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RESUMEN

La enfermedad periodontal es una patología basada en la reacción inflamatoria, por parte del huésped, ante un ataque biológico. Su progresión implica la destrucción de los tejidos de soporte dentario llegando incluso a la pérdida de piezas dentales. Se ha hallado relación entre la gravedad y rapidez en la progresión de la enfermedad periodontal y alteraciones de las defensas inmunológicas.

Existen numerosas patologías donde la enfermedad periodontal es un signo visible. Para la realización de este trabajo se eligieron tres, las cuales son: diabetes mellitus, infección por virus de inmunodeficiencia humana (VIH) y Síndrome de Down.

La justificación de esta elección se basa en, en el caso de diabetes mellitus, la extensión de la patología; en el caso de infección por VIH al ser la periodontitis un síntoma definible de la patología, ambos asociados frecuentemente en conjunto; y finalmente, por la singularidad de la afección respecto al Síndrome de Down.

Existe evidencia de que en los tres tipos de huéspedes existe una intervención anómala de marcadores de inflamación, como la interleuquina-1, el factor de necrosis tumoral alfa y la prostaglandina E2, así como también de linfocitos T y células polimorfonucleares.

Para contrarrestar estos defectos, actualmente se están elaborando múltiples opciones terapéuticas, basadas en mecanismos moleculares que se ajusten a las necesidades de tratamiento de cada individuo. Estas terapias serían de gran ayuda complementando el tratamiento periodontal básico conocido.

La relación entre el avance de la enfermedad periodontal y los mecanismos inmunológicos endógenos del huésped deja constancia de la importancia de un enfoque sistémico a la hora de tratar las manifestaciones clínicas orales de inmunodepresión.

ABSTRACT

Periodontal disease is a type of affection based on inflammatory reactions, initiated by the host's immune system when exposed to a biological attack. Its progression involves destruction of connective support tissue surrounding teeth finally causing tooth decay and loss. It is known there is an important correlation between periodontal disease gravity and disease progression and alterations in the immune cascade.

There are numerous pathologies where periodontal disease is a visible and important sign. For the making of this work, three systemic diseases were chosen; these are: diabetes mellitus, infection by human immunodeficiency virus (HIV) and Down's Syndrome. Justification of this selection is based on, in the case of diabetes mellitus given the extension of the pathology and its high incidence in modern society; regarding HIV because periodontitis is typically a sign of this disease and commonly associated with each other; and finally, Down's Syndrome was selected because of the rarity of the illness.

There is substantial evidence suggesting that in immunosuppressed individual, like the ones mentioned before there are signed of altered inflammatory responses concerning markers such as interleukin-1, tumor necrosis factor alpha, prostaglandin E2, T lymphocytes and polymorphonuclear cells.

In order to combat these defects, multiple therapies are being developed. These therapies take into consideration the molecular mechanisms behind the immune

abnormalities and can be adjusted to the requirements of each patient. Such treatments would be of great importance to complement the already stablished periodontal treatment.

The relationship between periodontal disease progression and endogenous immune processes leaves record of the significance in implementing a systemic approach when dealing with the clinical manifestations of immunodepression.

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1. INTRODUCCIÓN

Junto con el amplio desarrollo económico y social evidenciado desde comienzos del siglo pasado, han surgido cambios de estilo de vida que acarrean una mayor incidencia de enfermedades orales como lo son las de tipo periodontal. Según la Organización Mundial de la salud (OMS), las periodontopatías graves afectan a casi el 10% de la población mundial [(1)].

La periodontitis es una enfermedad crónica inflamatoria que afecta tanto al tejido gingival como al tejido óseo que le rodea, esta inflamación es la respuesta al constante ataque bacteriano al que se someten los tejidos bucales. El cúmulo de bacterias produce desechos metabólicos que, al ser reconocido por las células de defensa, dispara una respuesta inmune que a la larga afecta irreversiblemente todos los estratos histológicos del periodonto de manera directa o indirecta [(2)].

Las secuelas directas de la actividad bacteriana y sus subproductos se ven reflejados en la aparición de edema gingival y sangrado. Las consecuencias indirectas de la acción microbiana involucran una respuesta autodestructiva del sistema inmune en el huésped. La mayoría de la destrucción del tejido periodontal es causada por la movilización de células inmunes propias del cuerpo [(2).]

