreira et al. [50]) [50]. Table 2 summarizes the study design, subjects and sample size, diagnosis of RPLs, main results, and evidence level [31]. Radiographic criteria for the diagnosis of apical periodontitis, when are provided, are shown; two studies [46, 49] used the Strindberg's criteria [51], one study had longitudinal data and used clinical and radiographic analysis by supervising endodontists [45] and three others [47, 48, 50] the PAI system score [52].

Table 2 Studies included in the systematic review. Study design, subjects and sample size, diagnosis of radiolucent periapical lesions, and main results on association between diabetes and RFT with RPL and evidence level

Table 2 Studies included in the systematic review. Study design, subjects and sample size, diagnosis of radiolucent periapical lesions, main results on association between diabetes and RFT with RPL and evidence level.

Authors	Year	Study design	Subjects	Diagnosis of Radiolucent Periapical Lesions	Association Diabetes - RFT*RPL	Evidence level (31)
1. Falk et al.	1989	Cross-sectional	Controls: 77 Diabetics: 82	Periapical radiographs	NO; p=0.20 Diabetic women YES; p<0.01	C
2. Fouad & Burleson	2003	Longitudinal (≥ 2 y)	Controls: 459 Diabetics: 72	Periapical radiographs	NO; p=0.42 Preoperative RPL YES; p=0.0073	C
3. Britto et al.	2003	Cross-sectional	Controls: 23 Diabetics: 30 Type 1: 11 Type 2: 19	Periapical radiographs Strindberg criteria (52)	NO; p=0.82 Men with type 2 YES; p<0.05	D
4. Segura-Egea et al.	2005	Cross-sectional	Controls: 38 Type 2 diabetics: 32	Periapical radiographs PAI index (53)	NO; p=0.17	D
5. López-López et al.	2011	Cross-sectional	Controls: 50 Type 2 diabetics: 50 Well controlled Age / sex-matched	Digital panoramic radiographs PAI index (53)	NO; p=0.09	D
6. Marotta et al.	2012	Cross-sectional	Controls: 60 Type 2 diabetics: 30 Age / sex-matched	Full-mouth periapical and panoramic radiographs Strindberg criteria (52)	NO; p=0.21	D
7. Marques-Ferreira et at.	2014	Cross-sectional	Controls: 23 Diabetics: 23 Type 1: 4 Type 2: 17	Periapical and panoramic radiographs PAI index (53)	NO; p=0.06	D

RCT: root canal treatment; *RFT*: root-filled teeth; *RFT*RPL*: root-filled teeth with radiolucent periapical lesion; *RPL*: radiolucent periapical lesion

Meta-analysis

For each selected article, the results were extracted and compiled into a table of evidence, and descriptive statistics and odds ratios calculated (Table 3). When the OR is greater than 1, it indicates that diabetic patients show higher prevalence of RFT with RPLs than control subjects. The BDT was non-significant (Breslow-Day = 4.63; df = 6; $p = 0.59$), indicating homogeneity among the ORs of the included studies (Fig. 2, L'Abbé plot). Moreover, the proportion of variation through studies due to heterogeneity was very low ($I^2 = 0$ %; 95 % CI = 0 to 59 %). Mantel-Haenszel method and the Robins, Breslow, and Greenland variance formula, with fixed effects, provide a pooled OR = 1.42 (95 % CI = 1.11–1.80; $chi^2 = 7.60$; $p = 0.0058$), indicating that the calculated pooled OR differs significantly from 1. Forest plot shows the ORs for each study and the overall OR calculated from the meta-analysis (Fig. 3). These results indicate that diabetic patients have significantly higher prevalence of RFT with RPLs than control subject.

Table 3 Results extracted and compiled, descriptive statistics, and odds ratios calculated

Table 3 Results extracted and compiled, descriptive statistics and odds ratios calculated.

Authors	Year	No. RFT	Non-diabetic controls		Diabetic patients		Odds Ratio (95% CL)	*p* value
			RFT*RPL / Total RFT	RFT*RPL	RFT*RPL / Total RFT	RFT*RPL		
1. Falk et al.	1989	518	50 / 233	21%	75 / 285	26%	1.31 (0.85 - 2.01)	0.20
2. Fouad & Burleson	2003	531	144 / 459	31%	26 / 72	36%	1.24 (0.70 - 2.13)	0.42
3. Britto et al.	2003	99	19 / 43	44%	26 / 56	46%	1.09 (0.46 - 2.63)	0.82
4. Segura-Egea et al.	2005	32	12 / 20	60%	10 / 12	83%	3.33 (0.48 - 37.93)	0.17
5. López-López et al.	2011	60	6 / 25	24%	16 / 35	46%	2.67 (0.76 - 10.06)	0.09
6. Marotta et al.	2012	291	78 / 206	38%	39 / 85	46%	1.39 (0.81 - 2.39)	0.21
7. Marques-Ferreira et at.	2014	62	5 / 25	20%	16 / 37	43%	3.05 (0.84 - 12.48)	0.06
Overall		1593	314 /1011	31%	208 /582	36%	1.42 (1.11 - 1.80)*	0.006

RFT root-filled teeth. *RFT*RPL* root-filled teeth with radiolucent periapical lesions.

*Mantel-Haenszel and Robins-Breslow-Greenland variance formula: $Chi^2 = 7.60$ p = 0.0058.

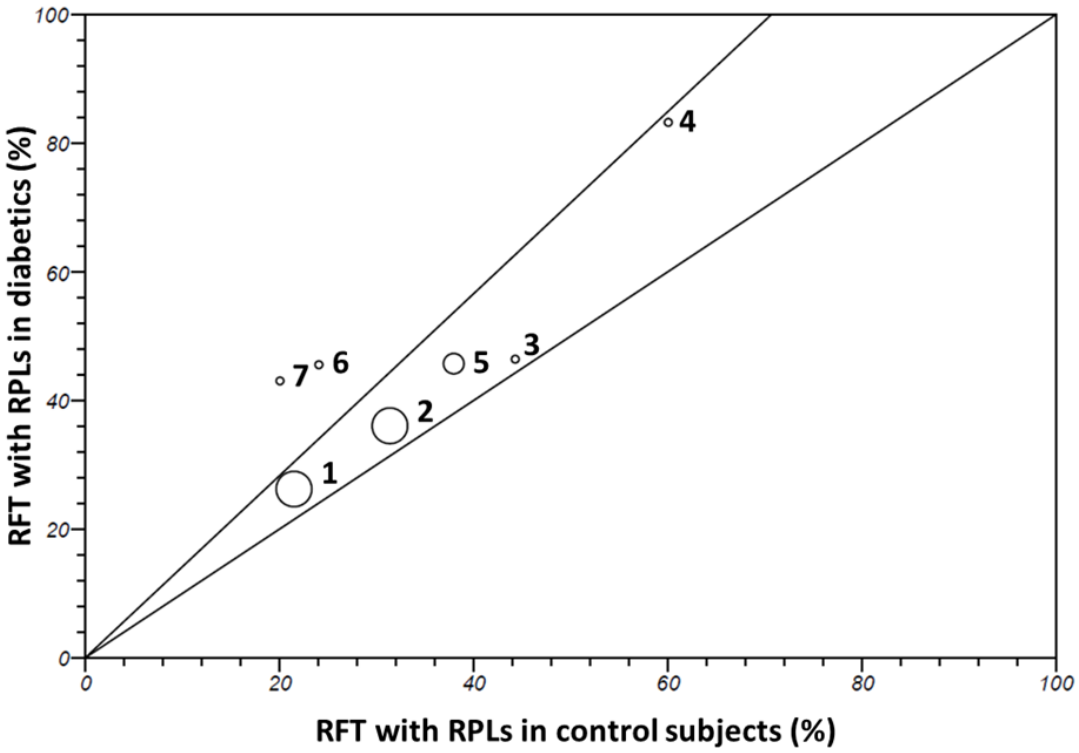

Fig. 2. L'Abbé plot showing the percentage of root-filled teeth (RFT) with radiolucent periapical lesions (RPLs) in the seven studies for the comparison of diabetic and controls. Size of circle is proportional to size of study. Study designations: (1) Falk et al. [44]); (2) Fouad and Burleson [45]); (3) Britto et al. [46]); (4) Segura-Egea et al. [47]); (5) López-López et al. [48]); (6) Marotta et al. [49]); and (7) Marques-Ferreira et al. [50])

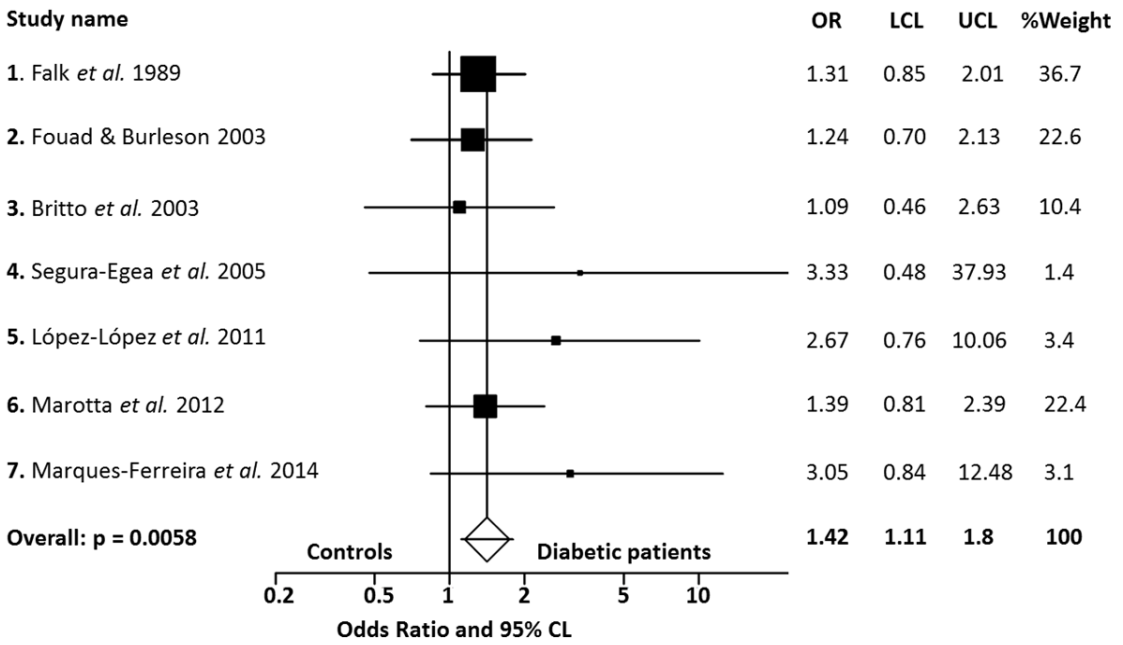

Fig. 3. Forest plot of odds ratios and 95 % confidence limits (CL) based on data from seven studies for the comparison of diabetic patients and control subjects with regard to the prevalence of RFT (root-filled teeth) with RPLs (radiolucent periapical lesions). The size of each rectangle is proportional to the total sample size for the diabetic/control comparison in that study. Overall estimate based on combined data from the seven studies. The size of the diamond is proportional to the percent weight of each study, i.e., the combined sample size for the diabetic/control comparison. The solid line indicates an odds ratio of 1.0. The dashed lineindicates the overall odds ratio. OR odds ratio, LCL lower confidence level, UCL upper confidence level

Interpretation and assessment of the included studies

The time frame of publication of the seven studies was 1989 and 2014; however, six of them were published between 2003 and 2014 (Table 2). One was a longitudinal study with two or more years of follow-up, in which successful versus uncertain/failed treatments were compared [45], and the other six were cross-sectional studies [44, 46–50]. The included studies represent data from 1368 subjects, 730 controls, and 319 diabetic patients.

In the study of Falk et al. [44], long-duration diabetics showed higher frequency of RFT with RPLs (26 %) compared to non-diabetic patients (21 %) (OR = 1.31; 95 % CL = 0.85–2.01; $p = 0.20$). However, diabetic women had significantly more RFT with RPLs than control women ($p < 0.01$). Fouad and Burleson [45] investigated 531 RCT, 72 in diabetic patients, finding increased likelihood of RPLs diabetics, but without statistical significance (OR = 1.24; 95 % CL = 0.70–2.13; $p = 0.20$). Nevertheless, the frequency of RPLs in RFT of diabetic patients with preoperative periradicular lesions was significant compared to controls ($p = 0.007$) and when controlling for a number of confounding variables [45]. The study of Britto et al. [46] assessed the periapical status of 99 subjects (56 diabetics) using periapical and panoramic radiographs. Strindberg's criteria [51] were used to diagnose RPLs. The results did not find significant difference in the percentage of RFT with RPLs between controls [44 %] and diabetics [46] (OR = 1.09; 95 % CL = 0.46–2.63; $p = 0.82$). However, type 2 diabetic men were more likely to have residual RPLs in their RFT ($p < 0.05$). The study sample in this investigation showed a striking prevalence of RPLs, finding one or more teeth with RPLs in 97 and 87 % of diabetic patients and control subjects, respectively. Segura-Egea et al. [47] included in their study 38 control subjects and 32 diabetic patients, using periapical radiographs and PAI score system [52] to assess the periapical status. RPLs were found in 83 % of RFT in the diabetic group, whereas only 60 % of RFT in the control group had periapical lesions (OR = 3.33; 95 % CL = 0.48–37.93; $p = 0.17$). The study of López-López et al. [48] compared the prevalence of RFT with RPLs in well-controlled diabetic patients and control subjects. In this study, patients and controls were age- and sex-matched, and diabetic patients had glycated hemoglobin levels (HbA1c) ≤ 6.5 %. Periapical status of RFT was assessed using panoramic digital radiographs and the PAI index [52]. The results showed that the percentage of RFT with RPLs was almost twice higher in diabetic patients (46 %) than in control subjects (24 %), but the difference was not statically significant (OR = 2.67; 95 % CL = 0.76–10.06; $p = 0.09$).

Marotta et al. [49], in another cross-sectional study, used periapical and panoramic radiographs and Strindberg's criteria [51] for the diagnostic of RPLs in RFT of diabetic and control subjects. They found that RPLs were significantly

more common in untreated teeth from diabetics (10 %) than in nondiabetic controls (7 %) ($p = 0.03$). However, there was not significant difference in the prevalence of RPLs associated with RFT in diabetics (46 %) and control subjects (38 %) (OR = 1.39; 95 % CL = 0.81–2.39; $p = 0.21$). Finally, the study conducted by Marques-Ferreira et al. [50] compared the success rate of RFT in two groups of 23 patients, healthy control group and diabetic group. Periapical status was assessed radiographically using the PAI score system [52]. The results demonstrated no significant differences between both groups in the prevalence of RFT with RPLs (OR = 3.05; 95 % CL = 0.84–12.48; $p = 0.06$).

5. DISCUSSION

Since the mid-twentieth century to today, numerous animal [53–60] and human studies [2, 26, 27, 40, 45–50, 61] have investigated the possible relationship between endodontic infections and DM. The endodontic variables analyzed in human studies have been the prevalence of RPLs, the prevalence of RCT, and the outcome of RCT, assessed as the percentage of RFT with or without RPLs, or as the prevalence of tooth extraction after nonsurgical RCT (NSRCT) [14]. Even though the results of these studies are not conclusive, available scientific evidence suggest an association between DM and a higher prevalence of RPLs, greater size of RPLs, and frequency of odontogenic infections [14, 19]. On the contrary, the existing data about the association of diabetes with the prevalence of RCT are sparse and inconclusive [14]. Finally, several studies have investigated the potential relationship between diabetes mellitus and the survival of root canal-treated teeth analyzing the prevalence of tooth extraction after NSRCT [41–43]. Three of these studies [17, 42, 43] provide a very significant OR ($p < 0.01$) for the contribution of diabetes to decreased retention of RFT. Four studies have provided longitudinal evaluation of the success of root canal treatment longitudinally [17, 18, 41, 45]. The Marending et al. [18] paper showed that diabetes was one of a number of medical problems that significantly influenced the outcomes. The three other studies [17, 41, 45] agreed that when the treatment of all teeth is considered, diabetes did not affect

the outcome. The Fouad and Burleson study [45] showed that when only teeth with preoperative lesions are considered, and when controlling for a number of important confounding variables, teeth from diabetics were more significantly classified as uncertain or failing, at two or longer years after treatment.

The objective of this systematic review and meta-analysis has been to analyze the potential association between diabetes mellitus and the percentage of RFT with or without RPLs. The observational epidemiological studies involved were “outcomes” research, including one longitudinal study with two or more years of follow-up [45], level of evidence 2, and six cross-sectional studies [44, 46–50], level of evidence 3 [31]. The homogeneity of the seven studies (Breslow-Day = 4.63; df = 6; $p = 0.59$; and $I^2 = 0$ %; 95 % CI = 0 to 59 %) was high. Thus, the variations across studies were casual rather than due to heterogeneity.

The reasonable time frame of publication of the studies included in this review (1989 to 2014) reinforces the possibility of comparison, discarding important changes in dental concepts, materials, and/or treatments over time [62, 63]. The analysis of the study designs is also very important in a systematic review like this. However, in the present review, most of the included studies were cross-sectional studies. Cross-sectional studies demonstrate differences in the prevalence of PAP, but longitudinal studies could show differences between diabetic and control subjects regarding the healing process of the periapical pathosis.

Individually, none of the studies provides significant OR regarding the association of diabetes with the prevalence of RFT with periapical lesions. However, pooled OR provided by MH method, with fixed effects, was significant (OR = 1.42; 95 % CI = 1.11–1.80; $p = 0.006$) indicating that diabetes is associated to the prevalence of RFT with RPLs. It can be concluded that available scientific evidence supports the association between diabetes and persistent apical periodontitis. This result is in agreement with the studies showing that diabetic patients have delayed periapical repair and greater likelihood of RFT loss [17, 42, 43, 45].

The biological mechanisms linking periapical status of RFT and diabetes mellitus could be the following: (1) diabetes predisposes to chronic inflammation, (2) diabetes reduces tissue repair capacity, (3) diabetes impaired the immune response enhancing the susceptibility to infections, and (4) diabetes impaired bone turnover and delayed wound healing [14, 23, 64, 65]. In inflamed periapical tissues of endodontically treated teeth, diabetes could compromise immune response, upregulating periapical inflammation and altering bone turnover and wound healing, increasing the prevalence of apical periodontitis in RFT [14].

Considering that diabetes is the third most prevalent chronic medical condition among dental patients [66], endodontic providers should be aware of the relationship between the outcome of endodontic treatment and diabetes, should keep current data on the diabetic status of their patients, and should inform diabetic patients of the risks involved in endodontic therapy for them.

6. CONCLUSION

Available scientific evidence indicates that diabetes is significantly associated with higher prevalence of periapical radiolucencies in endodontically treated teeth. Well-designed prospective studies are required to further investigate the association between diabetes and RCT outcome and to definitively determine the precise increased risk of treatment failure in diabetic patients. However, at this time, diabetes should be recognized as an important putative pre-operative prognostic factor in endodontic treatment.

Compliance with ethical standards

Conflict of interest: The authors declare that they have no conflict of interest.

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Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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CAPÍTULO II

Association between diabetes and nonretention of root filled teeth: a systematic review and meta-analysis

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ABSTRACT

Previous studies have found an association between the outcome of root canal treatment (RCT) and diabetic status. This systematic review and meta-analysis aimed to analyse the potential relationship between diabetes and the occurrence of extracted root filled teeth (RFT). The clinical PICO question was as follows: in adult patients with RFT, does the absence or presence of diabetes influence the prevalence of RFT extraction? The key words used in the systematic search were as follows: (Diabetes OR Diabetes Mellitus OR Hyperglycaemia OR Diabetic) AND (Endodontic OR Endodontics OR Endodontic Treatment OR Root Canal Treatment OR Root Canal Preparation OR Root Canal Therapy OR Root Filled Teeth OR Endodontically Treated Teeth) AND (Extraction OR Retention OR Survival OR Success OR Failure OR Outcome). The primary outcome variable was odds ratio (OR) for the frequency of extracted RFT in diabetics and healthy subjects. The method of DerSimonian–Laird with random effects was used to calculate the overall OR. Three hundred titles were identified, and three studies achieved the inclusion criteria. Data from 54 936 root canal treatments, 50 301 in nondiabetic control subjects and 4635 in diabetic patients, were analysed. The calculated overall odds ratio (OR = 2.44; 95% CI = 1.54–3.88; *P* = 0.0001) implies that diabetics had a significantly higher prevalence of extracted RFT than healthy nondiabetic subjects. The results of available studies indicate a significant relationship between DM and increased frequency of nonretained root filled teeth. Diabetes mellitus should be considered an important preoperative prognostic factor in root canal treatment.

Keywords: diabetes mellitus, meta-analysis, nonretention, root canal treatment outcome, root filled teeth, tooth extraction.

1. INTRODUCTION

Apical periodontitis (AP) is an inflammatory process surrounding the apex of a root, subsequent to bacterial infection of the root canal system (Siqueira & Rôças 2014). Apical periodontitis is associated with a bone lesion characterized radiographically by a radiolucent image around the root apex of the affected tooth (Bender & Seltzer 2003). AP is a remarkable health problem, being one of the most prevalent diseases in the world (Figdor 2002). The prevalence of AP increases with age and ranges between 34–61% of individuals (Buckley & Spångberg 1995, Chen *et al*. 2007). Radiographic signs of periapical disease are found in 2.8–5.1% of teeth (Eriksen 1998, Jiménez-Pinzón *et al*. 2004, Caplan *et al*. 2006, López-López *et al*. 2012). The incidence of new cases of AP over a 24-year period is as high as 27–41%, depending on age (Buckley & Spångberg 1995). Root canal treatment (RCT) is the treatment of choice for teeth with AP (Ørstavik & Pitt Ford 2007), with the prevalence of RCT being 41–59% of individuals and 2–6.4% of teeth (Eriksen 1998, Jiménez-Pinzón *et al*. 2004, Caplan *et al*. 2006, López-López *et al*. 2012). Ten per cent of young military recruits had at least one root filled tooth (RFT) (Winward *et al*. 2014).

The outcome of RCT has traditionally been studied based on clinical parameters, radiographic assessment of periapical status and histopathological evaluation of extirpated tissue (Lazarski *et al*. 2001). According to clinical and radiographic evaluation criteria, follow-up studies have reported success rates of 53–95% (Jokinen *et al*. 1978, Ingle 1985, Ng *et al*. 2011). Preoperative factors (systemic conditions, impaired immune response, root fractures, anatomic irregularities, periodontal diseases, etc.) (Marending *et al*. 2005, Segura-Egea *et al*. 2015), intra-operative factors (poor initial therapy, incomplete aseptic control, inadequate instrumentation or root filling) and postoperative factors (crown fractures or improper coronal restoration) determine the prognosis of RCT (Vire 1991, Ng *et al*. 2011).