Asimismo, se cree que lipopolisacáridos de origen bacteriano poseen la capacidad de estimular la producción de citoquinas y mediadores de inflamación, como lo son los metabolitos del ácido araquidónico, por ejemplo, prostaglandina E2 (PGE-2); al entrar en contacto con células encargadas de la protección inmunológica en el huésped. Estas

citoquinas y mediadores de inflamación luego promueven la liberación de enzimas tipo metaloproteinasas de la matriz extracelular, causando pérdidas importantes de tejido de soporte y eventualmente pérdida de hueso [2].

Existe gran cantidad de evidencias que apoyan la teoría de asociación entre periodontitis y numerosas enfermedades sistémicas, éstas evidencias se basan en una diversidad de factores, por ejemplo, la distribución sistémica de patógenos periodontales y movilización de células activadoras de inflamación [2]. Esto ocurre en casos como la diabetes, la infección por VIH o en síndromes congénitos como el síndrome de Down.

En el caso de la diabetes, esta patología induce una serie de cambios inmunes que potencian la producción de citoquinas inflamatorias por parte de diferentes células polimorfonucleares y monocitos, además de disminuir los factores de crecimiento respecto a los macrófagos. La suma de estas dos condiciones predispone al organismo a un proceso de inflamación mantenida gracias a la reacción de estos marcadores ante endotoxinas bacterianas [3].

Con respecto a los pacientes seropositivos, presentan funcionamiento deficiente junto con un escaso número de linfocitos, específicamente linfocitos T4 en sangre periférica y en menor medida también están implicados los linfocitos T8. El bajo recuento de linfocitos, sobretodo, T4, se relaciona con la gravedad de las manifestaciones clínicas periodontales en paciente infectado por VIH [4]. En pacientes que padecen infección por VIH la rápida progresión de la enfermedad periodontal se asocia a una disminución en la cantidad de neutrófilos

disponibles, siendo la neutropenia un factor común en muchos pacientes seropositivos que a su vez presentan patología periodontal [5].

En casos de pacientes con Síndrome de Down, se conoce que existe una disminución de la capacidad fagocítica y quimiotaxis de neutrófilos, sumado a una actividad de monocitos alterada. Incluso se ha demostrado que este tipo de paciente presenta igualmente, limitada función de linfocitos T y B y monocitos. Estas disfunciones son indicadores de la agresividad con la que la enfermedad periodontal avanza en este tipo de pacientes [6].

Si bien se ha demostrado la eficacia del mantenimiento periodontal tradicional no quirúrgico, basado en técnicas de higiene oral, limpiezas profilácticas, RAR (raspado y alisado radicular), así como la eficacia de técnicas quirúrgicas como la utilización de colgajos tipo Widman modificados [7]; actualmente está resurgiendo otro enfoque terapéutico dirigido a la enfermedad periodontal basado en actuar a nivel molecular tanto sobre el huésped como sobre los organismos que mas frecuentemente se encuentran tras esta patología.

En la siguiente sección de este trabajo se detallará brevemente el concepto principal y bases científicas de cada tratamiento; un análisis de su eficacia en la aplicación clínica se comentará más adelante.

La terapia fotodinámica está basada en la interacción de dos tipos de sustancias, una fotoactiva y la otra fotosensible, misma reacción se dispara mediante la aplicación de luz a una determinada longitud de onda [8] El concepto se apoya en que durante la interacción de ambas sustancias se crean radicales libres de oxígeno que tiene un efecto citotóxico contra

especies bacterianas anaerobias subgingivales [8,9]. Dentro del campo de odontología periodontal se recomienda una longitud de onda entre 800nm a 980nm [9].

Otro método terapéutico se enfoca en el uso de la melatonina, una molécula producida principalmente en la glándula pineal durante las horas nocturnas [10]. Esta hormona está implicada en el proceso de remodelación ósea ya que actúa sobre los osteoblastos y también osteoclastos [10], su actividad es principalmente osteoformadora y tiene a su vez capacidades supresores contra los osteoclastos [10,11]. El uso de melatonina como coadyuvante terapéutico en la enfermedad periodontal se explica también debido a la habilidad de la melatonina de reducir la cantidad de radicales libres que agravan la extensión de la enfermedad periodontal [10].

La terapia de péptidos antimicrobianos se centra en la capacidad de estos marcadores de la saliva como herramientas esenciales en la defensa del huésped contra el ataque de bacterias y diversos microrganismos [12]. Actualmente se están realizando diversos sistemas de administración de moléculas miméticas de péptidos antimicrobianos que puedan actuar sobre una especie bacteriana en concreto [12]. Según las investigaciones estas moléculas pueden ser eficaces contra cultivos de *P. aeruginosa* y *S. mutans*.