Persistent apical periodontitis indicates RCT failure, and the subsequent untoward events include root canal retreatment, apical surgery and extraction. The assessment of the outcome of RCT can be made by quantifying the

incidence of these events (Lazarski *et al*. 2001). The analysis of more than 100.000 cases of RCT revealed an overall incidence 6.4% of untoward events, 3.6% extractions, 1.9% root canal retreatments and 1% periradicular surgery (Lazarski *et al*. 2001). Another study conducted in Taiwan found untoward events in 9.7% of RFT after a 5-year follow-up, with the most common untoward event being tooth extraction (71.1%) followed by root canal retreatment (24.1%) and apical surgery (4.8%) (Chen *et al*. 2008).

The percentage of retention of RFT is an indicator that allows the outcome of RCT to be assessed. A study conducted in the Netherlands in 1983 evaluated the outcome of RCT in servicemen and reported that 55% of root filled teeth had been retained after 17 years (Meeuwissen & Eschen 1983). Tooth loss after RCT correlated with the number of proximal contacts, age, history of facial injury, number of missing teeth and abutment status (Caplan & Weintraub 1997). Extractions after RCT may be due to prosthetic (59%), periodontal (32%) and endodontic causes (9%) (Vire 1991).

Diabetes mellitus (DM) is a systemic disease with a possible association with AP (Segura-Egea *et al*. 2012, 2015). DM is a metabolic disorder due to pancreatic β-cells dysfunction, with a deficiency in insulin secretion, and/or peripheral insulin resistance, resulting in hyperglycaemia as the main feature (ECDCDM 2000, Mealey & Oates 2006). The function of leucocytes is altered in diabetes, with increased release of pro-inflammatory cytokines and decreased secretion of macrophage growth factors, facilitating the development of chronic inflammatory processes and reducing tissue repair ability (Iacopino 2001). Additionally, the levels of advanced glycation end-products (AGEs) are elevated in diabetic patients, increasing tissue oxidative stress and upregulating inflammatory responses (Fouad & Huang 2015). Moreover, poorly controlled diabetics have further immunological alterations in leucocyte function and wound healing (Delamaire *et al*. 1997, Iacopino 2001, Salvi *et al*. 2008).

A recent meta-analysis has demonstrated a significant association between diabetes and the frequency of RFT with radiological signs of persistent apical periodontitis, in agreement with studies showing a delayed periapical repair in

diabetic patients (Segura-Egea *et al*. 2016). Consequently, increased failure of root canal treatment with greater likelihood of RFT loss would be expected in diabetic patients.

In this study, a systematic review and meta-analysis were carried out to investigate the potential relationship between diabetes and the occurrence of extracted RFT.

2. REVIEW

The clinical PICO question to be answered was as follows: in adult patients with RFT, does the absence or presence of diabetes influence the prevalence of RFT extraction?

Literature search strategy

The systematic review was carried out following conventional methods (Stroup *et al*. 2000, Bader 2004). After formulating the PICO question, the search plan was designed and the articles found in the search were selected according to the previously established criteria for inclusion and exclusion. Subsequently, the quality of the articles was evaluated and their results collected and analysed (Pak *et al*. 2012). The search was carried out in MEDLINE/PubMed, Web of Science, Scopus and the Wiley Online Database. The groupings of Mesh terms and key words used were as follows: (Diabetes OR Diabetes Mellitus OR Hyperglycaemia OR Diabetic) AND (Endodontic OR Endodontics OR Endodontic Treatment OR Root Canal Treatment OR Root Canal Preparation OR Root Canal Therapy OR Root Filled Teeth OR Endodontically Treated Teeth) AND (Extraction OR Retention OR Survival OR Success OR Failure OR Outcome) (Table 1).

Table 1. List of the MeSH and key word combinations used for the search strategy.

((‘diabetes mellitus’[MeSH Terms] OR (‘diabetes’[All Fields] AND ‘mellitus’[All Fields]) OR ‘diabetes mellitus’[All Fields]) OR (‘diabetes mellitus’[MeSH Terms] OR (‘diabetes’[All Fields] AND ‘mellitus’[All Fields]) OR ‘diabetes mellitus’[All Fields] OR ‘diabetes’[All Fields] OR ‘diabetes insipidus’[MeSH Terms] OR (‘diabetes’[All Fields] AND ‘insipidus’[All Fields]) OR ‘diabetes insipidus’[All Fields]) OR Diabetic[All Fields] OR (‘hyperglycaemia’[All Fields] OR ‘hyperglycaemia’[MeSH Terms] OR ‘hyperglycaemia’[All Fields])) AND (Endodontic[All Fields] OR (‘endodontics’[MeSH Terms] OR ‘endodontics’[All Fields]) OR (Endodontic[All Fields] AND (‘therapy’[Subheading] OR ‘therapy’[All Fields] OR ‘treatment’[All Fields] OR ‘therapeutics’[MeSH Terms] OR ‘therapeutics’[All Fields])) OR ((‘dental pulp cavity’[MeSH Terms] OR (‘dental’[All Fields] AND ‘pulp’[All Fields] AND ‘cavity’[All Fields]) OR ‘dental pulp cavity’[All Fields] OR (‘root’[All Fields] AND ‘canal’[All Fields]) OR ‘root canal’[All Fields]) AND (‘therapy’[Subheading] OR ‘therapy’[All Fields] OR ‘treatment’[All Fields] OR ‘therapeutics’[MeSH Terms] OR ‘therapeutics’[All Fields])) OR (‘root canal preparation’[MeSH Terms] OR (‘root’[All Fields] AND ‘canal’[All Fields] AND ‘preparation’[All Fields]) OR ‘root canal preparation’[All Fields]) OR (‘root canal therapy’[MeSH Terms] OR (‘root’[All Fields] AND ‘canal’[All Fields] AND ‘therapy’[All Fields]) OR ‘root canal therapy’[All Fields]) OR ((‘plant roots’[MeSH Terms] OR (‘plant’[All Fields] AND ‘roots’[All Fields]) OR ‘plant roots’[All Fields] OR ‘root’[All Fields]) AND Filled[All Fields] AND (‘tooth’[MeSH Terms] OR ‘tooth’[All Fields] OR ‘teeth’[All Fields])) OR (‘tooth, nonvital’[MeSH Terms] OR (‘tooth’[All Fields] AND ‘nonvital’[All Fields]) OR ‘nonvital tooth’[All Fields] OR (‘endodontically’[All Fields] AND ‘treated’[All Fields] AND ‘teeth’[All Fields]) OR ‘endodontically treated teeth’[All Fields])) AND (extraction[All Fields] OR (‘retention (psychology)’[MeSH Terms] OR (‘retention’[All Fields] AND ‘(psychology)’[All Fields]) OR ‘retention (psychology)’[All Fields] OR ‘retention’[All Fields]) OR (‘mortality’[Subheading] OR ‘mortality’[All Fields] OR ‘survival’[All Fields] OR ‘survival’[MeSH Terms]) OR success[All Fields] OR failure[All Fields] OR outcome[All Fields])

Several endodontic journals and the references of significant papers and reviews were hand-searched. The last search was made on 23 March 2018.

Study selection and inclusion and exclusion criteria

The titles and abstracts of the published studies collected in the search were screened by three investigators (D.C-B., J.M-G. and J.J.S-E.). Articles that did not meet the inclusion criteria were excluded. All remaining articles were obtained, and full text reviewed independently by four reviewers (D.C-B., J.M-G., P.M-M. and J.J.S-E) according to the established inclusion criteria: (i) the type of study: epidemiological studies published from January 1988 to February 2018; (ii) studies comparing diabetic and nondiabetic patients; and (iii) studies establishing the outcome of RCTs and recording data on the frequency of RFT retention in diabetic patients and control subjects.

The following were established as exclusion criteria: (i) experimental studies (laboratory and animals) and (ii) studies including only diabetic patients. When there was disagreement among the reviewers, the basis for the decision was consensus.

Evidence quality evaluation and data extraction

The quality of the methodology used in each study was assessed, and the results were read and analysed carefully. From each of the selected studies, the following data were recorded: name of the authors, date of publication, type of study design, sample size, quantitative results and odds ratio values, and quality level according to Oxford CEBM guidelines (OCEBM 2009).

Outcome variables and statistical analysis

As a measure of the effect and as a primary outcome variable, the odds ratio (OR) calculated in each study for the relationship between the retained RFT and the diabetic state was collected. To calculate the pooled OR, the DerSimonian–Laird method with random effects was used, calculating 95% confidence intervals for the OR. The Breslow-Day test (BDT) and the I^2 test were used to assess heterogeneity among the calculated ORs (Higgins & Thompson 2002). L'Abbé plots (L'Abbé *et al*. 1987) were used to test homogeneity. To show the OR results, a Forest plot (Lewis & Clarke 2001) was used, along with the DerSimonian–Laird pooled estimate. StatsDirect software was used to carry out the meta-analysis (Freemantle 2000). Significance level of $P < 0.05$ was considered.

Search results

Figure 1 presents the search strategy, which provided three hundred titles. Removing duplicates for both searches (204 items) and articles published before 1980 (3 items), 93 articles were obtained. Subsequently, the titles and the summary of the obtained studies were analysed, selecting 15 for full-text reading. Then, 12 studies were disallowed: two of them studied loss of teeth in periodontal patients (Faggion *et al*. 2007, Dannewitz *et al*. 2016), six studies only provided data regarding periapical lesions (Britto *et al*. 2003, Segura-Egea *et al*. 2012, 2016, Rudranaik *et al*. 2016, Arya *et al*. 2017, Smadi 2017), and four others did not present results on the frequency of tooth extraction after NSRCT in diabetics and controls (Fouad & Burleson 2003, Doyle *et al*. 2007, Lin *et al*. 2014, Marques-Ferreira *et al*. 2014).

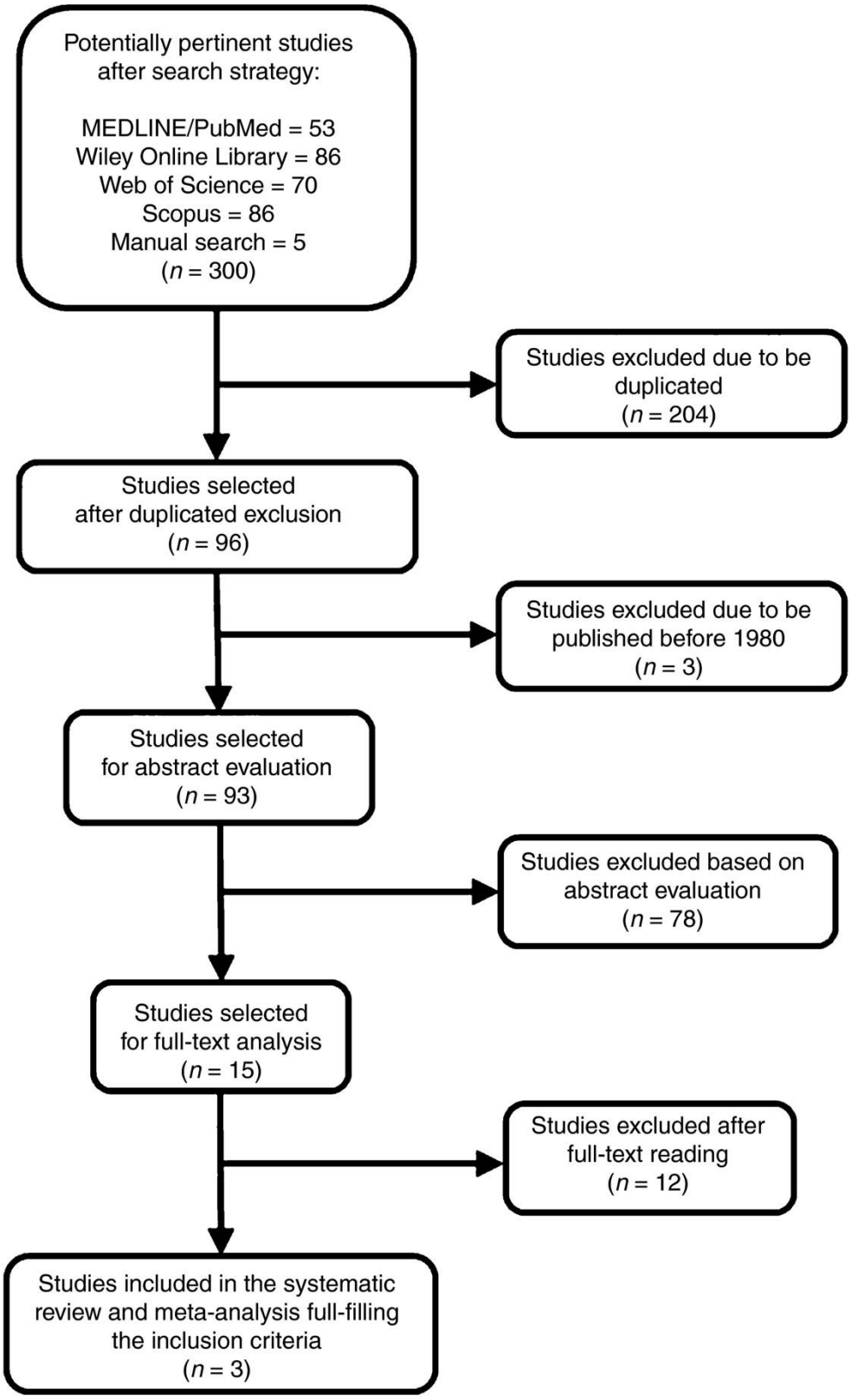

Figure 1. Flow diagram showing the process by which the studies were selected.

Study characteristics

Three studies were included in the final analysis: (i) Mindiola *et al*. (2006), (ii) Wang *et al*. (2011) and (iii) Ng *et al*. (2011). Table 2 summarizes the study design, sample size, main data and level of evidence (OCEBM 2009).

Table 2. Studies included in the systematic review. Study design, subjects and sample size, main results on association between diabetes and extracted RFT and evidence level

Authors (Year)	Study design	RCT	Association diabetes – Extracted*RFT	Evidence level (Oxford CEBM 2009)
1. Mindiola *et al.* (2006)	Longitudinal (retrospective 10 years)	Controls: 3753 Diabetics: 232	Yes; $P < 0.00005$	3b
2. Wang *et al.* (2011)	Longitudinal (prospective 2 years)	Controls: 44 976 Diabetics: 4358	Yes; $P < 0.0001$	3b
3. Ng *et al.* (2011)	Longitudinal (prospective 2–4 years)	1° RCT: Controls: 737 Diabetics: 22 2° RCT: Controls: 835 Diabetics: 23	Yes; $P = 0.0005$	3b

RCT, root canal treatment; RFT, root filled teeth; Extracted*RFT, extracted root filled teeth.

Meta-analysis

Table 3 shows the compilation of the results of the selected studies, with the calculated descriptive statistics and odds ratios (Table 3). The ORs of the included studies were nonhomogeneous (Breslow-Day test = 7.03; df = 2; $P = 0.03$) (Fig. 2, L'Abbé plot), with high heterogeneity ($I^2 = 70.8\%$; 95% CI = 0% to 89.3%), so the random effects model was used to calculate the weights. DerSimonian–Laird method with random effects was performed, providing a pooled OR = 2.44 (95% CI = 1.54–3.88; $\chi^2 = 14.40$; $P = 0.0001$), as shown in the Forest plot (Fig. 3), indicating that the probability that root filled teeth are extracted is more than twice as high in diabetics compared to healthy patients.

Table 3. Results extracted and compiled, descriptive statistics and odds ratios calculated

		Nondiabetic controls		Diabetic patients			
Authors (Year)	N° RFT	Extracted* RFT/Total RFT	Extracted* RFT (%)	Extracted*RFT/ Total RFT	Extracted* RFT (%)	Odds ratio (95% CI)	*P*
1. Mindiola *et al.* (2006)	3985	145/3753	3.9	24/232	10.3	2.87 (1.74–4.56)	<0.00005
2. Wang *et al.* (2011)	49 334	1361/44 976	3.0	231/4358	5.3	1.79 (1.55–2.07)	<0.0001
3. Ng *et al.* (2011)	1617	69/1572	4.4	7/45	15.6	4.01 (1.46–9.52)	0.0005
Overall	54 936	1575/50 301	3.1	262/4635	5.7	2.44 (1.54–3.88)*	0.0001

RFT, root filled teeth; Extracted*RFT, extracted root filled teeth.
*DerSimonian–Laird variance formula: $\chi^2 = 14.40$; $P = 0.0001$.

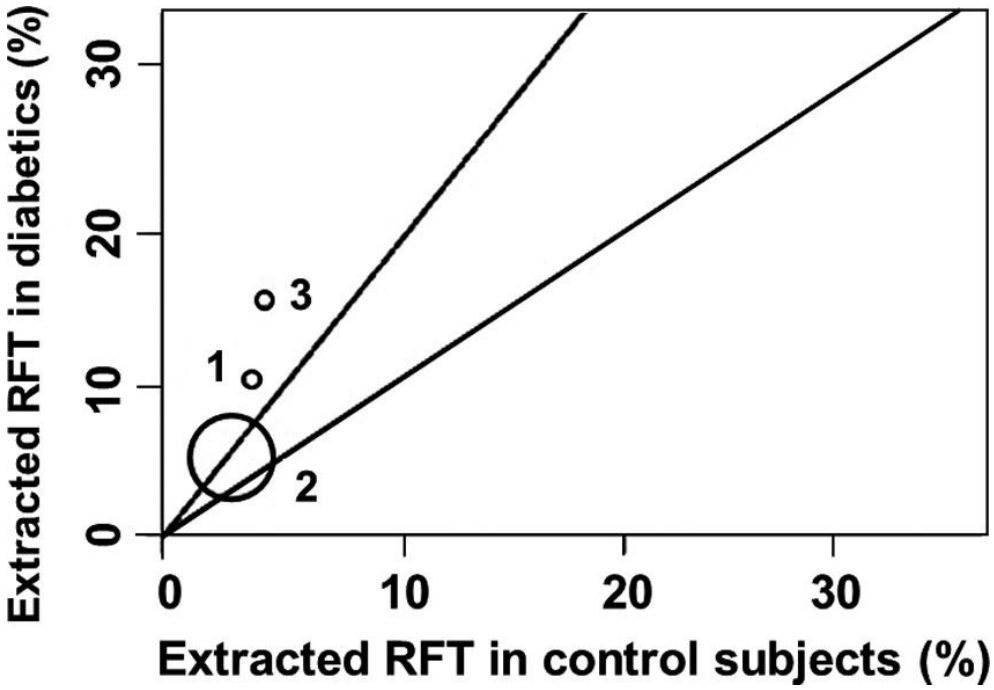

Figure 2. L'Abbé plot presenting the frequency of extracted root filled teeth (RFT) in each of the three studies in diabetic patients and healthy controls. Circles of different sizes represent the weights of the sample of each study (1. Mindiola et al. 2006; 2. Wang et al. 2011; 3. Ng et al. 2011).

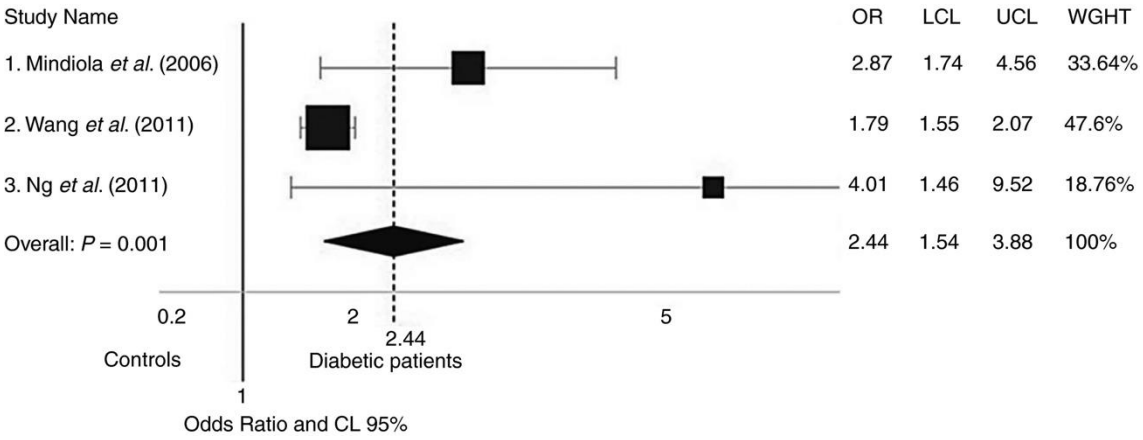

Figure 3. Forest plot of ORs and 95% confidence limits (CL) for the comparison of diabetics and healthy control subjects regarding the frequency of extracted root filled teeth (RFT). Overall estimate is based on data from the three studies. Black squares represent the point estimate of the odds ratio and have areas proportional to study size. Lines represent 95% confidence intervals. The diamond shows the summary statistic for the three studies. The solid line indicates an odds ratio of 1.0, and the dashed line indicates the overall odds ratio. OR, odds ratio; LCL, lower confidence level; UCL, upper confidence level.

Interpretation and assessment of the included studies

The period of time in which the three studies were published was 2006 and 2011 (Table 2). One of them was a retrospective longitudinal study with 10-year follow-up (Mindiola *et al*. 2006), and the other two were prospective studies with 2- to 4-year follow-up (Ng *et al*. 2011, Wang *et al*. 2011). These studies included data from 54 936 teeth with RCT, 50 301 in control patients and 4635 in diabetic patients.

In the study of Mindiola *et al*. (2006), factors associated with nonretention of teeth after RCT were evaluated and confirmed that the presence of diabetes increased the extraction of root filled teeth (10.3%) compared to healthy control subjects (3.9%) (OR = 2.87; 95% CL = 1.74–4.56; $P < 0.00005$).

Wang *et al*. (2011) investigated 49 334 RCT, 4358 in diabetic patients, finding an increased risk of tooth extraction after RCT in patients with DM (5.3%; HR 1.70) than in patients without DM (3.0%) during a 2-year follow-up period (OR = 1.79; 95% CL = 1.55–2.07; $P < 0.0001$).

Ng *et al*. (2011) analysed factors which affected the outcomes of RCT, including the patients' medical condition. They identified a higher rate of extracted RFT in patients with diabetes (15.6%) than healthy counterparts (4.4%) (OR = 4.01; 95% CL = 1.46–9.52; $P = 0.0005$).

3. DISCUSSION

The aim of this study was to analyse the possible relationship between diabetes and the incidence of extracted RFT. The systematic review included the best available evidence: one retrospective longitudinal study, with 10-year follow-up (Mindiola *et al*. 2006), level of evidence 3b and two prospective studies with 2- to 4-year follow-up (Ng *et al*. 2011, Wang *et al*. 2011), both also 3b level of evidence. The homogeneity of the three studies (Breslow-Day = 7.03; df = 2; $P = 0.03$; and $I^2 = 70.8\%$; 95% CI = 0% to 89.3%) was low, suggesting a limitation in the results and indicating that a random effects meta-analysis model should be performed. Overall, the OR provided by DerSimonian–Laird, with random effects, was significant (OR = 2.44; 95% CI = 1.54–3.88; $P = 0.0001$) suggesting a relationship between diabetes and the loss of RFT. Therefore, it could be concluded that diabetes contributes to the loss by extraction of RFT in diabetic patients.

Despite only three studies meeting the inclusion criteria, this meta-analysis analysed a large sample size, providing data from nearly 55 000 teeth with RCT. Moreover, it is important to analyse the design of the studies. Taking into account that the three articles included in this systematic review are longitudinal studies, their results can be explained by the differences in the healing process of apical periodontitis amongst diabetic and healthy subjects.

A probable association between DM and endodontic infections has been investigated in numerous animal (Kohsaka *et al*. 1996, Fouad *et al*. 2002, van Nice 2006, Bain *et al*. 2009, Kodama *et al*. 2011, Astolphi *et al*. 2013, Cintra *et al*. 2013, 2014, Wolle *et al*. 2013, Pereira *et al*. 2016) and human studies (Bender *et al*. 1963, Falk *et al*. 1989, Ueta *et al*. 1993, Bender & Bender 2003, Bender & Seltzer 2003, Britto *et al*. 2003, Fouad & Burleson 2003, Mindiola *et al*. 2006, Doyle *et al*. 2007, Ng *et al*. 2011, Wang *et al*. 2011, Mohamed *et al*. 2013, Sánchez-Domínguez *et al*. 2015) over more than 50 years, analysing the frequency of radiolucent periapical lesions and RCT, as well as the prevalence of RFT with radiolucent periapical lesions as endodontic variables.

The success of RCT has been assessed as the prevalence of radiolucent periapical lesions in RFT, regarding healing periapical lesion (Ueta *et al*. 1993, Doyle *et al*. 2007, Ilgüy *et al*. 2007, Iqbal & Kim 2008, Lin *et al*. 2014). Although the available scientific evidence suggests a relationship between diabetes and a higher frequency of RPLS, greater size of periapical lesions and greater incidence of odontogenic infections (Segura-Egea *et al*. 2012, 2015), the results were not conclusive. Segura-Egea *et al*. (2016) conducted a meta-analysis investigating the relationship between DM and the frequency of RFT with radiolucent periapical lesions. Even though individually, none of the seven included studies provided a significant OR regarding this correlation, pooled OR of the meta-analysis (OR 1.42; 95% CI = 1.11–1.80; $P = 0.006$) indicated that DM was significantly associated with a higher frequency of persistent apical periodontitis, diagnosed radiographically, in RFT. These results agree with those of the present study, with an OR = 2.44 ($P = 0.0001$), which indicates that diabetics are two and a half times more likely to lose RFT. Taking the results of both meta-analysis together supports the concept that diabetes is associated with an increased failure of RCT. Thus, diabetes mellitus should be considered one of the main preoperative indicators of increased risk of failure of RCT.

The higher prevalence of radiolucent periapical lesions in RFT and the delayed periapical repair found in diabetic patients (Sánchez-Domínguez *et al*. 2015, Segura-Egea *et al*. 2016) would suggest an increase in

untoward events following RCT, that is translated into a high incidence of extractions, retreatments and apical surgery in patients with diabetes mellitus.

Although the biological mechanisms by which diabetes mellitus leads to a greater loss of teeth are not well-known, they might be related to: (i) chronic inflammatory conditions predisposed by DM, (ii) reduced tissue repair capacity due to DM, (iii) affected immune response increasing susceptibility to infections resulting from DM and (iv) alteration in the mechanisms of bone turnover and apical repair in DM (Garber *et al*. 2009, Gurav 2013, Fouad & Huang 2015, Segura-Egea *et al*. 2015). Therefore, diabetes mellitus could compromise the immune response, increasing periapical inflammation and deteriorating bone turnover and wound healing in the periapical tissues of RFT, leading to post-treatment endodontic disease, and an increase in the prevalence of nonretention of root filled teeth, and an increase in the prevalence of tooth extraction (Segura-Egea *et al*. 2015).

Taking into account that the available scientific evidence demonstrates a significant association between diabetes and periodontal disease (Katz 2001, Soskolne & Klinger 2001), another possible mechanism by which diabetes could reduce the survival of root filled teeth would be a deterioration in their periodontal status. Periodontal disease is the main cause of tooth loss in adult patients (Ong 1998). Therefore, it is legitimate to assume that an undetermined percentage of the root filled teeth that are lost in diabetic patients is due to periodontal causes. However, the literature that was analysed in this systematic review did not control for periodontal disease and no conclusions can be drawn in this regard. This could cause a bias in the results of this review. Future investigations studying the association between the outcome of RCT and diabetes should control for periodontal disease.

Another possible confounding factor causing bias in the results of this systematic review could be age of the patients. The incidence of both diabetes and AP increases with age (Buckley & Spångberg 1995, Chen *et al*. 2007, 2008). Moreover, Mindiola *et al*. (2006) found that increasing age contributes to decreased retention of root filled teeth. Taking into account that the OR estimates

retrieved from the three articles included in the meta-analysis are crude and are not adjusted for the effect of age, the present findings must be interpreted cautiously. However, one of the studies included in this systematic review (Wang *et al*. 2011) carried out a multivariate analysis with Cox regression models. They calculated the hazard ratio (HR), adjusted for age, gender and tooth type, concluding that DM was significantly associated with tooth extraction after completion of RCT (HR = 1.29; 95% CI = 1.11–1.50; *P* = 0.008).

Lastly, in view of the association between diabetes and the outcome of RCT (higher rate of persistent apical periodontitis, as reported previously by Segura-Egea *et al*. (2016), and decreased retention of RFT), and taking into account that diabetes mellitus is considered the third most prevalent condition in medically compromised dental patients (Dhanuthai *et al*. 2009), dentists must translate this into their clinical practice, investigating a possible diabetic state in patients who have lost several RFT. Thus, dentists should always ask about the systemic health status of patients, in particular, on whether their blood sugar level has been checked recently.

4. CONCLUSIONS

The results of available studies indicate a significant relationship between DM and increased frequency of nonretained root filled teeth. Diabetes mellitus should be considered an important preoperative prognostic factor in root canal treatment. However, well-designed prospective studies are required to determine the exact contribution of diabetes to the increased risk of post-treatment endodontic disease and the mechanisms by which it occurs.

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CAPÍTULO III

Endodontics and diabetes: association versus causation

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ABSTRACT

Endodontic Medicine has gained more attention and is becoming a more important issue in Endodontics. As an example, more than one hundred articles on this topic have been published in the last eight years. Several of these studies have found an association between endodontic variables, that is the prevalence of apical periodontitis, the prevalence of root canal treatment (RCT) and the outcome of RCT assessed as root filled teeth (RFT) with radiolucent periapical lesions (RPL) or non-retained RFT, and several systemic diseases, such as diabetes, cardiovascular disease, smoking habits, osteoporosis, inherited coagulopaties, biological medications, low birth weight or physical fitness. However, the demonstration of association does not prove by itself the existence of a cause–effect relationship. Two variables can be related statistically to each other without either variable directly affecting the values of the other thus resulting in a non-causal relationship. Causality is assumed when one variable is shown to contribute to the development of the other, and its removal is shown to reduce the frequency of disease. Therefore, once a significant statistical association has been found between two variables, it is necessary to exclude the presence of bias, which would imply that the association is artefactual, and to analyse if the causation criteria defined by Hill (Proceedings of the Royal Society of Medicine 1965; 58: 295-300) are fulfilled to establish a causal relationship. Only if they are satisfied, can it be concluded that the association is causal. The aim of this study was to analyse the difference between association and causation, applying the criteria of causality to the specific case of the association between endodontic disease and diabetes mellitus.

Keywords: apical periodontitis, causation criteria, diabetes mellitus, endodontic medicine, root canal treatment, systematic review.

1. INTRODUCTION

When pulp necrosis is established, bacteria with their toxins, immunological agents, and the products of pulp degeneration and tissue necrosis, reach the periradicular tissues through several pathways, mainly the apical foramen, giving rise to inflammatory and immunologic reactions causing apical periodontitis (Segura-Egea et al. 2013). Apical periodontitis is a prevalent disease with studies conducted in European countries, using periapical and panoramic radiographs or CBCT, reporting a prevalence of apical periodontitis ranging from 34 to 61% of adults and 2–14% of teeth, with a mean of five per cent (Jiménez-Pinzón et al. 2004, Segura-Egea et al. 2004, Gulsahi et al. 2008, López-López et al. 2012a,b, Dutta et al. 2014, Van der Veken et al. 2017).

On the other hand, root canal treatment is also very prevalent. In Europe, data from several epidemiological studies suggest that around 2–12% of teeth have been root filled (Jiménez-Pinzón et al. 2004, Segura-Egea et al. 2004, López-López et al. 2012a,b, Dutta et al. 2014, Van der Veken et al. 2017).

Endodontic Medicine

Taking into account that both apical periodontitis and root canal treatment are prevalent conditions, two questions could be asked: first, does the periapical inflammatory process or root canal treatment compromise general health? and second, do systemic diseases influence periapical health or the outcome of root canal treatment? Endodontic Medicine is trying to answer these questions (Segura-Egea et al. 2015). The term ‘Endodontic Medicine’ could be considered by some to be redundant because Endodontics is part of Dentistry and Dentistry is part of Medicine. So, why use the term Endodontic Medicine? It could be argued that the medical aspects of Endodontics are being eclipsed by the technical and mechanical aspects of endodontic therapy (Segura-Egea et al. 2015). The technological development of Endodontics, which occupies the main part of most endodontic congresses, should not forget that Endodontics is not only root canal treatment, rotary files, gutta-percha, operative microscope,

electronic apex locator, etc. On the contrary, the principal objective of Endodontology is the study of the biological and clinical aspects of endodontic diseases. Consequently, the main contribution that Endodontic Medicine can make is to highlight the biological and medical aspects of Endodontology, studying the systemic consequences of apical periodontitis and root canal treatment, as well as the influence of systemic diseases on periapical inflammation, periapical repair and root canal treatment outcome (Kvist & van der Sluis 2015, Segura-Egea et al. 2015).

From focal infection theory to Endodontic Medicine

The possible relationship between apical periodontitis and systemic diseases is not a new topic. In the early 20th century, the theories of focal infection and elective localization described an association between systemic inflammatory complications with bacteria found in dental infections. Miller (1891) became the first to reveal the existence of bacteria in samples of dental pulp tissue, proposing that oral microorganisms or their products may have a role in the development of a variety of diseases in sites distant from the oral cavity. Consequently, Miller advised treating and filling root canals (Pallasch & Wahl 2003). On the contrary, in 1910, William Hunter, a British surgeon, lecturing in Montreal at McGill University, criticized bad dentistry and held oral infections and oral sepsis responsible for many diseases, such as kidney diseases, colitis, anaemia, gastritis and many others, igniting the fire of focal infection (Hunter 1900). Almost at the same time, Frank Billings, in Chicago, published case reports claiming that tonsillectomies and tooth extraction cured infections in distant organs. He replaced the Hunter's term oral sepsis with focal infection (Billings 1914). In addition, Edward Rosenow, a pupil of Billings, developed the principle of elective localization, according to which microorganisms have affinities for particular organs. He published many articles over a period of fifteen years on this subject, relating periapical infection with the colonization of bacteria in different organs (Rosenow 1928).

Endodontics came under particular scrutiny: all pulpless teeth, including those in which radiographs did not reveal evidence of infection, were considered a probable focus of infection, and the extraction of healthy teeth was justified to prevent focal infection. An American dentist, Weston Price, published results supporting the local infection theory in relation to endodontically treated teeth, recommending eliminating all pulpless teeth (Price 1925). He suggested that the treatment of dental infections must always imply the extraction of the affected tooth. During that period, millions of tonsils, adenoids and teeth were removed in an 'orgy of extractions' as described by Grossman (Grossman 1955, 1960, Pallasch & Wahl 2000).

The reaction of many endodontists was to investigate more deeply the pathogenesis of apical periodontitis. It was shown that root canal treatment cured apical periodontitis (Grossman 1940, Easlick 1951). Of course, nowadays, the advances experienced by medicine and dentistry have discredited the focal infection theory.

It seemed that this problem had been forgotten and overcome. However, in recent decades, numerous epidemiological studies have found an association between periodontal disease and important systemic diseases, such as diabetes mellitus (Katz 2001, Soskolne & Klinger 2001), coronary heart disease (Dörfer et al. 2004, Grau et al. 2004), osteoporosis (Bullon et al. 2005) and pregnancy outcome (Jeffcoat et al. 2003, Marin et al. 2005). The term Periodontal Medicine was proposed to name the field of Periodontology encompassing the study of the contribution of periodontal infections on systemic conditions, and the study of the connections of other systemic pathologies and periodontitis (Williams & Offenbacher 2000). Although the scientific evidence supporting an aetiopathological role for periodontal pathogens is substantial, the multifactorial nature of systemic chronic diseases makes it difficult to establish a definitive causal role for periodontal pathobionts in systemic infections (Kumar 2017). However, the evidence of the possible association between periodontal diseases and systemic diseases has focused attention on the diagnosis and treatment of periodontal disease, improving the oral and, possibly, systemic health of patients with periodontal conditions. Subsequently, Endodontic Medicine has followed the

same step as Periodontal Medicine on the basis that there is a now a substantial body of evidence to suggest the existence of an association between endodontic disease and several systemic diseases (Cotti & Mercuro 2015, Kvist & van der Sluis 2015, Segura-Egea et al. 2015).

The results of epidemiological studies on periodontal and endodontic medicine are posing a serious problem, the risk of the focal infection theory re-emerging. Interestingly, the website of the American Association of Endodontists provides information and advice to patients to counteract the miss-information that is publicized by individuals and groups who still promote the concepts inherent in the focal infection theory (American Association of Endodontists 2014). In fact, several recent articles have discussed whether research on the relationship between periodontal or endodontic diseases and systemic health could mean the revival of the focal infection theory (Pallasch & Wahl 2000, 2003, Tjäderhane 2015).

Why is this happening? It can be hypothesized that the results of studies on the possible relationship between oral infections and systemic conditions are being translated to people, to the media and, unfortunately, in some cases to doctors and dentists, as if it had already been proven that this association is causal (Hujoel et al. 2006, Niederman & Weyant 2012). Results that only demonstrate the association between endodontic or periodontal diseases and certain systemic diseases, such as cardiovascular disease or diabetes, are being interpreted as if the causal link is already proven.

On the other hand, the problem of the possible causal link between endodontic infection and systemic diseases does not only involve descriptive issues of science but also moral matters of society. If apical periodontitis can cause diabetes or cardiovascular disease it becomes an ethical problem and not only a scientific one (Hofmann 2011).

The aim of this study was to analyse the difference between association and causation, applying the criteria of causality to the specific case of the association between endodontic disease and systemic diseases, taking as an example the case of diabetes mellitus.

2. METHODOLOGICAL APPROACH

Although the objective of this work is not to perform a systematic review, it has been necessary to review the scientific evidence on the relationship between diabetes and endodontic pathosis. Epidemiological studies carried out on the association between diabetes and apical periodontitis or root canal treatment published in English until 8 October 2018 were identified and analysed. An electronic search of PubMed, Web of Science and Scopus was conducted using appropriate keywords: (endodontic OR dental pulp OR pulpitis OR apical periodontitis OR periapical granuloma OR root canal treatment OR root filled teeth) AND (diabetes OR diabetic) AND (epidemiological OR cross-sectional OR retrospective OR case-control OR prospective OR longitudinal OR cohort OR clinical trial OR systematic review). Human cross-sectional and prevalence studies, retrospective and case–control studies, prospective and cohort studies, and systematic reviews were included. Animal and experimental studies as well as case reports or case series studies were excluded. Seventy-six articles were selected, and its results were analysed.

3. INTERPRETATION OF THE STUDIES ON ENDODONTIC MEDICINE: CAUSATION OR ASSOCIATION

Many epidemiological studies have been conducted investigating the possible association of apical periodontitis and endodontic treatment with various systemic conditions. The first three systemic conditions investigated were diabetes mellitus, cardiovascular diseases and smoking habits.

Firstly, with the studies of Bender et al. (1963), diabetes mellitus was the first systemic disease whose possible association with apical periodontitis was suggested. Since that pioneer paper, numerous studies have been conducted investigating this association (Fouad & Burleson 2003, Segura-Egea et al. 2005, 2012, 2016, López-López et al. 2011, Marotta et al. 2012, Sánchez-Domínguez et al. 2015, Cabanillas-Balsera et al. 2019).

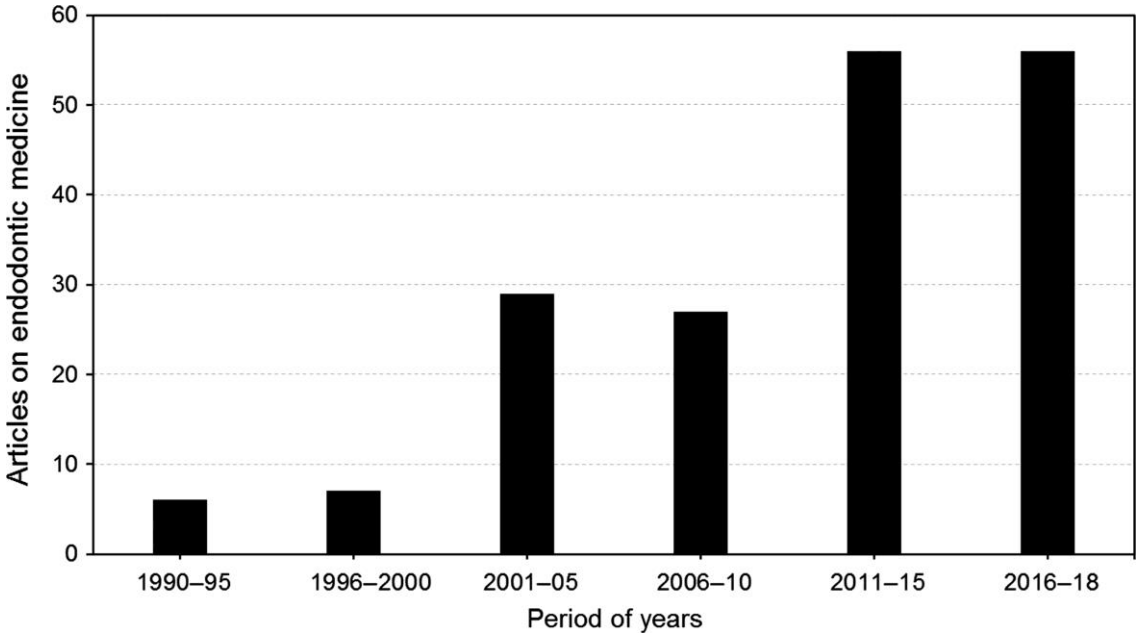
Secondly, the potential relationship between cardiovascular disease and apical periodontitis has also been widely investigated (Caplan et al. 2006, Segura-Egea et al. 2010, 2011, Cotti et al. 2011, Cotti & Mercuro 2015, Liljestrand et al. 2016, Berlin-Broner et al. 2017, Virtanen et al. 2017, Aminoshariae et al. 2018).

And thirdly, many articles have been published on the influence of tobacco smoking on periapical and endodontic status (Krall et al. 2006, Segura-Egea et al. 2008, 2011, 2015, López-López et al. 2012a,b, Walter et al. 2012, Rodriguez et al. 2013).

In addition, the potential association of many other diseases with apical periodontitis and root canal treatment has also been investigated, such as inherited coagulation disorders (Castellanos-Cosano et al. 2013a,b), osteoporosis (López-López et al. 2015), biological medications (Cotti et al. 2014), physical fitness (Hoppe et al. 2017), cirrhosis and chronic liver disease (Castellanos-Cosano et al. 2013a,b, Grønkjær et al. 2016), low birth weight (Leal et al. 2015), end-stage renal disease (Khalighinejad et al. 2017) and inflammatory bowel disease (Piras et al. 2017).

Therefore, in the last few decades one of the topics that is being given more attention in endodontic research is Endodontic Medicine. A search in PubMed using the keywords: (endodontic OR apical periodontitis OR endodontic disease) AND (systemic disease OR systemic health), located a total of 218 items in 30 years (Fig. 1), with more than a hundred in the last eight years.

Figure 1. Search results in PubMed of articles published in the last three decades about Endodontic Medicine. The keywords used in the search were as follows: (endodontic OR apical periodontitis OR endodontic disease) AND (systemic disease OR systemic health).



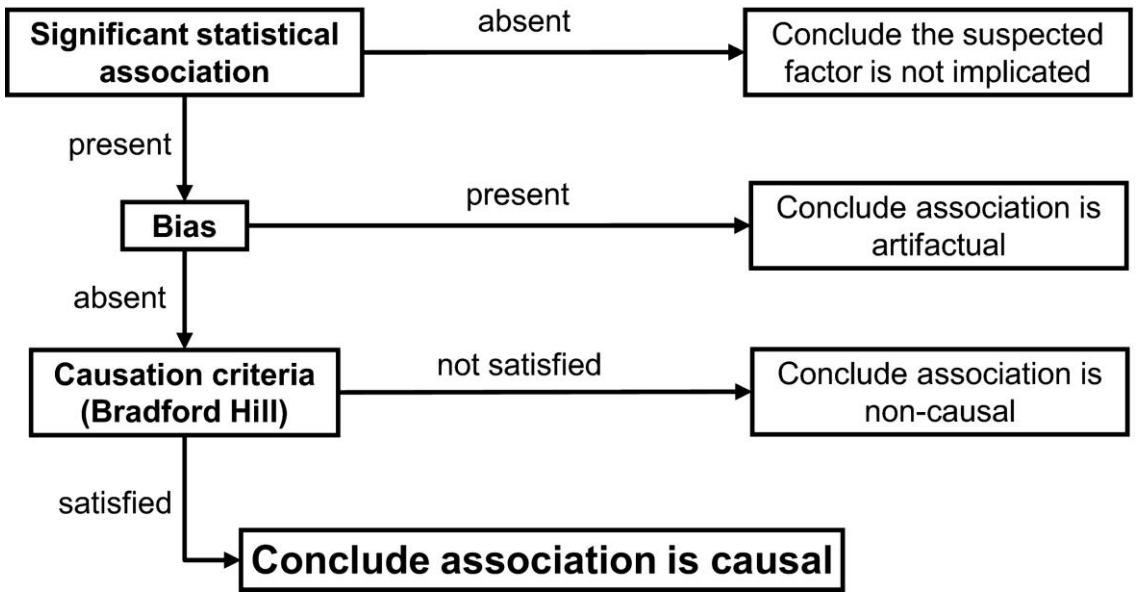
Interpretation of the statistical results of epidemiological studies

The application of statistical methods to the results of epidemiological studies determines if there is an association between two variables. But the demonstration of an association, by itself, is not proof that there is a cause–effect relationship. Two variables can be statistically related to each other without either variable directly affecting the values of the other setting up a non-causal relationship. Causality is assumed when one variable (be it diabetes or oral infections) is shown to contribute to the development of the other, and its removal is shown to reduce the frequency of disease (Hill 1965).

Therefore, once a significant association has been found between two variables, it is necessary to exclude the presence of bias, which would imply that the association is artefactual, and to analyse if the causation criteria defined by

Hill (1965) are fulfilled to establish a causal relationship. If they are satisfied, it could be concluded that the association is causal (Fig. 2).

Figure 2. Causation versus association.



Hill's causation criteria

The connection between cigarette smoking and lung cancer was demonstrated by Doll & Hill (1950). Sir Austin Bradford Hill, trying to answer the question 'What aspects of the association should especially be considered before deciding that the most likely interpretation of it is causation?', defined a list of causation criteria to provide epidemiologic evidence of the existence of causal relationship (Hill 1965) (Table 1). Although not explicitly, the discussion of scientific papers reporting results on the possible association of endodontic pathosis with some systemic disease, should evaluate and analyse the fulfilment of these criteria. However, unfortunately, the discussions of many of the articles published on endodontic medicine do not describe these criteria.

Table 1. Hill causation criteria (Hill 1965)

Criteria	Definition
Strength of the association	Refers to the size of the relative risk/odds ratio found. The greater the strength of the association the more likely that it is causal.
Temporality	One of the variables (the cause) must precede the other variable (the effect).
Biological gradient	Refers to the change in effect provoked by differing amount, intensity or duration of the cause.
Consistency	Different studies, carried out by different investigators, conducted on different populations and in different countries, resulted in the same association.
Plausibility	The suspected causation is biologically plausible. But what is biologically plausible depends upon the biological knowledge of the day.
Coherence	The cause–effect interpretation of the association should not seriously conflict with the generally known facts of the natural history and biology of the disease.
Experiment	Occasionally it is possible to appeal to experimental, or semi-experimental, evidence.
Analogy	In some circumstances it would be fair to judge by analogy.
Specificity	The association is limited to specific subjects and to particular sites and types of disease.

4. DIABETES MELLITUS – ENDODONTIC DISEASE: CAUSATION OR ASSOCIATION?

Taking as an example the possible association between endodontic disease and diabetes mellitus, the achievement of Hill's criteria (strength of the

association, temporal relationship, dose–response gradient, consistency of the association, coherence and plausibility of the association) will be analysed. Firstly, it is necessary to review briefly the scientific evidence and, secondly, consider if the Hill criteria of causation are fulfilled.

Scientific evidence on the association between endodontic disease and diabetes

The endodontic variables analysed in these epidemiological studies are as follows: a) the prevalence of apical periodontitis, b) the prevalence of root canal treatment and c) the outcome of root canal treatment, assessed as c.1) the prevalence of root filled teeth with or without periapical lesions or c.2) the prevalence of tooth extraction after root canal treatment.

(a) Prevalence of apical periodontitis in diabetic and control subjects

The first question to be answered is whether there is an association between the prevalence of apical periodontitis and diabetes. This association was proposed by Bender et al. (1963). They observed a high percentage of diabetics amongst patients with odontogenic infections, together with greater periapical inflammatory reactions and delayed periapical healing in poorly controlled diabetic patients. They proposed that the increased local inflammation as a consequence of apical periodontitis causes an intensification of diabetes with a rise in the blood glucose, placing the patient in an uncontrolled diabetic status and developing a vicious circle. Since then, six studies have found a significantly greater prevalence of periapical lesions in diabetics compared to healthy subjects (Bender et al. 1963, Falk et al. 1989, Ueta et al. 1993, Segura-Egea et al. 2005, López-López et al. 2011, Marotta et al. 2012), one study reported that the frequency of periradicular lesions was higher in long-term diabetic patients than in short-term diabetic patients (Mesgarani et al. 2014), and another study

reported the size of periapical lesions in diabetic patients was larger (Falk et al. 1989).

On the contrary, other studies (Britto et al. 2003, Correia-Sousa et al. 2015, An et al. 2016, Smadi 2017) have not found a significant association. So, prospective studies must be conducted to confirm whether there is or not a relationship between apical periodontitis and diabetes.

(B) PREVALENCE OF ROOT CANAL TREATMENT IN DIABETIC AND CONTROLS SUBJECTS

The second question can be formulated as whether there is association between the prevalence of root canal treatment and diabetes. In addition to studying the prevalence of apical periodontitis, six studies have also investigated the frequency of root canal treatment in diabetic and control subjects. Three studies did not find a greater prevalence of RCT in diabetic patients compared to controls (Falk et al. 1989, Segura-Egea et al. 2005, Marotta et al. 2012), but three studies did (López-López et al. 2011, Correia-Sousa et al. 2015, Smadi 2017). Therefore, there is no conclusive evidence about the association of diabetes with the prevalence of RCT.

(C) OUTCOME OF RCT IN DIABETIC AND CONTROL SUBJECTS

Finally, the third question that can be formulated is whether an association exists between DM and the outcome of RCT. This possible relationship can be investigated analysing the prevalence of RFT with persistent AP, or investigating the prevalence of tooth extraction after root canal treatment.

(c.1) Prevalence of RFT with apical periodontitis

Studies investigating the prevalence of RFT with apical periodontitis in diabetic and healthy control subjects, have demonstrated delayed periapical healing in diabetic subjects, with a lower rate of repair associated with root filled teeth (Bender et al. 1963, Arya et al. 2017), and slower reduction of periapical lesions in poorly controlled diabetic patients (Cheraskin & Ringsdorf 1968). Other studies have found a greater percentage of RFT with AP in diabetics, compared to control subjects, but without a significant difference (Falk et al. 1989, Britto et al. 2003, Fouad & Burleson 2003, Segura-Egea et al. 2005, López-López et al. 2011, Marotta et al. 2012, Marques-Ferreira et al. 2014). However, some of these studies have found significant differences only in diabetic women (Falk et al. 1989), or only in diabetic men (Britto et al. 2003) or in cases with preoperative periapical lesions (Fouad & Burleson 2003). Another study found a significantly higher prevalence of RFT with AP in all diabetics compared to control subjects (Smadi 2017).

(c.2) Retention of RFT

The possible relationship between diabetes and outcome following root canal treatment can also be investigated comparing the prevalence of tooth extraction after treatment in diabetic patients and normal healthy subjects. Six studies have analysed this topic demonstrating a greater likelihood of RFT loss in diabetic patients (Mindiola et al. 2006, Ng et al. 2011, Wang et al. 2011, Lin et al. 2014) and a marginal association between RFT loss and diabetes (Doyle et al. 2007). In summary, it can be concluded that the prognosis of root filled teeth is worse in diabetic patients, who are more likely to lose their root filled teeth.

Compliance with Hill's criteria when analysing the association between diabetes and endodontic disease

It has been demonstrated that several endodontic variables, such as the prevalence of apical periodontitis, the prevalence of root canal treatment and the

prevalence of root filled teeth with radiolucent periapical lesions, are associated with diabetic status. As a consequence, it is essential to assess whether Hill's causation criteria are met to determine whether or not the association is causal.

(A) STRENGTH OF THE ASSOCIATION

The first criteria refer to the size of the relative risk found. Relative risk can be determined in cohort studies and clinical trials from the incidence data. However, the odds ratio calculated in cross-sectional and case–control studies is a good approximation to the relative risk, especially when the outcome is rare (Bland & Altman 2000). The greater the strength of the association the more likely that it is to be causal (Hill 1965).

Most epidemiological studies evaluating the relationship between Endodontics and diabetes are cross-sectional, nevertheless only some of them have determined the strength of the association by calculating the odds ratio values. A value of OR equal to 1 implies that the first variable (generally the exposure) does not affect the probabilities of the second variable (the outcome) (Bland & Altman 2000). When the OR is >1, it implies that the exposure is associated with higher odds of the outcome. When the OR is <1, the exposure is associated with lower odds of the outcome. The confidence interval (CI) is used to estimate the precision of the OR. A 95% CI means that when sampling the same population on several occasions, the calculated interval would comprise the right population parameter in approximately 95% of the cases, always assuming the absence of bias or confounding factors (Morris & Gardner 1988). A large CI indicates a low level of precision of the OR, whereas a small CI indicates a higher precision of the OR. However, the 95% CI does not determine the statistical significance, as it is inappropriate to interpret an OR with 95% CI that spans the null value (e. g. OR = 1) as indicating evidence for lack of association between the exposure and outcome.

In the cross-sectional studies conducted to analyse the relationship between diabetes and Endodontics, the ORs calculated are not constant and are not always significant (Table 2). Moreover, the estimated 95% CI overlap, in many cases, the null value, indicating that the OR could be 1 or less. However, there are six studies analysing the outcome of RCT in diabetics and control subjects in which the P value is significant, the OR values ranged from 1.3 to 5.3, and their lower limits of the 95% CI ranged from 1.2 to 2.0 (Table 2). At a 10% disease rate in the control group, the reference OR values reflecting a 'weak association', a 'moderate association' and a 'strong association' are 1.5, 2.5 and 4.1 (Chen et al. 2010).

Table 2. Strength of the association 'endodontics/diabetes'

Study	Variable	Odds ratio	Age adjustment	*P*
Segura-Egea *et al.* (2005)	Prevalence of AP	3.2	No	0.04*
López-López *et al.* (2011)	Prevalence of AP	3.9	No	<0.01*
Segura-Egea *et al.* (2005)	Prevalence of RCT	0.6	No	0.25
López-López *et al.* (2011)	Prevalence of RCT	2.3	No	<0.05*
Falk *et al.* (1989)	Prevalence of RFT-AP	1.3	No	>0.05
Fouad & Burleson (2003)	Prevalence of RFT-AP	8.1	Yes	>0.05
Segura-Egea *et al.* (2005)	Prevalence of RFT-AP	3.3	No	0.05
López-López *et al.* (2011)	Prevalence of RFT-AP	2.7	No	0.05
Smadi (2017)	Prevalence of RFT-AP	4.1	No	0.02*
Arya *et al.* (2017)	Prevalence of RFT-AP	5.3	No	<0.05*
Wang *et al.* (2011)	Prevalence of retained RFT	1.8	Yes	0.003*
Ng *et al.* (2011)	Prevalence of retained RFT	3.3	Yes	<0.01*
Lin *et al.* (2014)	Prevalence of retained RFT	1.3	Yes	0.0001*

AP, Apical periodontitis; RCT, Root canal treatment; RFT, Root filled teeth.
*Significant *P* value.

An important point to keep in mind is the age of the patients included in studies. Since incidence of both diabetes and AP and RCT increases with age, a spurious association could be found if the age of the patients is not taken into account in the design of the study. In addition, long-term diabetics are expected to be older than short-term diabetics. Therefore, it is important to indicate which studies made adjustments for the age in the analysis of their results and in the calculation of the OR (Table 2). As it can be seen, most studies calculated ORs without adjusting for age. Therefore, the age of the patients is also an important point to take into account in the design of new studies on the association between diabetes and endodontics.

In conclusion, the OR values do not support the existence of association between Endodontics and diabetes. Only the outcome of RCT could be considered moderately associated with the diabetic state.

(B) TEMPORAL RELATIONSHIP OF THE ASSOCIATION

This second criterion means that one of the variables (the cause) must precede the other variable (the effect). Taking into account that cross-sectional studies measure both variables, the exposure and the outcome, at the same time, they cannot establish a temporal relationship. On the contrary, follow-up studies, especially longitudinal studies, allow to establish a temporal relationship.

Regarding the temporal relationship between Endodontics and diabetes, no longitudinal study is available. The published studies are cross-sectional, focusing on the prevalence of AP, RCT and AP in teeth with RCT. But prevalence is not very useful to establish causality (Hernan 2004, Rothman & Greenland 2005). A high prevalence of periapical radiolucent lesions may reflect a high incidence of apical periodontitis, but also a delay in the healing of these lesions.

However, two cross-sectional studies (Falk et al. 1989, Mesgarani et al. 2014) provide some information about the possible temporal relationship. Both studies found worse periapical status in long-term diabetic patients compared to short-term diabetics. The longer the duration of diabetes, the greater the prevalence of AP and the extension of periapical lesions. However, prospective studies are needed, despite being more difficult to develop and more expensive, to definitively establish the temporal relationship.

(C) DOSE–RESPONSE GRADIENT OF THE ASSOCIATION

The third criterion refers to the change in effect provoked by differing amount, intensity or duration of the cause. If a dose–response gradient can be demonstrated, the likelihood that the association is causal increases.

Two studies have analysed the association of glycated haemoglobin (HbA1c) levels with the prevalence of endodontic variables, and found a significant association between higher HbA1c levels and the prevalence of apical periodontitis (Sánchez-Domínguez et al. 2015), the prevalence of RFT (Smadi 2017) and the prevalence of RFT with AP (Smadi 2017). However, no studies have been carried out comparing the prevalence levels of AP or RCT with the prevalence of diabetes.

(D) CONSISTENCY OF THE ASSOCIATION

The fourth causation criterion implies that different studies, carried out by different investigators, and conducted on different populations, and sometimes in different countries, resulted in the same association. Therefore, the greater the number of studies finding the association, the more consistency and more likely that the association is causal.

Seven studies have found a higher prevalence of teeth with radiolucent periapical lesions in diabetic patients compared to healthy controls (Table 3). Nevertheless, only three of them (Segura-Egea et al. 2005, López-López et al. 2011, Marotta et al. 2012) were significant. Four other studies found no significant differences (Falk et al. 1989, Britto et al. 2003, Correia-Sousa et al. 2015, Smadi 2017). Therefore, the association between diabetes and apical periodontitis is not consistent. A systematic review with meta-analysis is needed to reach a definitive conclusion.

Table 3. Consistency of the association between the prevalence of AP and diabetes

Study	Controls (%)	Diabetics (%)	*P*
Falk *et al.* (1989)	1.8	3.6	>0.05
Britto *et al.* (2003)	87	97	>0.05
Segura-Egea *et al.* (2005)	58	81	0.04*
López-López *et al.* (2011)	42	74	<0.01*
Marotta *et al.* (2012)	7	10	0.03*
Correia-Sousa *et al.* (2015)	2.4	2.4	>0.05
Smadi (2017)	12	13	>0.05

*Significant *P* value.

In relation to the association between the prevalence of RCT and diabetes (Table 4), again there are three studies finding significant differences between diabetics and controls (López-López et al. 2011, Correia-Sousa et al. 2015, Smadi 2017), and three others that did not (Falk et al. 1989, Segura-Egea et al. 2005, Marotta et al. 2012). The results are not consistent, and a systematic review with meta-analysis is required to reach a definitive conclusion.

Table 4. Consistency of the association between the prevalence of Root canal treatment (RCT) and diabetes

Study	Controls (%)	Diabetics (%)	*P*
Falk *et al.* (1989)	13	16	>0.05
Segura-Egea *et al.* (2005)	42	31	0.25
López-López *et al.* (2011)	50	70	<0.05*
Marotta *et al.* (2012)	15	13	>0.05
Correia-Sousa *et al.* (2015)	4.3	6	<0.05*
Smadi (2017)	1.8	4.2	<0.05*

*Significant *P* value.

Finally, the association between diabetes and the prevalence of RFT with periapical radiolucencies has been analysed in eight studies (Table 5). Only one study reported significant differences between diabetic patients and healthy controls (Smadi 2017), with seven studies not finding any differences (Falk et al. 1989, Britto et al. 2003, Fouad & Burleson 2003, Segura-Egea et al. 2005, López-López et al. 2011, Marotta et al. 2012, Marques-Ferreira et al. 2014). However, in this case, a systematic review with meta-analysis has been carried out (Segura-Egea et al. 2016). This review concluded that diabetic patients have a significantly greater prevalence of radiolucent periapical lesions associated with root filled teeth, compared to control subjects (OR = 1.42; 95 % CL = 1.11–1.80; P = 0.006). Therefore, it can be concluded that the association between diabetes and the prevalence of RFT with periapical radiolucencies is consistent and diabetes is significantly associated with a higher prevalence of radiolucent periapical lesions in RFT.

Table 5. Consistency of the association between the prevalence of root filled teeth (RFT) with AP and diabetes

Study	Controls (%)	Diabetics (%)	*P*
Falk *et al.* (1989)	21	26	0.20
Fouad & Burleson (2003)	31	36	0.42
Britto *et al.* (2003)	44	46	0.82
Segura-Egea *et al.* (2005)	60	83	0.17
López-López *et al.* (2011)	24	46	0.09
Marotta *et al.* (2012)	38	46	0.21
Marques-Ferreira et al. (2014)	20	43	0.06
Smadi (2017)	19	28	0.02*

*Significant *P* value.

On the other hand, it has been commented previously that the prognosis of RFT is worse in diabetic patients, who are more likely to lose their root filled teeth. A recently published systematic review with meta-analysis has concluded that diabetics have a significantly higher prevalence of extracted RFT than healthy nondiabetic subjects (OR = 2.44; 95% CI = 1.54–3.88; P = 0.0001) (Cabanillas-Balsera et al. 2019). However, this does not allow the direct conclusion that losing teeth in diabetic patients is because of endodontic failures. Diabetics have more caries and/or worse oral hygiene, two variables that could be acting as confounding factors (Kanjirath et al. 2011, Arheiam & Omar 2014).

E) COHERENCE OF THE ASSOCIATION AND BIOLOGICAL PLAUSIBILITY

The fifth and sixth criteria analyse whether the suggested association is consistent with existing biological and medical knowledge and with the natural history and biology of the disease. In this sense, what is biologically plausible depends upon the biological knowledge of the day and, in fact, it can never be

ruled out that the observed association observe may be new to science or medicine. The association between endodontic diseases and diabetes does not raise conflicts with the generally known facts of the natural history and biology of both diseases. On the contrary, there are biological mechanisms by which diabetes could affect the periapical status and vice-versa (Segura-Egea et al. (2015). In diabetic patients, impaired innate immunity, hyperglycaemia and high serum levels of advanced glycation end products (AGEs), would predispose to chronic inflammation, diminishing tissue repair capacity, impairing bone turnover, and delaying periapical wound healing in RFT, increasing the prevalence of persistent apical periodontitis. Few studies have investigated these suggested mechanisms, so the fulfilment of the criteria of coherence and biological plausibility cannot be definitively stablished. In relation to the clinical studies, Rudranaik et al. (2016) found that type 2 diabetics had chronic and larger sized lesions when compared to control subjects, showing delayed clinical and radiographic healing. However, Rudranaik et al. (2016) used very strict criteria (Strindberg 1956) to assess periapical status, so slower healing could easily be interpreted as failure. If they had used the PAI index (Ørstavik et al. 1986), including 'healing' lesions, the outcome and the interpretation could be categorized as slower healing, as shown in the studies of Fouad & Burleson (2003) and Arya et al. (2017). In short, taking together the results of the clinical studies (Fouad & Burleson 2003, Rudranaik et al. 2016, Arya et al. 2017) diabetic patients are associated with successful root canal treatment but with a slower healing rate.

Regarding the possible repercussion of periapical inflammation on diabetic health, chronic periapical inflammation involves activation of the broad axis of innate immunity through the lipopolysaccharide from anaerobic gram-negative bacteria, and could promote an increase in the overall insulin resistance, altering the metabolic control in diabetic patients (Segura-Egea et al. 2015).

In summary, an attempt has been made to analyse each of the Hill criteria to the association between Endodontics-diabetes. The association between diabetes and the prevalence of apical periodontitis and RCT has only a tentative link with causation. On the contrary, the scientific evidence demonstrates a larger

percentage of RFT with apical periodontitis and lower retention of root filled teeth in diabetic patients compared to control subjects. The significant ORs calculated in two systematic reviews with meta-analysis (Segura-Egea et al. 2016, Cabanillas-Balsera et al. 2019) give strength to the association between diabetes and RCT outcome.

However, although the association between the outcome of RCT and diabetes seems to fulfil most of Hill's causation criteria, the design of the studies on which this conclusion is based does not rule out the presence of confounding variables. In particular, the higher percentage of RFT with apical periodontitis and lower retention of RFT teeth in diabetics could reflect not only the success rate of RCT and the healing of AP, but also the incidence of caries and periodontal disease in diabetic subjects. Unfortunately, studies relating these variables (diabetes, caries, periodontal disease, AP, RFT and extractions, including the primary cause of extraction) are lacking.

These conclusions should be translated to the clinical practice. Dentists should be aware of the relationship between DM and the outcome of RCT, considering diabetes as a preoperative factor that could influence the outcome of the root canal treatment.

5. CONCLUSIONS

The results of the studies on Endodontic Medicine cannot be interpreted without taking account of the causation criteria. The OR values evaluated separately, although being high and significant, do not indicate by themselves causal associations. The two variables analysed are associated by having common risk factors, but without the existence of a cause–effect relationship between them. The analysis of the temporal relationship, the dose–response gradient, the consistency of the association, the coherence and biological plausibility of the association should be analysed and discussed to be able to conclude that the association is causal.

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DISCUSIÓN

Diabetes mellitus y pronóstico del tratamiento de conductos

El primer objetivo de este trabajo de tesis doctoral es determinar la posible asociación entre la diabetes mellitus y el fracaso del tratamiento endodóntico. Desde hace varias décadas, se han llevado a cabo numerosas investigaciones tanto en estudios animales como en humanos analizando diferentes variables que pueden verse afectadas por esta asociación.

Las revisiones sistemáticas con metaanálisis llevadas a cabo indican que la diabetes mellitus se asocia significativamente con una mayor prevalencia de lesiones radiolúcidas periapicales en dientes endodonciados (OR = 1.42; IC 95% = 1.11–1.80; p < 0,05) (Segura-Egea *et al.* 2016) y con una mayor prevalencia de dientes endodonciados extraídos (OR = 2.44; IC 95% = 1.54–3.88; p < 0.05) (Cabanillas-Balsera *et al.* 2019). Posteriormente, una "*umbrella review*" o "revisión de revisiones" que incluyó ambos metaanálisis (Nagendrababu *et al.* 2020*a*), ha ratificado estas asociaciones. Por tanto, podríamos concluir que la diabetes mellitus es un factor pronóstico negativo en el tratamiento endodóntico.

Sin embargo, para poder aseverar una posible relación, deben existir mecanismos biológicos que justifiquen y den explicación a esta vinculación.

En este sentido, los pacientes con diabetes mellitus presentan principalmente tres alteraciones que podrían estar relacionadas con la mayor probabilidad de fracaso del tratamiento endodóntico (Segura-Egea *et al.* 2015):

a) Deterioro de la inmunidad innata. La diabetes mellitus altera la función celular de la inmunidad innata, primera línea de defensa contra los patógenos. La fagocitosis mediada por neutrófilos disminuye y se estimula un aumento de la producción de citoquinas proinflamatorias por activación de los macrófagos (Lima *et al.* 2013). Sin embargo, la hiperglucemia característica de la diabetes mellitus puede generar disfunción macrofágica, resultando en un estado inflamatorio que deteriora la proliferación celular y la reparación tisular del huésped (Garber *et al.* 2009).

b) Productos finales de glicación avanzada (AGEs). Los AGEs se sintetizan mediante la glucemia no enzimática y la oxidación de proteínas, lípidos y ácidos nucleicos durante la hiperglucemia crónica.
Los AGEs van a unirse a receptores específicos en macrófagos (RAGE) aumentando el estrés oxidativo celular y activando el factor nuclear-kappa beta (NF-κβ), generando un aumento de citoquinas proinflamatorias, como la IL-1β o TNF-α (Cai *et al.* 2012).
Por otro lado, la unión de los AGE al colágeno provoca alteraciones en el metabolismo óseo, reduciendo la formación ósea y la proliferación y diferenciación de células osteoblásticas. Además, los AGE son causa de disfunción endotelial, disminuyendo el aporte de oxígeno, nutrientes y células defensivas a los tejidos periapicales dañados (Lima *et al.* 2013, Tanaka *et al.* 2013).

c) Hiperglucemia. El estado hiperglucémico, además de provocar AGEs y alteraciones estructurales en la pulpa dental y los tejidos periapicales por el deterioro de la vascularización, provoca apoptosis de osteoblastos y fibroblastos, inhibición de la producción de colágeno e inhibición de la proliferación y diferenciación de las células osteoblásticas. Esto, junto con un incremento de la actividad de las células osteoclásticas diferenciadas, predispone a un aumento de la reabsorción ósea (Dienelt & Zur Nieden 2011).

Como resultado, la diabetes mellitus predispone a la inflamación crónica, con aumento de IL-1β, IL-6, IL-8, IL-10, TNF-α y activación del ligando del receptor para el factor nuclear kappa B (RANKL), disminuyendo la capacidad reparativa de los tejidos, provocando un aumento de la susceptibilidad a las infecciones, y retrasando la cicatrización de heridas. De esta manera, la diabetes mellitus puede comprometer la respuesta inmune periapical, predisponiendo al fracaso del tratamiento endodóntico (Figura 15).

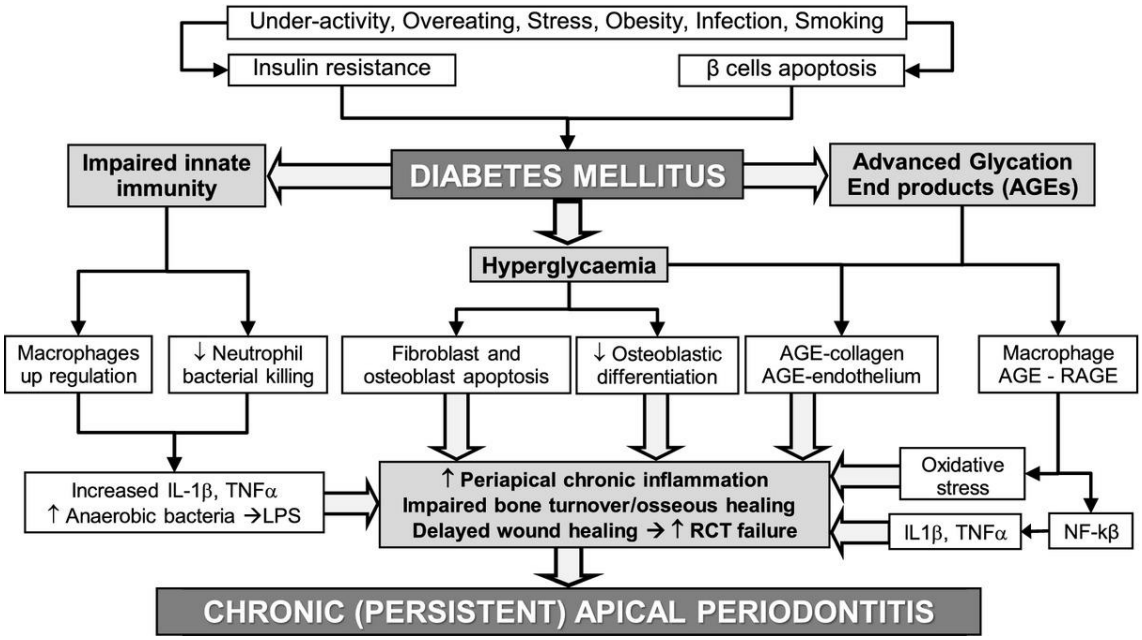

Figura 15. Mecanismos biológicos por los cuales la diabetes mellitus (DM) puede influir en el estado periapical (Segura-Egea et al. 2015).

Por otro lado, la inflamación crónica periapical puede inducir o perpetuar un estado inflamatorio crónico sistémico. El LPS de bacterias gram-negativas anaeróbicas causantes de la periodontitis apical se une a sus receptores específicos en las células inmunes (TLR) y activa las vías intracelulares, específicamente la NF-Kβ en los macrófagos que regulan positivamente las citocinas proinflamatorias, como IL-1β, IL-6, IL-8, TNF-α y PGE2, lo que contribuye a un estado sistémico proinflamatorio (Pickup 2004, Segura-Egea *et al.* 2015).

La activación de estas vías inflamatorias como respuesta a una periodontitis apical en células inmunes, células endoteliales, adipocitos, páncreas, hepatocitos y células musculares podría promover un desarrollo y aumento de la resistencia general a la insulina, alterando el control metabólico en pacientes con diabetes mellitus y/o periodontitis apical crónica (Segura-Egea *et al.* 2012).

Esto podría generar un ciclo donde la periodontitis apical predispone a la diabetes mellitus mediante la generación de un estado sistémico proinflamatorio, que a su vez, predispone al fracaso del tratamiento de conductos y al mantenimiento de la periodontitis apical persistente (Figura 16).

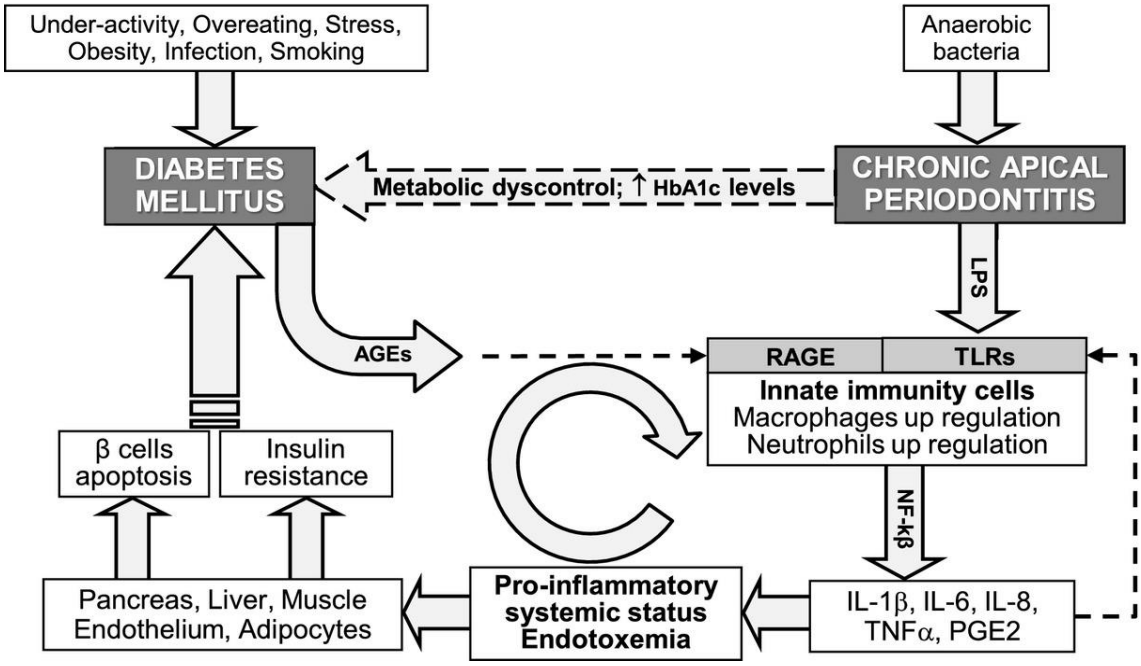

Figura 16. Mecanismos biológicos por los cuales el estado periapical podría influir en el control metabólico (Segura-Egea et al. 2015).

SEGUNDA PARTE

HÁBITO TABÁQUICO Y PRONÓSTICO DEL TRATAMIENTO DE CONDUCTOS

CAPÍTULO IV

Smoking and Radiolucent Periapical Lesions in Root Filled Teeth: Systematic Review and Meta-Analysis

Capítulo publicado en:

Cabanillas-Balsera D; Segura-Egea JJ; Bermudo-Fuenmayor M; Martín-González J; Jiménez-Sánchez MC; Areal-Quecuty V; Sánchez-Domínguez B; Montero-Miralles P; Velasco-Ortega E (2020) Smoking and Radiolucent Periapical Lesions in Root Filled Teeth: Systematic Review and Meta-Analysis. *Journal of Clinical Medicine* **9**, 3506.

ABSTRACT

Aim: This systematic review and meta-analysis aimed to investigate the association between smoking habits and the prevalence of radiolucent periapical lesions (RPLs) in root-filled teeth (RFT).

Methods: The Population, Intervention, Comparison, and Outcome (PICO) question was: in adult patients who have RFT, does the absence or presence of a smoking habit affect the prevalence of RPLs associated with RFT? Systematic MEDLINE/PubMed, Wiley Online Database, Web of Science, Scopus, and PRISMA protocol were used to evaluate and present the results. Studies comparing smokers with control non-smoker subjects, including RFT, and providing data on the prevalence of RFT with RPLs, were included. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used for certainty in the evidence. The risk of bias was assessed according to Cochrane Collaboration common scheme for bias and ROBINS-I tool. Cumulative meta-analysis was performed with a random effects model. PROSPERO registration code: CRD42020165279.

Results: Four studies reported data on inclusion criteria, representing data from 9257 root-filled teeth—4465 from non-smokers and 4792 from smoker patients. The meta-analysis provided an odds ratio indicating a significant association between smoking and higher prevalence of root filled teeth with radiolucent periapical lesions (OR = 1.16; 95% CI = 1.07–1.26; p = 0.0004). The certainty of the literature assessment was moderate per GRADE. The ROBINS-I tool classified three studies as low risk of bias, and the fourth as moderate risk of bias.

Conclusions: Moderate, quality scientific evidence indicates a weak but significant relationship between smoking and the prevalence of RPLs in RFT. Smoking can be considered a negative prognostic factor for the outcome of root canal treatment. Endodontic providers should be aware of the relationship between smoking and persistent apical periodontitis, assessed as RPLs, in RFT.

Keywords: endodontic medicine; persistent apical periodontitis; radiolucent periapical lesion; root canal treatment outcome; root-filled teeth; smoking habits

1. INTRODUCTION

Apical periodontitis (AP) is an inflammatory reaction in the periradicular tissues, induced and maintained by bacterial infection of the root canal system [1]. The prevalence of AP is 0.6–20% for teeth [2,3]. AP is radiographically diagnosed by a disruption of the lamina dura and a radiolucent area encircling the root apex, namely, a radiolucent periapical lesion (RPL) [4]. Teeth with AP, when restorable, should be treated with root canal treatment (RCT) [5]. A key goal of RCT is to seal the apical third of the root canal, interrupting the passage of bacterial antigens from the pulp space to the periapical tissues. If this is not achieved, the root-filled tooth continues to show a radiolucent image around its apex, suffers from apical periodontitis [6,7,8], and presents—to some extent and severity—periapical inflammation [9]. RFT with AP in asymptomatic patients exhibited less pronounced and relatively smaller areas of inflammation [9]. Although radiographic signs of AP are found in 25 to 61% of asymptomatic RFT [3], not in all cases imply the failure of RCT. The healing after RCT may result in the formation of fibrous tissue composed of dense collagen fibers, few cells, and little or no inflammation, which may be regarded as scar tissue [10].

Apical periodontitis is not always the result of inadequate endodontic technique (including deficient aseptic control, missed canals, inadequate instrumentation, etc.) [11,12]. Sometimes, the systemic status of the patient, such as pro-inflammatory status or impaired immune response, can restrict periapical healing [13,14]. This could explain the association between diabetes and the failure of endodontic treatment, as recently demonstrated [15,16,17]. In short, the factors involved in the development of PAP and failure of RCT are many—it is difficult to assess the role that each of them plays. Knowing the possible influence of each one on the outcome of RCT can help to improve the information given to patients regarding the prognosis of RCT. In addition, it could help explain cases of patients in whom the failure of RCT is more frequent. This could be the case with tobacco smoking.

Habitual smoking, a systemic condition characterized by a pro-inflammatory status and impaired immune response and wound healing, has been associated

with poor prognosis of periodontal disease, oral cancer, oral mucosa lesions, caries, and high failure rate of dental treatments [18,19]. Defensive and reparative responses of dental pulp are decreased in smokers [20], and tobacco smoking is a risk factor for periapical disease—AP being more prevalent in smokers [21,22,23,24,25,26], probably because of impaired bone healing [27]. A recent systematic review and meta-analysis concluded that tobacco smokers have a prevalence of periapical periodontitis and root canal treatments greater than 2.5 times the prevalence of non-smokers [28]. In addition, another study indicates that RCT is almost two times more prevalent in smokers, with a dose–response relationship [23]. Nevertheless, other studies have found no significant differences in the prevalence of AP and RCT between smokers and non-smoking subjects [13,29,30].

The possible effect of smoking on the outcome of endodontic treatment has been investigated in several epidemiological studies, with contradictory conclusions [31,32,33]. The primary objective of this study was to carry out a systematic review and meta-analysis investigating the possible association between smoking habits and the failure of RCT, the primary outcome measure being the prevalence of RPLs in RFT.

2. METHODS

The protocol of this systematic review has been developed and registered in the PROSPERO database (PROSPERO 2020 CRD42020165279). The systematic review has been developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [33].

2.1. Review Question

The clinical Population, Intervention, Comparison, and Outcome (PICO) question to be answered was as follows: in adult patients who have root filled teeth, does the presence or the absence of smoking habits affect the prevalence

of RFT with RPLs? PICO (Population, Intervention, Comparison, and Outcome) schema for all the included studies to elaborate upon this research question were used to establish the eligibility criteria as follows:

Population: adult patients having root-filled teeth.

Intervention: presence of smoking habits; smoker.

Comparison: absence of smoking habits; non-smoker.

Outcome: prevalence of RFT with RPLs.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria established were: (a) epidemiological studies published from January 1980 to June 2020; (b) studies comparing smoking patients with non-smoking subjects; (c) studies including RFT; (d) studies providing data on the prevalence of RFT with RPLs, both in smoking patients and in control non-smoking subjects. Exclusion criteria were defined as: (a) studies carried out in animals or in cell culture, and (b) studies reporting data only from smoking subjects. When there was no initial agreement among the reviewers, consensus was reached through dialogue.

2.3. Literature Search

Once the PICO question was established, the search strategy was designed [34,35]. Studies located in the search were selected according inclusion and exclusion criteria, quality evaluation, and data extraction and analysis. A literature search in MEDLINE/PubMed, Scopus, Web of Science, and Wiley Online Database was achieved, using the following Mesh terms and keywords: (tobacco OR smoking OR smoker) AND (endodontics OR periapical periodontitis OR periapical diseases OR apical periodontitis OR periradicular lesion OR periapical

radiolucency OR radiolucent periapical lesion OR root canal treatment OR root canal preparation OR root canal therapy OR root filled teeth OR endodontically treated teeth) (Box 1).

Box 1. MeSH and key words combinations used for the search strategy for the Population, Intervention, Comparison, and Outcome (PICO) question: In adult patients who have root filled teeth, does the absence or presence of smoking habits affect the prevalence of root filled teeth with radiolucent periapical lesions?

((“tobacco”[MeSH Terms] OR “tobacco”[All Fields] OR “tobacco products”[MeSH Terms] OR (“tobacco”[All Fields] AND “products”[All Fields]) OR “tobacco products”[All Fields]) OR (“smoking”[MeSH Terms] OR “smoking”[All Fields]) OR (“smokers”[MeSH Terms] OR “smokers”[All Fields] OR “smoker”[All Fields])) AND ((“endodontics”[MeSH Terms] OR “endodontics”[All Fields]) OR (“periapical periodontitis”[MeSH Terms] OR (“periapical”[All Fields] AND “periodontitis”[All Fields]) OR “periapical periodontitis”[All Fields]) OR (“periapical diseases”[MeSH Terms] OR (“periapical”[All Fields] AND “diseases”[All Fields]) OR “periapical diseases”[All Fields]) OR (“periapical periodontitis”[MeSH Terms] OR (“periapical”[All Fields] AND “periodontitis”[All Fields]) OR “periapical periodontitis”[All Fields] OR (“apical”[All Fields] AND “periodontitis”[All Fields]) OR “apical periodontitis”[All Fields]) OR (Periradicular[All Fields] AND Lesion[All Fields]) OR (Periapical[All Fields] AND Radiolucency[All Fields]) OR (Radiolucent[All Fields] AND Periapical[All Fields] AND Lesion[All Fields]) OR ((“dental pulp cavity”[MeSH Terms] OR (“dental”[All Fields] AND “pulp”[All Fields] AND “cavity”[All Fields]) OR “dental pulp cavity”[All Fields] OR (“root”[All Fields] AND “canal”[All Fields]) OR “root canal”[All Fields]) AND (“therapy”[Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “therapeutics”[MeSH Terms] OR “therapeutics”[All Fields])) OR (“root canal preparation”[MeSH Terms] OR (“root”[All Fields] AND “canal”[All Fields] AND “preparation”[All Fields]) OR “root canal preparation”[All Fields]) OR (“root canal therapy”[MeSH Terms] OR (“root”[All Fields] AND “canal”[All Fields] AND “therapy”[All Fields]) OR “root canal therapy”[All Fields]) OR ((“plant roots”[MeSH Terms] OR (“plant”[All Fields] AND “roots”[All Fields]) OR “plant roots”[All Fields] OR “root”[All Fields]) AND Filled[All Fields] AND (“tooth”[MeSH Terms] OR “tooth”[All Fields] OR “teeth”[All Fields])) OR (“tooth, nonvital”[MeSH Terms] OR (“tooth”[All Fields] AND “nonvital”[All Fields]) OR “nonvital tooth”[All Fields] OR (“endodontically”[All Fields] AND “treated”[All Fields] AND “teeth”[All Fields]) OR “endodontically treated teeth”[All Fields]))

A hand-search was also carried out in main endodontic journals (International Endodontic Journal, Journal of Endodontics, and Australian Endodontic Journal) and in the references of significant papers and reviews. The last search was made in June of 2020.

Electronic and manual searches provided the titles and abstracts of articles related to the aims of the studies, which were categorized by three independent researchers (D.C.-B., M.C.J.-S., and J.J.S.-E.) according to the inclusion and exclusion criteria. Articles selected were reviewed in full by five investigators (D.C.-B., J.M.-G., E.V.O., M.C.J.-S., and J.J.S.-E.).

2.4. Data Extraction

The methodology of selected studies was examined and main features were extracted and compiled, including: authors, date of publication, study design, subjects and sample size, main quantitative results and odds ratio values, and diagnoses of RPLs. Data extraction was performed by seven investigators (D.C.-B., J.M.-G., M.C.J.-S., E.V.O., B.S.-D., P.M.-M., and J.J.S.-E.). Disagreements were resolved by discussion among the six and reaching an agreement by majority.

2.5. Outcome Variables and Statistical Analysis

The primary outcome measure was the prevalence of RFT with RPL. Odds ratio (OR), with its 95% confidence interval (CI), was calculated in every selected study trying to measure the effect of the relationship between smoking habits and the outcome of RCT. A random-effect model meta-analysis, on the basis of the DerSimonian–Laird method, was performed to determine the pooled OR and its 95% CI. To determine the heterogeneity amongst trials, the Breslow–Day test (BDT) and the Higgins I2 test were employed, taking into account that substantial heterogeneity is considered if I2 test is higher than 50% [36]. To illustrate the homogeneity, L'Abbé plots [37] were used. To show the OR results, a forest plot

[38] was used, along with the DerSimonian–Laird pooled estimate. Finally, a level of $p = 0.05$ was considered significant. The meta-analyses were calculated with the StatsDirects software (London, UK) [39].

2.6. Quality Evidence Assessment and Risk of Bias in Individual Studies

Quality evidence assessment and risk of bias in individual studies. The quality of evidence of the included studies was analyzed according to the guidelines provided by the Centre for Evidence-Based Medicine at Oxford [40]. The certainty in the evidence was assessed using the GRADE tool (GRADEpro GDT: GRADEpro Guideline Development Tool (Software)) available from gradepro.org: https://gdt.gradepro.org/app/handbook/handbook.html#h.rkkjpmwb6m6z [41].
The GRADE tool has five domains: risk of bias, inconsistency, imprecision, indirectness, and publication bias, which can be downgraded and reduce the quality of the evidence [42]. Articles were assessed independently by 5 reviewers (J.J.S.E., J.M.G., D.C.B., E.V.O., and M.C.J.S.) and cases of disagreements in the risk of bias were discussed until a consensus was achieved. The risk of bias of the included studies was assessed according to Cochrane Collaboration common scheme for bias and ROBINS-I tool [43], initially described to assess nonrandomized studies of interventions, but currently also available for observational designs (https://methods.cochrane.org/robins-i-tool).

3. RESULTS

The search strategy is presented in Figure 1. After searching databases and hand-searching relevant bibliographies/papers, 1075 articles were recovered. Excluding duplicates articles (n = 733) and publications before 1980 (n = 3), 339 articles were checked to satisfy the selection criteria by title and abstract, declaring 14 articles for full text review. Among these, ten articles were excluded for the following reasons: four did not deal with the specific topic [25,26,44,45],

five did not provide necessary data for meta-analysis [13,46,47,48,49], and one did not provide data on the frequency of AP at the root-filled teeth [50] (Table 1).

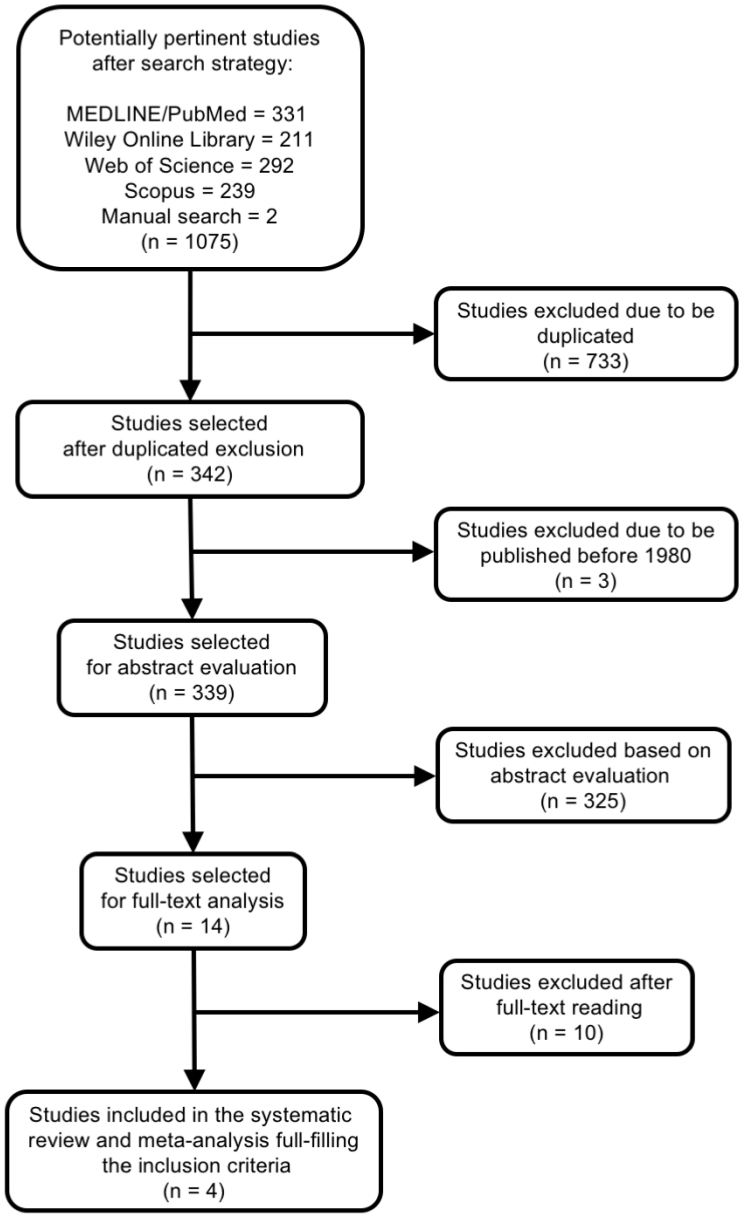

Figure 1. Selection process of the studies included in the systematic review and meta-analysis.

Table 1. Studies excluded in the systematic review of association between smoking habits and the prevalence of radiolucent periapical lesions (RPLs) in root-filled teeth (RFT). Excluded reason, authors, and year of these studies.

Excluded Reason	Authors	Year/Reference
Not specific topic	1. Kirkevang et al.	2007/[46]
	2. López-López et al.	2012/[25]
	3. Oginni et al.	2015/[26]
	4. Olcay et al.	2018/[44]
Not provide necessary data to meta-analysis	5. Marending et al.	2005/[13]
	6. Peršić Bukmir et al.	2016/[49]
	7. Al-Nazhan et al.	2017/[48]
	8. Pirani et al.	2018/[46]
	9. Alghofaily et al.	2018/[47]
Not provide data of RPLs in RFT	10. Doyle et al.	2007/[50]

3.1. Study Characteristics

Four studies were finally included in the analysis: (1) Segura-Egea et al. (2008) [24]; (2) Segura-Egea et al. (2011) [51]; (3) Jansson (2015) [52]; (4) Sopińska and Bołtacz-Rzepkowska (2020) [53]. Study design, study sample, diagnosis of RPL, main results, and evidence level are summarized in Table 2.

Table 2. Studies about smoking habits and the prevalence of root filled teeth (RFT) with radiolucent periapical lesions (RPLs) included in the systematic review. Study design, subjects and sample size, diagnosis of RPL, main results, and evidence level.

Authors/Year/Ref.	Study Design	Subjects	Diagnosis of RPLs	Main Results	Evidence Level
Segura-Egea et al. 2008 [24]	Cross-sectional	Controls: 71 Smokers: 109	14 periapical radiographs Paralleling technique Periapical Index (PAI)	No association; $p = 0.6868$	4
Segura-Egea et al. 2011 [51]	Cross-sectional	Controls: 50 Smokers: 50	14 periapical radiographs Paralleling technique Periapical Index (PAI)	No association; $p = 0.9857$	4
Jansson 2015 [52]	Cross-sectional	Controls: 576 Smokers: 576	18 periapical radiographs Widened periodontal space and not visible lamina dura	Association; $p = 0.00045$	4
Sopińska and Bołtacz-Rzepkowska 2020 [53]	Cross-sectional	Controls: 317 Smokers: 386	Panoramic radiograph Twice width periodontal space or demarcated with osteosclerotic border	No association; $p = 0.451$	4

3.2. Meta-Analysis

Data from selected articles were analyzed and summarized in an evidence table containing the descriptive statistics and ORs calculated (Table 3). An overall OR greater than one implies that smoker patients present a higher prevalence of RFT with RPLs, compared to control subjects. Homogeneity among included studies was examined by Breslow–Day test (BDT)—the result was non-significant (Breslow–Day = 0.71; df = 3; p = 0.87) (Figure 2, L'Abbé plot). Moreover, heterogeneity test value (I^2 = 0%; 95% CI = 0% to 67.9%) was very low, so the proportion of variation through studies due to heterogeneity is not probable. The weights were calculated using a random effects model, allowing the study outcomes to vary in a normal distribution. Global OR was calculated using DerSimonian–Laird method with random effects, resulting in an OR = 1.16

(95% CI = 1.07–1.26; *p* = 0.0004). The ORs for each study and the pooled OR from the meta-analysis are shown in a forest plot (Figure 3). The results of the meta-analysis indicate that the prevalence of RFT associated with RPLs in smoking patients differs significantly from the prevalence in control subjects.

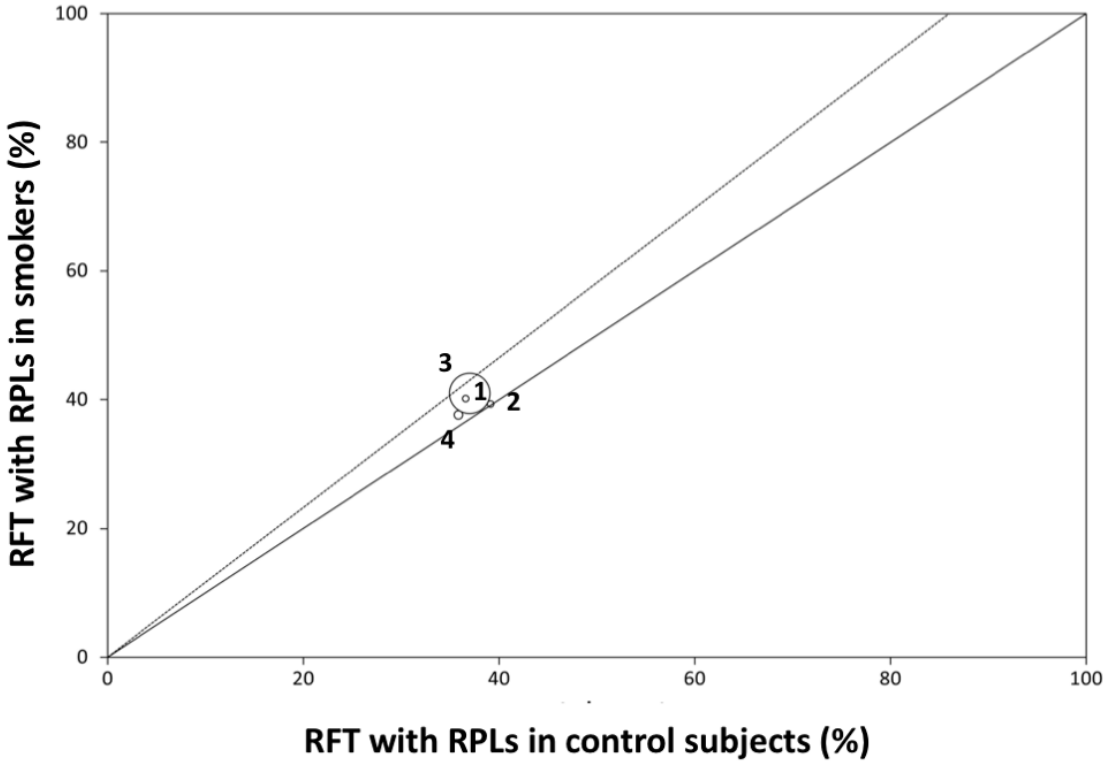

Figure 2. L'Abbé plot presenting the prevalence of root filled teeth (RFT) with radiolucent periapical lesions (RPLs) in each of the four studies in smoker patients and healthy controls. Circles of different sizes represent the weights of the sample of each study (1) Segura-Egea et al. (2008) [24]; (2) Segura-Egea et al. (2011) [51]; (3) Jansson (2015) [52]; (4) Sopińska and Bołtacz-Rzepkowska (2020) [53].

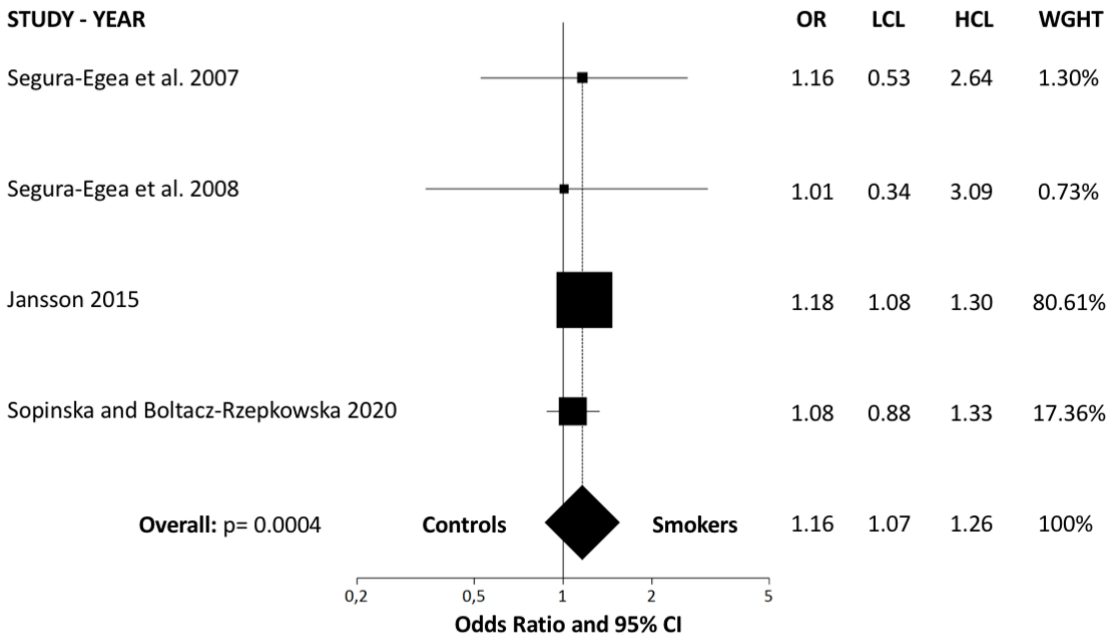

Figure 3. Forest plot of ORs and 95% confidence limits (CLs) for the comparison of smokers and healthy control subjects regarding the prevalence of root filled teeth (RFT) with radiolucent periapical lesions (RPLs). Overall estimate is based on data from the four studies. Black squares represent the point estimates of the OR and have areas proportional to study size. Lines represent 95% confidence intervals. The diamond shows the summary statistics for the four studies. The solid line indicates an OR of 1.0, and the dashed line indicates the overall odds ratio. OR: odds ratio; LCL: lower confidence level; UCL: upper confidence level.

Table 3. Studies about smoking habits and the prevalence of root filled teeth (RFT) with radiolucent periapical lesions (RPLs). Results extracted and compiled, descriptive statistics, and calculated odds ratios.

Authors/Ref.	No. RFT	Control Subjects		Smoker Patients		Odds Ratio (95% CI)	*p*
		RFT*RPL/Total RFT	RFT*RPL (%)	RFT*RPL/Total RFT	RFT*RPL (%)		
1. Segura-Egea et al. 2008 [24]	153	15/41	37%	45/112	40%	1.16 (0.53–2.64)	$p = 0.69$
2. Segura-Egea et al. 2011 [51]	84	9/23	39%	24/61	39%	1.01 (0.34–3.09)	$p = 0.99$
3. Jansson 2015 [52]	7368	1363/3684	37%	1510/3684	41%	1.18 (1.08–1.30)	$p = 0.0005$
4. Sopińska and Bołtacz-Rzepkowska 2020 [53]	1652	257/717	36%	352/935	38%	1.08 (0.88–1.33)	$p = 0.451$
Overall	9257	1644/4465	36.82%	1931/4792	40.30%	**1.16 * (1.07–1.26)**	***p*= 0.0004**

* DerSimonian–Laird variance formula: $Chi^2 = 12.338298$, $p = 0.0004$.

3.3. Interpretation and Assessment of the Included Studies

The four studies included in the meta-analysis (**Figure 4**) were cross-sectional, all published between 2008 and 2020. The data obtained from the studies, 9257 RFT, 4465 in non-smoker control subjects and 4792 in smoker patients, were compiled.

Certainty assessment							Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Extracted root-filled teeth								
4	observational studies	not serious [a]	not serious [b]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	⨁⨁⨁◯ MODERATE	IMPORTANT

Figure 4. GRADE Working Group grades of evidence: Smoking habits and the prevalence of radiolucent periapical lesions in root-filled teeth. Explanations: a. Detailed in Figure 5: Risk of bias summary, b. I^2 = 0%. High certainty: the authors have a lot of confidence that the true effect is similar to the estimated effect. Moderate certainty: the authors believe that the true effect is probably close to the estimated effect. Low certainty: the true effect might be markedly different from the estimated effect. Very low certainty: the true effect is probably markedly different from the estimated effect.

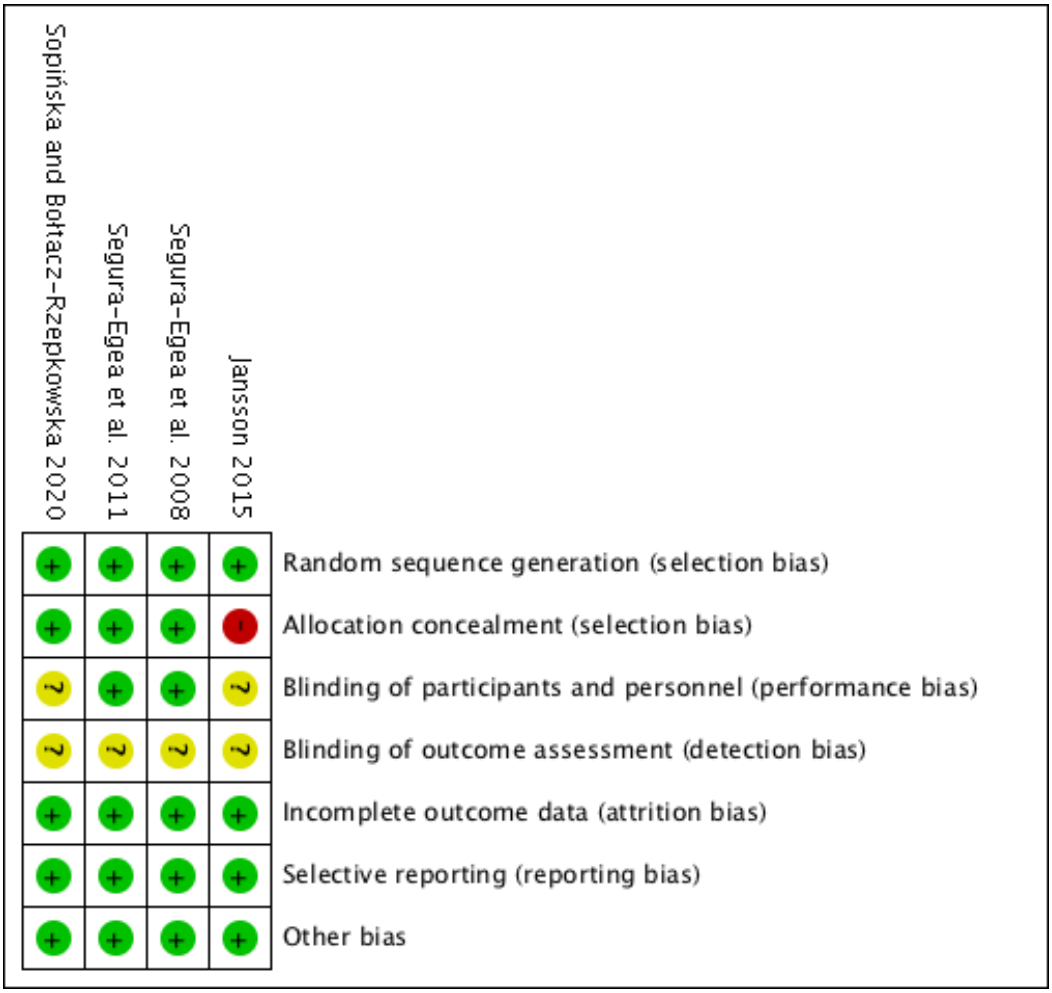

Figure 5. Risk of bias summary of studies included according to the Cochrane Collaboration's tool for assessing risk of bias. + Low risk of bias. − High risk of bias. ? Unclear risk of bias.

The prevalence of apical periodontitis amongst smokers was investigated in the study of Segura-Egea et al. [24], who concluded there is a significantly association between smoking and increased prevalence of AP and higher frequency of RCT. However, although the presence of AP in RFT was higher in smoker patients (71%) with respect to non-smokers (55%), the difference was not significant (OR = 1.16; 95% CI = 0.53–2.64; p = 0.69).

Another study by Segura-Egea et al. [51], carried out in hypertensive patients, analyzed the interrelationship between endodontic variables and smoking habits. Although significantly higher prevalences of AP and RCT were found in smokers, the frequency of RFT with AP in smoker hypertensive patients (64.9%) was not higher than in non-smoker patients (64.3%) (OR = 1.01; 95% CI = 0.34–3.09; p = 0.99).

The study of Jansson et al. [52] aimed to investigate the relationship between the presence of AP in RFT and marginal bone loss. The results showed a significant correlation between smoking and the prevalence of RFT with AP, this prevalence being 41% in smokers and 37% in non-smoker subjects (OR = 1.18; 95% CI = 1.08–1.30; p = 0.00045). However, multiple regression analysis indicated that the relative frequency of RFT with AP was significantly associated with more marginal bone loss, irrespective of age, number of remaining teeth, relative frequency of root-filled teeth, and smoking habits.

Finally, the recent study conducted by Sopińska and Bołtacz-Rzepkowska [53] aimed to evaluate the influence of smoking on the prevalence of AP in the population of the Łódź region, Poland. Results show no difference in the frequency of RFT with AP between smokers (37.6%) and control subjects (35.8%) (OR = 1.08; 95% CI = 0.88–1.33; p = 0.451).

3.4. Quality Evidence and Risk of Bias Assessment

The scores for the methodological quality of the articles included in this systematic review are given in Table 2. The Centre for Evidence-Based Medicine

at Oxford [40] scores for the studies were low, all of them rated with level 4. The GRADE tool demonstrated a moderate quality of the evidence for the included studies (Figure 4). According to ROBINS-I tool, from the four included studies, three were classified as low risk of bias, with only one or two domains as unclear risk of bias (Segura-Egea et al. 2008, Segura-Egea et al. 2011, Sopińska and Bołtacz-Rzepkowska 2020), and the other was classified as moderate risk of bias with one domain as high and two domains as unclear risk of bias (Jansson 2015) (Figure 5).

4. DISCUSSION

This study aimed to analyze the possible link between smoking habits and the outcome of RCT. Therefore, a systematic review and meta-analysis has been conducted, including the available evidence about the prevalence of RFT with RPLs. After the literature search, four studies were included in the final analysis, all analyzing the prevalence of RFT with RPLs [24,48,49,50,51,52,53] in both smokers and non-smoker subjects. The four studies were cross-sectional studies.

The four included studies analyzed 9257 root-filled teeth, 4465 in non-smokers and 4792 in smoker patients. The random effects model was used to calculate overall ORs, allowing the study outcome to vary in a normal distribution. The heterogeneity value in the primary outcome measure was null (0%), suggesting that there is no variability between the studies. For the association between smoking habits and the prevalence of RFT with RPL, the DerSimonian–Laird method reported an overall OR = 1.16, statistically significant (p = 0.0004). Thus, the results of the present meta-analysis suggest that smoking habits increase the risk of failure of RCT and the prevalence of RPLs in RFT. The RFT of a smoking patient are 1.16 times more likely to have radiolucent periapical lesions compared to non-smoking subjects.

Smoking has been recognized as an important risk factor for cardiovascular disease [54] and periodontal disease, increasing inflammation of the

periodontium and marginal bone loss [52,55,56,57]. Moreover, a significant association between AP and smoking habits has been described [21,22,25,42]. The results of the systematic review carried out by Aminoshariae et al. [58] analyzing the association between smoking and the prevalence of apical periodontitis, suggest that smoking was associated with the prevalence of AP in cross-sectional studies and case control studies. A systematic review with meta-analysis has just been published reporting a significant association between smoking and the loss of root-filled teeth [59]. However, the associations between smoking and the prevalence of AP have not been investigated so far by meta-analysis. The results of the present study fill this knowledge gap.

Smoking could influence the outcome of RCT, probably impairing periapical status of RFT, maintaining the periapical bone destruction, and decreasing the healing after RCT [14]. The effect of tobacco smoking on periapical disease has biological plausibility and can be explained by several biological mechanisms [14]. Smoking habits provoke impaired functions of leukocytes, macrophages, and T-cell lymphocytes, with decreased levels of antibodies [60], and increased levels of pro-inflammatory mediators, such as IL-6, TNF-α, and C-reactive protein [61,62,63,64]. Smoking also causes morphological and functional alterations of the microcirculation. Increased carboxyhemoglobin levels and oxidative stress injure microvascular function, decreasing the oxygen supply and nutrient delivery [65]. It can be hypothesized that inflamed periapical tissues in smokers could experience restrictions in nutrients and oxygen supply [14]. On the other hand, tobacco smoking has been shown to cause delay fibroblast migration to the wound area and fibroblast dysfunction [66]. Finally, a local and direct pro-inflammatory effect of smoking on periapical tissues has been demonstrated. In smokers with granuloma due to AP, the products of lipid peroxidation, as 8-iso-PGF(2a) and products of the LOX-pathway, were increased at the expense of cyclooxygenase products [67]. Therefore, smoking decreases bone healing and tissue response, due to high stimulation of osteoclastic cells and reduced angiogenesis [29,68].

The results of the present systematic review and meta-analysis should be valued with caution. According to the Centre for Evidence-Based Medicine at

Oxford [40], the quality level of the four included studies is low. This could be considered a limitation of the study. However, the ROBINS-I tool classified as low risk of bias three of the included studies, and the GRADE tool demonstrated a moderate strength of evidence, indicating that the true effect is probably comparable to the estimated effect. Prospective studies comparing the outcome of endodontic treatment in smokers and non-smokers should be carried out, taking into account the amount of tobacco smoked and the time during which the patients have been smokers.

The present systematic review has some limitations. The included studies considered that a radiolucency associated with a RFT was a sign of AP. However, in a cross-sectional study it is not possible to know if the RPL is disease or healing in progress. Furthermore, the healing after RCT may result in the formation of scar tissue [10]. The method to assess the periapical status is an important factor that should be taken into account, and it is different in each of the studies included in the review. Moreover, the included studies used conventional radiographs or panoramic radiographs for the diagnosis of AP. Future studies evaluating periapical lesions should include three-dimensional diagnostic methods, such as CBCT. CBCT allows radiological signs to be identified with greater sensitivity, so it better evaluates changes in hard tissue and periapical bone repair [69,70].

5. CONCLUSIONS

Available scientific evidence indicates a weak but significant relationship between smoking and apical periodontitis in root filled teeth. However, the quality of the evidence is moderate. Better-designed longitudinal studies are necessary to define with accuracy the impact of smoking on the outcome of RCT. Meanwhile, habitual smoking should be considered a preoperative risk factor for RCT, since it reduces or limits its success, increasing the frequency of periapical lesions in endodontically treated teeth.

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CAPÍTULO V

Cigarette Smoking and Root Filled Teeth Extraction: Systematic Review and Meta-Analysis

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ABSTRACT

Aim: The aim of this systematic review and meta-analysis was to investigate the possible association between smoking habits and the occurrence of root-filled teeth (RFT) extraction.

Material and Methods: The Population, Intervention, Comparison, and Outcome (PICO) question was in adult patients who had RFT, does the absence or presence of smoking habits affect the prevalence of extracted RFT? Systematic MEDLINE/PubMed, Wiley Online Database, Web of Science, and PRISMA protocol was used to evaluate and present the results. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used for certainty in the evidence. The risk of bias was assessed according to Cochrane Collaboration common scheme for bias and ROBINS-I tool. Cumulative meta-analysis was performed with a random effects model. PROSPERO registration code: CRD42020165279.

Results: After search strategy, 571 articles were recovered, seven were selected for full-text analysis, and two reported data on inclusion criteria, including 516 RFT, 351 in non-smokers, and 165 in smoker subjects. The meta-analysis provided an odds ratio indicating significant association between smoking and the prevalence of extracted RFT (OR = 3.43, 95% CI = 1.17–10.05, $p = 0.02$, $I^2 = 64\%$). The certainty of the literature assessment was low per GRADE. Both studies were considered as moderate risk of bias.

Conclusions: Tobacco smoking should be considered a negative prognostic factor for the outcome of root canal treatment, although the quality of the evidence is low. RFT of smoking patients are three times more likely to be extracted. Continuing to smoke after endodontic treatment may increase the risk of treatment failure. However, the overall strength of evidence is low. This must be considered a limitation of the present study and the conclusion should be valued with caution.

Keywords: endodontic medicine; endodontics; root canal treatment outcome; smoking habits; root-filled teeth extraction; tobacco smoking

1. INTRODUCTION

Periapical inflammatory reaction caused and maintained by bacterial antigens from the root canal is named apical periodontitis [1]. Apical periodontitis (AP) is a very prevalent disease, ranging 0.6–20% of teeth [2,3]. The diagnosis of AP is made by analyzing the patient's symptoms and signs, and can be confirmed radiographically by the disruption of the lamina dura and the presence of a radiolucent area encircling root apex, namely radiolucent periapical lesion (RPL) [4]. To cure AP, it is necessary to interrupt the passage of antigens from inside the root canal to the periapical tissue. This is achieved through root canal treatment (RCT) [5]. RCT can fail for different reasons [6], such as inadequate endodontic technique (including deficient aseptic control, missed canals, inadequate instrumentation, etc.) [7,8], root resorption, root fractures, or high bone lost [9,10,11], persisting periapical inflammation [12]. When it is not possible to perform non-surgical retreatment or apical surgery, RFT should be removed [13,14].

As mentioned above, the causes involved in extraction of RFT are many, being difficult to assess the role that each of them plays. One of the factors that has been studied in recent years is the systemic state of the patient [15,16]. Some systemic diseases can induce a pro-inflammatory status, altering immune response and impairing periapical healing [15,17]. This is the case of diabetes, which has recently been identified as a risk factor for non-retention of RFT [18].

Smoking coincides with diabetes in causing a systemic pro-inflammatory state and impaired immune response, having been associated with oral pathologies such as severe periodontal disease, pre-malignant lesions of the oral mucosa, oral cancer, caries, and high rate of treatment failure [19,20]. The dental pulp and periapical tissues of smokers show diminished defensive and reparative responses [21], as well as impaired bone healing [22]. Therefore, it is expected that the prevalence of AP is higher in smokers and, subsequently, that they also have a higher prevalence of RFT. A recently published systematic review with meta-analysis has concluded that smokers are 2.5 times more likely to have AP, being RCT almost three times more prevalent in smokers, compared to non-

smoker subjects [23]. Moreover, a dose-response relationship between tobacco smoking and RCT have been found [24]. However, the possible effect of smoking on the outcome of endodontic treatment and its influence on RFT loss is uncertain, reaching several epidemiological studies contradictory conclusions [15,25,26]. The aim of this systematic review and meta-analysis was to investigate the possible association between smoking habits and the prevalence of extracted RFT.

2. MATERIALS AND METHODS

The protocol of this systematic review has been developed and registered in the PROSPERO database (PROSPERO 2020 CRD42020165279). The systematic review has been developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [27].

2.1. Review Question

The present review focused on the following research question: Does the presence or absence of smoking habits affect the prevalence of extracted RFT in adult patients? PICO (Population, Intervention, Comparison, and Outcome) schema for all the included studies to elaborate upon this research question were used to establish the eligibility criteria as follows:

Population: Adults patients with root-filled teeth.

Intervention: Presence of smoking habits, smoker.

Comparison: Absence of smoking habits, non-smoker.

Outcome: Extraction of root-filled teeth.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria established were (a) epidemiological studies published between January 1980 to June 2020; (b) studies comparing smoking patients with non-smoking subjects; (c) studies including RFT; (d) studies providing data on the prevalence of extracted RFT, both in smoker subjects and in control non-smoking patients. Exclusion criteria were defined as (a) studies carried out in animals or in cell culture, and (b) studies reporting data only from smoking subjects. When there was no initial agreement among the reviewers, consensus was reached through dialogue.

2.3. Literature Search

Once the PICO question was established, the search strategy was designed [28,29]. Studies located in the search were selected according to inclusion and exclusion criteria, quality evaluation, and data extraction, and analysis. A literature search in MEDLINE/PubMed, Scopus, Web of Science, and Wiley Online Database was achieved using the following Mesh terms and keywords (Box 1): (Tobacco OR Smoking OR Smoker) AND (endodontic OR endodontics OR endodontic treatment OR root canal preparation OR root canal therapy OR root filled teeth OR endodontically treated teeth) AND (extraction OR retention OR dental avulsion OR avulsion OR tooth loss OR survival OR success OR failure OR outcome).

Box 1. MeSH and key words combinations used for the search strategy for the Population, Intervention, Comparison, and Outcome (PICO) question: In adult patients who had root filled teeth, does the absence or presence of smoking habits affect the prevalence of extracted root filled teeth?

((“tobacco”[MeSH Terms] OR “tobacco”[All Fields] OR “tobacco products”[MeSH Terms] OR (“tobacco”[All Fields] AND “products”[All Fields]) OR “tobacco products”[All Fields]) OR (“smoking”[MeSH Terms] OR “smoking”[All Fields]) OR (“smokers”[MeSH Terms] OR “smokers”[All Fields] OR “smoker”[All Fields])) AND (endodontic[All Fields] OR (“endodontics”[MeSH Terms] OR “endodontics”[All Fields]) OR (endodontic[All Fields] AND (“therapy”[Subheading] OR “therapy”[All Fields] OR “treatment”[All Fields] OR “therapeutics”[MeSH Terms] OR “therapeutics”[All Fields])) OR (“root canal preparation”[MeSH Terms] OR (“root”[All Fields] AND “canal”[All Fields] AND “preparation”[All Fields]) OR “root canal preparation”[All Fields]) OR (“root canal therapy”[MeSH Terms] OR (“root”[All Fields] AND “canal”[All Fields] AND “therapy”[All Fields]) OR “root canal therapy”[All Fields]) OR ((“plant roots”[MeSH Terms] OR (“plant”[All Fields] AND “roots”[All Fields]) OR “plant roots”[All Fields] OR “root”[All Fields]) AND filled[All Fields] AND (“tooth”[MeSH Terms] OR “tooth”[All Fields] OR “teeth”[All Fields])) OR (“tooth, nonvital”[MeSH Terms] OR (“tooth”[All Fields] AND “nonvital”[All Fields]) OR “nonvital tooth”[All Fields] OR (“endodontically”[All Fields] AND “treated”[All Fields] AND “teeth”[All Fields]) OR “endodontically treated teeth”[All Fields])) AND (extraction[All Fields] OR (“retention, psychology”[MeSH Terms] OR (“retention”[All Fields] AND “psychology”[All Fields]) OR “psychology retention”[All Fields] OR “retention”[All Fields]) OR ((“dental health services”[MeSH Terms] OR (“dental”[All Fields] AND “health”[All Fields] AND “services”[All Fields]) OR “dental health services”[All Fields] OR “dental”[All Fields]) AND (“fractures, avulsion”[MeSH Terms] OR (“fractures”[All Fields] AND “avulsion”[All Fields]) OR “avulsion fractures”[All Fields] OR “avulsion”[All Fields])) OR (“fractures, avulsion”[MeSH Terms] OR (“fractures”[All Fields] AND “avulsion”[All Fields]) OR “avulsion fractures”[All Fields] OR “avulsion”[All Fields]) OR (“tooth loss”[MeSH Terms] OR (“tooth”[All Fields] AND “loss”[All Fields]) OR “tooth loss”[All Fields]) OR (“mortality”[Subheading] OR “mortality”[All Fields] OR “survival”[All Fields] OR

A hand-search was also carried out in main endodontic journals (International Endodontic Journal, Journal of Endodontic, and Australian Endodontic Journal) and in the references of significant papers and reviews. The last search was made in June of 2020.

Electronic and manual searches provided the titles and abstracts of articles related to the aims of the studies, which were categorized by three independent researchers (D.C.-B., J.M.-G., and J.J.S.-E.) according to the inclusion and exclusion criteria. Articles selected were full-text reviewed by four investigators (D.C.-B., J.M.-G., P.M.-M., and J.J.S.-E.).

2.4. Data Extraction

The methodology of selected studies was examined, and main features were extracted and compiled including, authors, date of publication, study design, subjects and sample size, main quantitative results and odds ratio values, and diagnosis of RPLs. Data extraction was performed by four investigators (D.C-B., J.M-G., M.C.J-S., and J.J.S-E). Disagreements were resolved by discussing between the four and reaching an agreement by majority. When necessary to clarify the data, the authors of the included studies were consulted.

2.5. Outcome Variables and Statistical Analysis

The primary outcome was the prevalence of extracted RFT. Odds ratio (OR), with its 95% confidence interval (CI) was calculated in every selected study trying to measure the effect of the relationship between smoking habits and the outcome of RCT. A random-effect model meta-analysis, on the basis of inverse variance method, was performed to determine the pooled OR and its 95% CI.

To estimate the variance and heterogeneity amongst trials, the Tau^2 and the Higgins I^2 tests were employed, taking into account that substantial heterogeneity is considered if I^2 test is higher than 50% [30]. A funnel plot was plotted to

illustrate the possible existence of publication bias [31]. To show the OR results, a forest plot [32] was used, along with the inverse variance pooled estimate. Finally, a level of $p = 0.05$ was considered significant. The meta-analyses were calculated with the 5.4 RevMan software (Review Manager Web. The Cochrane Collaboration, 2019. Available at revman.cochrane.org) [33].

2.6. Quality Evidence Assessment and Risk of Bias in Individual Studies

The quality of evidence of the included studies was analysed according to the guidelines provided by the Centre for Evidence-Based Medicine at Oxford [34]. The certainty in the evidence was assessed using the GRADE tool (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. Available from
gradepro.org: https://gdt.gradepro.org/app/handbook/handbook.html#h.rkkjpmwb6m6z [35]. The GRADE tool has five domains: risk of bias, inconsistency, imprecision, indirectness, and publication bias, that can be downgraded and reduce the quality of the evidence [36]. Articles were assessed independently by 4 reviewers (J.J.S.E., J.M.G., D.C.B., and M.C.J.S.) and cases of disagreements in the risk of bias were discussed until a consensus was achieved.

The risk of bias of the included studies was assessed according to Cochrane Collaboration common scheme for bias and ROBINS-I tool [37], initially described to assess nonrandomized studies of interventions, but currently also available for observational designs (https://methods.cochrane.org/robins-i-tool).

3. RESULTS

The search strategy is presented in Figure 1. After searching databases and hand-searching relevant bibliographies/papers, 571 articles were recovered. Excluding duplicates articles ($n = 384$) and publications before 1980 ($n = 1$), 186 articles were checked to satisfy the selection criteria by titles and abstract, declaring seven articles for full text review. Applying inclusion and exclusion

criteria and assessing the level of evidence and the quality of all full articles read, only two were included in the meta-analysis. Five articles were excluded because of two reasons (Table 1): absence of data about how many RFT existed at the beginning of the study [38,39,40,41], and absence of data about how many RFT were extracted [17].

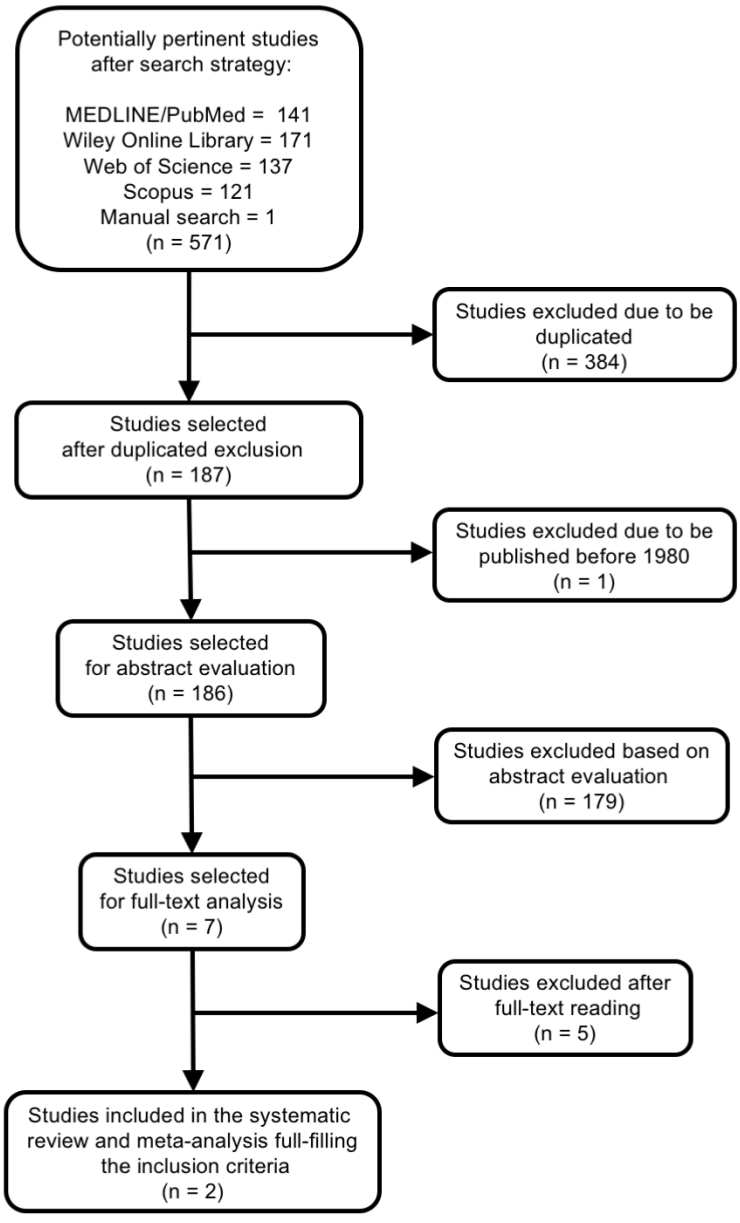

Figure 1. Flow diagram showing the process by which the studies about tobacco smoking and the prevalence of root filled teeth extraction were selected.

Table 1. Studies excluded in the systematic review of association between smoking habits and the prevalence of root-filled teeth extraction. Excluded reason, authors, and year of these studies.

Excluded Reason	Authors	Year
Not provide necessary data to meta-analysis (absence initial n° RFT)	1. Zadik et al.	2008 [38]
	2. Zhong et al.	2010 [39]
	3. Touré et al.	2011 [40]
	4. Olcay et al.	2018 [41]
Not provide necessary data to meta-analysis (absence n° RFT extracted)	5. Marending et al.	2005 [17]

3.1. Study Characteristics

Finally, two studies were included in the analysis: 1. Doyle et al. [20], and 2. Khalighinejad et al. [42]. Study design, smokers and controls subjects, main data, and evidence level [34] are summarized in Table 2.

Table 2. Studies about smoking habits and the prevalence of root filled teeth extraction included in the systematic review. Study design, subjects and sample size, main results, and evidence level [34].

Authors	Year	Study Design	RCT	Association Diab.-Extr.RFT	Evidence Level [34]
1. Doyle et al.	2007 [20]	Retrospective chart review (follow up 1 years)	Controls: 158 Smokers: 38	YES; $p = 0.0004$	3b
2. Khalinghinejad et al.	2017 [42]	Longitudinal (retrospective 9 years)	Controls: 193 Smokers: 127	YES; $p = 0.003$	3b

RCT: root canal treatment; RFT: root-filled teeth; Extracted*RFT: extracted root-filled teeth.

3.2. Meta-Analysis

A table of evidence was elaborated with data of both selected articles (Table 3). The estimated variance among the two studies was examined by Tau^2 test, resulting non-significant ($Tau^2 = 0.41$; $Chi^2 = 2.81$; df = 1; $p = 0.09$).

Table 3. Studies about smoking habits and the prevalence of root filled teeth extraction. Results extracted and compiled, descriptive statistics and odds ratios calculated.

Authors	Year	Number of RFT	Non-Smoker Controls		Smoker Patients		OR (95% C.I.)	*p*
			Extracted*RFT/ Total RFT	Extracted*RFT (%)	Extracted*RFT/ Total RFT	Extracted*RFT (%)		
Doyle et al.	2007 [20]	196	5/158	3.2%	7/38	18.4%	6.9 (2.1–23.2)	0.0004
Khalinghinejad et al.	2017 [42]	320	32/193	16.6%	39/127	30.7%	2.2 (1.31–3.81)	0.003
OVERALL		516	37/351	10.5%	46/165	27.9%	**3.43 (1.2–10.1) ***	**0.002**

RFT: root-filled teeth. Extracted*RFT: extracted root filled teeth. * Inverse variance method: $Chi^2 = 2.80$; $p = 0.002$.

Heterogeneity test value ($I^2 = 64\%$) was high; therefore, both weights were calculated using the random effects model, considering there was variation among the included studies and allowing the study outcomes to vary in a normal distribution (Figure 2, Funnel plot).

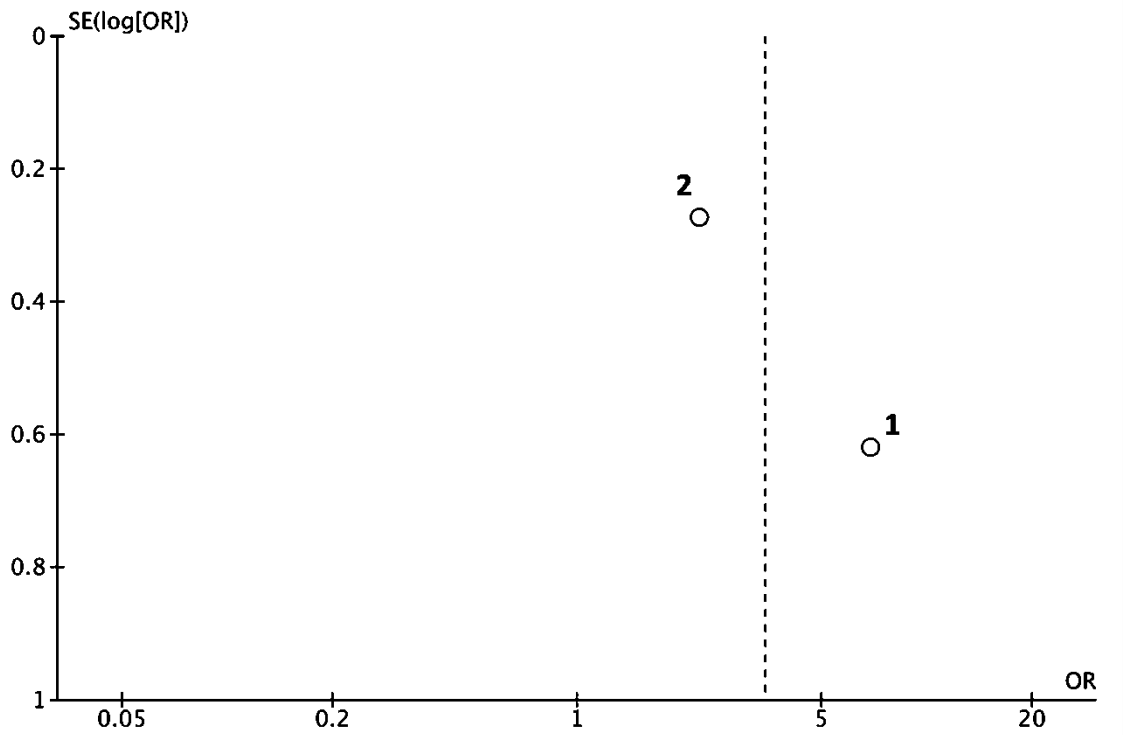

Figure 2. Funnel plot for estimates in meta-analysis of extracted root-filled teeth (RFT) in smoker subjects. Studies with higher power and lower standard error are placed towards the top. Studies with lower power are placed towards the bottom. 1. Doyle et al. (Scott L. Doyle et al., [20]) and 2. Khalighinejad et al. (Khalighinejad et al., [42]).

Overall OR was calculated using inverse variance method with random effects, resulting an OR = 3.43 (95% CI = 1.17–10.05; p = 0.02). The ORs for each study and the pooled OR from the meta-analysis were shows in a forest plot (Figure 3). This result indicates that there is a significant difference in the prevalence of extracted RFT between smoking patients and control subjects.

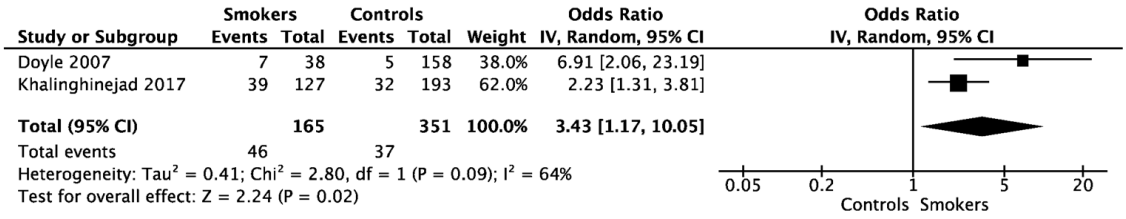

Figure 3. Forest plot of ORs and 95% confidence limits (CL) for the comparison of smokers and healthy control subjects regarding the frequency of extracted root-filled teeth (RFT). Overall estimate is based on data from the two studies. Black squares represent the point estimate of the odds ratio and have areas proportional to study size. Lines represent 95% confidence intervals. The diamond shows the summary statistic for the two studies. The solid line indicates an odds ratio of 1.0, and the dashed line indicates the overall odds ratio. OR: odds ratio; LCL: lower confidence level; UCL: upper confidence level.

3.3. Interpretation and Assessment of the Included Studies

The two studies included in the meta-analysis are retrospective, being published in 2007 [43] and 2017 [42]. With the results of the two studies, data from 516 RFT, 351 non-smokers, and 165 smokers were collected. In the study of Doyle et al. [43], the information from 367 patient's charts was collected for a period of time of 10 years and clinical data, number of RFT, periapical index of RFT, patient's habits, and type of restorations were determined. A positive association between smoking habits and the extraction of RFT was found. Smokers showed significantly higher percentage of extracted RFT (18.4%) compared with non-smokers (3.2%) (OR = 6.91; 95% CI = 2.06–23.19; p = 0.00043).

The second study, Khalighinejad et al. [42], classified RFT according to their periodontal status and in addition also collected personal data. Nine years after, the authors evaluated teeth that required extraction and the factors that were related to this. The outcome revealed an increased risk of RFT extraction between smokers (30.7%), compared with non-smokers (16.6%) (OR = 2.23; 95% CI = 1.31–3.81; p = 0.0029).

3.4. Quality Evidence Assessment

The scores [34] for the two studies were low, as both studies were scored with 3b (Table 2). The GRADE tool also demonstrated a low quality of the evidence for the included studies indicating that the true effect might be markedly different from the estimated effect (Table 4). Both included studies received the “serious” classification for the risk of bias, attending the limitations in the studies design and execution (see Figure 4—summary bias individual). Additionally, as detailed previously, the studies might have had substantial inconsistency, with an I^2statistic = 64% and Tau^2 = 0.41, so the “serious” for the inconsistency factor was received. The “not serious” classification was assigned for the indirectness and imprecision domains, and as other considerations, a strong association was evidenced, and a plausible residual confusion would reduce proved effect.

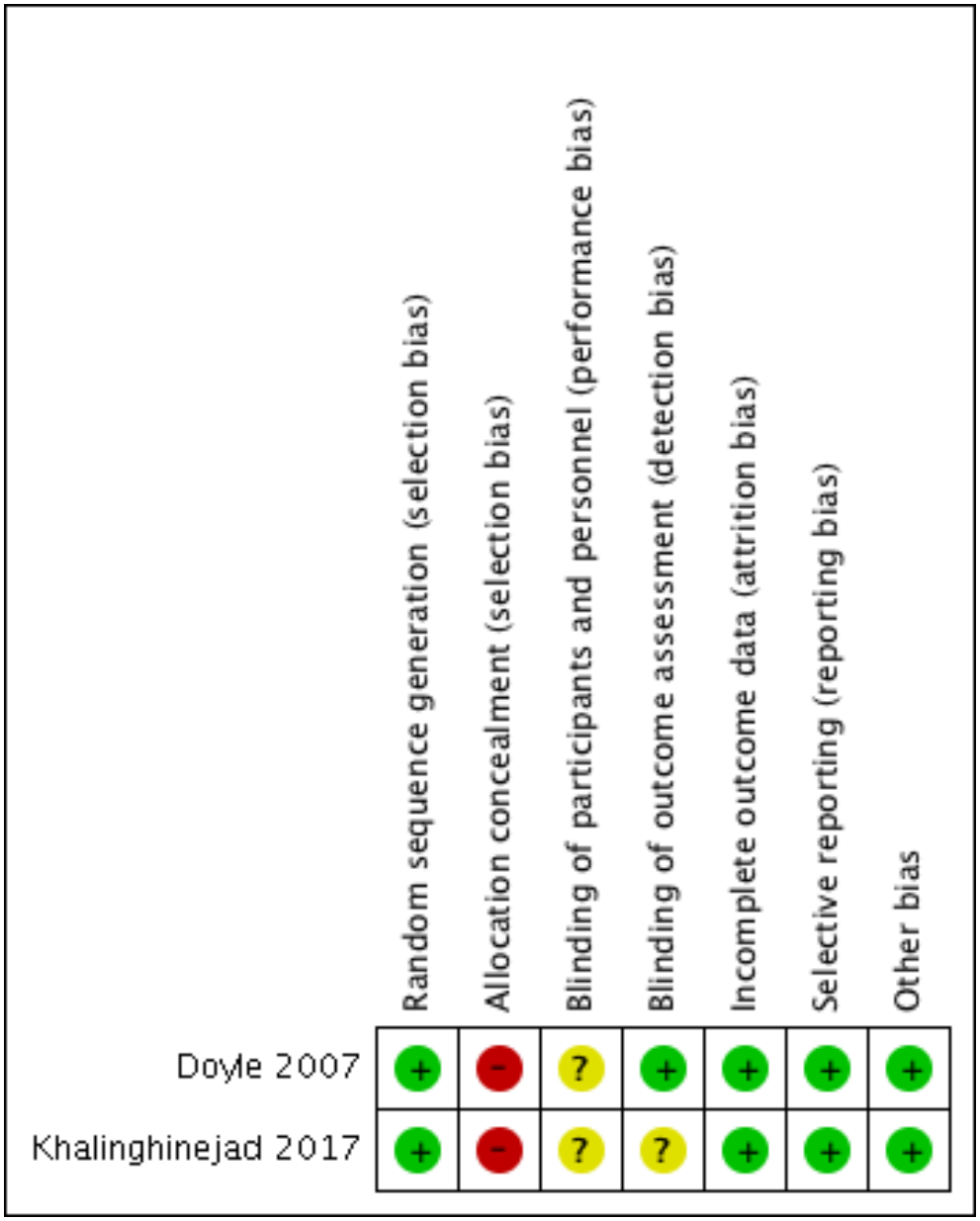

Figure 4. Risk of bias summary of included studies according the Cochrane Collaboration's tool for assessing risk of bias. + Low risk of bias. - High risk of bias. ? Unclear risk of bias.

Table 4. GRADE Working Group grades of evidence: Smoking habits and the prevalence of root filled teeth extraction.

Certainty Assessment							Certainty	Importance
Number of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations		
Extracted root filled teeth								
2	Observational studies	serious [a]	serious [b]	not serious	not serious	strong association all plausible residual confounding would reduce the demonstrated effect	⊕⊕◯◯ Low	IMPORTANT

Explanations: a. Detailed in Figure 4: Risk of bias summary, b. $I^2 = 64\%$ and $Tau^2 = 0.41$, High certainty: The authors have a lot of confidence that the true effect is similar to the estimated effect, Moderate certainty: The authors believe that the true effect is probably close to the estimated effect, Low certainty: The true effect might be markedly different from the estimated effect, Very low certainty: The true effect is probably markedly different from the estimated effect.

According to ROBINS-I tool, both studies were considered as moderate risk of bias: Doyle et al. [20] with one domain classified as high and other as unclear, and Khalighinejad et al [42] with two unclear with other high risk of bias (Figure 4).

4. DISCUSSION

This study aimed to analyze the possible link between smoking habits and the prevalence of extracted RFT. The results of the systematic review and meta-analysis carried out, including the available evidence about the prevalence of non-retained RFT, conclude that smoking is associated to RFT extraction.

After the literature search two studies providing follow-up data about RFT extraction were included: Doyle et al. [43] and Khalinghinejad et al. [42]. Both longitudinal studies analyzed the outcome of RCT in smokers and non-smoker patients, evaluating if the RFT was extracted or planned for extraction [42,43].

The random effects model was used to calculate overall ORs allowing the study outcomes to vary in a normal distribution. Furthermore, the heterogeneity value was moderate (64%), showing the relatively great variability between the studies. The inverse variance method reported an overall OR = 3.43 (p = 0.02),

indicating that smokers are 3.4 times more likely to lose RFT, compared to non-smoker subjects. Both included studies are longitudinal, allowing a temporal link to be established between cigarette smoking and losing endodontically treated teeth.

The implications that the results of this meta-analysis have in the daily dental clinic are very important. Moreover, translational medicine involves bringing the results of epidemiological studies into clinical practice. Dentists must know that tobacco smoking is a negative prognostic factor for the outcome of endodontic treatment. Smoking patients should also know that their prognosis for RCT has lower expectations of success. If, in addition to smoking, patients have other risk factors such as cardiovascular disease [44,45] or diabetes [18,46,47], smokers should know that their RFTs have very high likelihood to end up being lost.

The association between smoking and the prevalence of extracted RFT had not been investigated so far by meta-analysis. Thus, the result of the present study fill this knowledge gap. However, the quality level of the two included studies is low (3b), because of this, the results of the present systematic review and meta-analysis should be valued with caution. The GRADE tool demonstrated an overall low strength of evidence. This implies that true effect might be markedly different from the estimated effect. Although the sample size is high in both studies, there are important drawbacks in their design that lowers up to “serious” their classification for the risk of bias. This must be considered a limitation of this study.

The present systematic review has other limitations. One is the possible bias of the results by the reason of the tooth extractions. The loss of RFT is interpreted as RCT failure, but it could be due to other simultaneous cofactors, such as periodontal disease, trauma, or increasing the age of patients [48,49,50]. Only one of the studies took into consideration the periodontal status of RFT [42]. Smoking periodontal patients probably display higher prevalence of extractions, since smoking is associated to severe periodontitis [51]. Teeth with moderate or severe periodontitis could have even three times more risk to lost, especially if these teeth do not receive an adequate periodontal treatment or if the patient are

a smoker [42,52]. On the other hand, the two included studies did not take into account the dose-response effect. Then, it is impossible to determine if the alleged relationship meets the dose-effect criterion for be considered causal. Therefore, prospective studies are needed that take into account the dose-effect factor evaluating the amount of tobacco smoked and the time during which you have smoked. Another limitation of the present study is that grey literature has not been analyzed.

The results of this systematic review indicate that tobacco influences the post-endodontic periapical healing process, increasing three times the probability that treatment will fail and that the tooth will need to be extracted. The effect of cigarette smoking on periapical tissues repair after endodontic treatment has biological plausibility [15]. Several biological mechanisms can be argued. Tobacco smoking can affect the healing process of the RFT hindering bone repair and maintaining destructive periapical bone processes [15,53,54]. In this way, periapical lesion in the smoker's RFT could have a slower healing process, establishing persistent apical periodontitis, which would lead to tooth loss [15,55]. Cigarette smoking alters leukocytes, macrophages, and T-cell lymphocytes functions, decreasing antibodies levels [56], and increasing the levels of pro-inflammatory mediators (IL−6, TNF- α, C-reactive protein) [54,57,58,59]. Alterations in microcirculation, both morphological and functional, could also have an impact on periapical healing after endodontic treatment and cause the loss of the RFT. It is possible that the inflamed periapical tissues of smokers have an insufficient supply of nutrients and oxygen [15]. Cigarette smoking would increase the level of carboxyhemoglobin as well as oxidative stress, altering micro-vascularization and decreasing the supply of oxygen and nutrients to the repair periapical tissues [60]. Furthermore, smoking is associated to delay fibroblast migration to the wound area and fibroblast dysfunction [61]. It has been shown that cigarette smoking has local and direct pro-inflammatory effect on inflamed periapical tissues, with increased levels of products of lipid peroxidation, such as 8-iso-PGF (2a), and products of the LOX-pathway [62]. Lastly, cigarette smoking, stimulating osteoclastic cells and reducing angiogenesis, impairs bone healing and tissues reparative response [63,64].

5. CONCLUSIONS

The results of the available studies indicate a significant relationship between smoking and higher prevalence of non-retained RFT. Tobacco smoking should be considered a negative prognostic factor for the outcome of root canal treatment. Dentists should know that RFT are much more likely to be extracted in smokers, explaining to patients that maintaining smoking after undergoing endodontic treatment can increase the risk of treatment failure. However, the meta-analysis includes only two studies, both of low quality level and serious risk of bias. Therefore, the overall strength of evidence is low, and this must be considered a limitation of the present study. Because of this, the conclusion should be valued with caution. Better designed longitudinal studies are needed to accurately define the impact of smoking on the outcome of endodontic treatment.

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DISCUSIÓN

Hábito tabáquico y pronóstico del tratamiento de conductos

Como segundo objetivo de este trabajo de tesis doctoral se plantea determinar la posible asociación entre el hábito tabáquico y el fracaso del tratamiento endodóntico. Numerosas investigaciones han puesto de manifiesto el efecto perjudicial del tabaco sobre diferentes factores que pueden verse afectados por esta asociación.

Las revisiones sistemáticas con metaanálisis llevadas a cabo indican que el hábito tabáquico se asocia significativamente con una mayor prevalencia de lesiones radiolúcidas periapicales en dientes endodonciados (OR = 1.16; IC 95% = 1.07–1.26; $p < 0.05$) (Cabanillas-Balsera *et al.* 2020*b*) y con una mayor prevalencia de dientes endodonciados extraídos (OR = 3.43, IC 95% = 1.17–10.05; $p < 0.05$) (Cabanillas-Balsera *et al.* 2020*a*). Por tanto, el hábito tabáquico supone un factor pronóstico negativo en el éxito del tratamiento endodóntico.

Sin embargo, debemos identificar los posibles mecanismos biológicos que expliquen la posible asociación existente entre ambas variables.

En este sentido, el hábito tabáquico deteriora el proceso de reparación tisular, pudiendo relacionarse con el aumento de la probabilidad de fracaso del tratamiento endodóntica mediante los siguientes mecanismos (Figura 17) (Segura-Egea *et al.* 2015):

a) Alteración de la vascularización. El hábito tabáquico afecta tanto a la morfología como a la funcionalidad de la microcirculación, causando un daño endotelial debido a radicales libres y disminuyendo el aporte de oxígeno a la sangre. Esta disminución del suministro de nutrientes y oxígeno puede traducirse en un deterioro de la reparación de los tejidos periapicales (Freiman *et al.* 2004).

b) Reparación tisular deficiente. El tabaquismo provoca un retraso en la migración y disfunción de los fibroblastos, con alteración de la síntesis de colágeno y reparación tisular deficiente. Además, los fumadores presentan un aumento de la relación RANKL/osteoprotegerina, generando un incremento de la pérdida ósea (Raulin *et al.* 1988, Johannsen *et al.* 2014).

c) Alteración de la respuesta inmune. Los efectos del tabaco generan una perturbación de las respuestas inmunitarias innatas y adquiridas, con disfunción de leucocitos polimorfonucleares, macrófagos, linfocitos de células T y reducción de la quimiotaxis leucocitaria y los niveles de anticuerpos (Palmer *et al.* 2005, Johannsen *et al.* 2014).

d) Reacción inflamatoria sistémica. Fumar tabaco induce una reacción inflamatoria generalizada, con aumento del nivel sistémico de proteína C-reactiva y liberación de especies reactivas de oxígeno, colagenasa, serín-proteasas o citoquinas proinflamatorias como IL-1β y TNFα, todas ellas, sustancias con potencial de destrucción tisular (Barbieri *et al.* 2011).

e) Reacción inflamatoria local. Finalmente, el tabaquismo también genera un estado proinflamatorio local y directo sobre los tejidos periapicales, con aumento de la síntesis endógena en la periodontitis apical de eicosanoides e isoprostanos y metabolitos de lipooxigenasa (LOX) (Eder *et al.* 2012).

Como resultado, las alteraciones biológicas que produce el hábito tabáquico pueden generar un retraso o disminución en la curación de las lesiones periapicales.

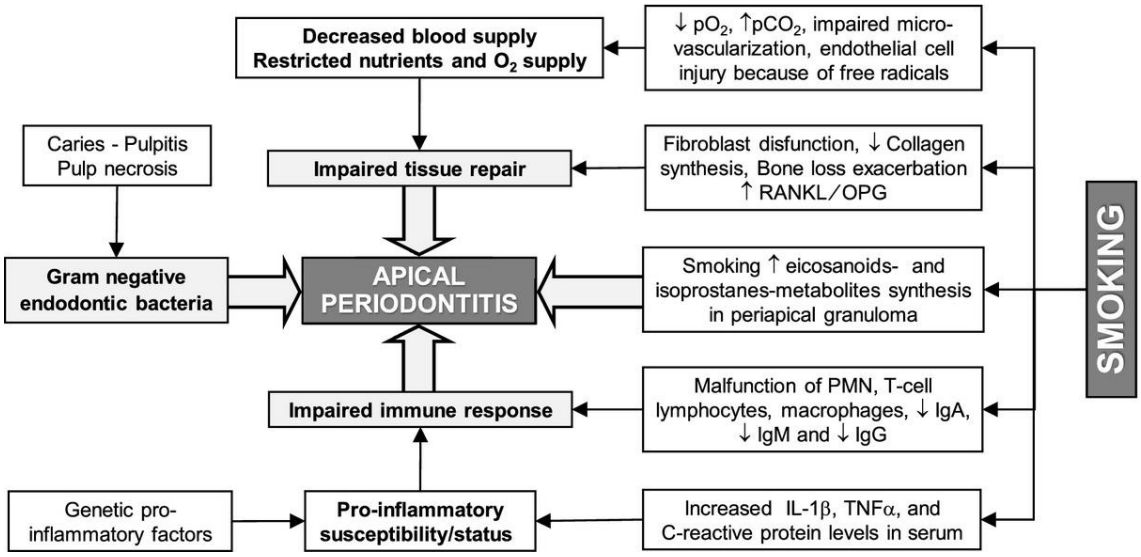

Figura 17. Mecanismos biológicos por los cuales el tabaquismo podría afectar el estado periapical (Segura-Egea et al. 2015).

CONCLUSIONES

La investigación de la evidencia científica disponible permite extraer las siguientes conclusiones:

PRIMERA. La diabetes mellitus se asocia significativamente con una mayor prevalencia de lesiones radiolúcidas periapicales en dientes tratados endodónticamente.

SEGUNDA. La diabetes mellitus se asocia significativamente con una mayor prevalencia de dientes endodonciados extraídos (o no retenidos).

TERCERA. El hábito tabáquico se asocia, débil pero significativamente, con una mayor prevalencia de lesiones radiolúcidas periapicales en dientes endodonciados.

CUARTA. El hábito tabáquico se asocia significativamente con una mayor prevalencia de dientes endodonciados extraídos (o no retenidos).

QUINTA. Tanto la diabetes mellitus como el hábito tabáquico deben considerarse como factores pronósticos preoperatorios negativos en el resultado del tratamiento de conductos.

SEXTA. Se requieren estudios prospectivos bien diseñados para determinar la contribución exacta de la diabetes mellitus y el hábito tabáquico al mayor riesgo de fracaso del tratamiento de conductos, así como estudios experimentales que permitan esclarecer los mecanismos biológicos implicados.

CONCLUSIONS

The research of the available scientific evidence allows the following conclusions to be drawn:

FIRST. Diabetes mellitus is significantly associated with higher prevalence of radiolucent periapical lesions in endodontically treated teeth.

SECOND. Diabetes mellitus is significantly associated with higher prevalence of root filled teeth extraction (or non-retention of root filled teeth).

THIRD. Smoking is, weak but significantly, associated with higher prevalence of radiolucent periapical lesions in endodontically treated teeth.

FOURTH. Smoking is significantly associated with higher prevalence of root filled teeth extraction (or non-retention of root filled teeth).

FIFTH. Both diabetes mellitus and smoking should be considered as negative preoperative prognostic factors for the outcome of root canal therapy.

SIXTH. Well-designed prospective studies are required to determine the exact contribution of diabetes mellitus and smoking to the increased risk of endodontic treatment failure, as well as experimental studies to clarify the biological mechanisms involved.

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