El tratamiento periodontal con vitamina D, se desarrolla en base a evidencia que relaciona la forma metabólica activa de la vitamina D, 1,25(OH)2D3 y el grado de densidad ósea, así como evidencia de reducción de fracturas óseas en pacientes bajo tratamiento suplementario de vitamina D [13,14]. Está establecido que niveles estables de vitamina D activa

se corresponden con mejoras en la actividad antibacteriana del sujeto [13] debido a su efecto antiinflamatorio mediante la inhibición de citoquinas producidas por agentes inmunológicos, y su efecto estimulador de monocitos y macrófagos [15].

El fundamento de la terapia periodontal utilizando antagonistas de la interleuquina-1 y el factor de necrosis tumoral explica que, estas moléculas, poseen un papel clave en la iniciación de la respuesta inflamatoria y consecuentemente, la destrucción de tejidos [16]. Estos agentes tienen la capacidad de disparar el sistema inmunológico exacerbando la capacidad de adhesión en leucocitos además de estimular la producción de citoquinas de tipo quimiocinas, que participan luego en el reclutamiento de leucocitos circulantes en sangre [16]. La interleuquina-1 y el factor de necrosis tumoral a su vez pueden inducir mediadores de inflamación sostenida como las prostaglandinas. Los antagonistas a estos compuestos proinflamatorios son considerados importantes en el campo de la periodoncia gracias a su acción inhibidora de osteoclastos, ayudando así a la preservación de tejido óseo [16].

2. OBJETIVOS

Objetivos Principales

1. Recopilar aquellas enfermedades sistémicas que más favorecen la prevalencia y desarrollo de la enfermedad periodontal
2. Reconocer los mecanismos celulares implicado en la patología periodontal, específicamente, en casos de diabetes, síndrome de Down y VIH
3. Establecer qué tipo de tratamientos, además de los ya conocidos, pueden recibir los pacientes sistémicos para ayudar a reducir la gravedad de las afectaciones clínicas de provenientes de la enfermedad periodontal.

Objetivos secundarios

a) Destacar el papel de los marcadores factor de necrosis tumoral alfa (TNF-α), interleuquina-1 (IL-1) y prostaglandina E2 (PGE-2)

b) Resaltar la influencia del déficit cuantitativo y cualitativo de celular polimorfonucleares, y recuento y función leucocitaria, específicamente T4, en el deterioro de la salud gingival.

c) Finalmente, mencionar las opciones de refuerzo al tratamiento periodontal básico, que se pueden ofrecer a los pacientes

    a. Terapia fotodinámica como coadyuvante antibacteriano
    b. Melatonina como herramienta de regeneración ósea
    c. Administración de péptidos antimicrobianos para reducir la carga bacteriana dentro de la cavidad oral.

d. Ingesta de suplementos de vitamina D

e. Inyecciones en papila interdental de inhibidores de interleuquina-1 (IL-1) y factor de necrosis tumoral (TNF)

3. MATERIALES Y MÉTODOS

Este trabajo fue realizado sobre una revisión bibliográfica basado en el análisis de artículos científicos encontrados en múltiples bases de datos proporcionadas por la Bliblioteca CRAI Dulce Chacon de la Universidad Europea de Madrid, como: Pubmed, Wiley Online Library y Researchgate.

Los criterios para la selección fueron: Idiomas: español e inglés. Palabras clave: periodontitis, systemic diseases, periodontitis, enfermedades sistémicas, enfermedad periodontal, salud oral, seropositivo, síndrome de Down, VIH, diabetes mellitus. La antigüedad de los artículos no fue un factor excluyente. De los 42 artículos analizados se apartaron de la selección aquellos que no mencionasen las bases moleculares y celulares de la enfermedad y aquellos artículos cuya propuesta terapéutica se basara solo en tratamiento periodontal básico o quirúrgico

4. DISCUSIÓN

Respuesta inmunológica de pacientes diabéticos frente a la enfermedad periodontal

a) **Factor de necrosis tumoral alfa (TNF-α, *tumor necrosis factor alpha*)**

Nishimura et al [17] mencionan el rol del TNF-α en la respuesta inmune de pacientes diabéticos. Mencionan que TNF-α es producido por adipocitos, así como también monocitos, y que sus niveles en sangre se encuentran elevados en pacientes con diabetes tipo 2. Nishimura et al. destacan niveles elevados de TNF-α como un factor de riesgo y agravante de la enfermedad periodontal. Los autores comentan que en pacientes que han desarrollado diabetes tipo 2, concentraciones séricas de TNF-α son particularmente altas, actuando sobre fibroblastos para aumentar la producción de enzimas degradantes de la matríz y activando osteoclastos cuya actividad se asocia a la reabsorción ósea [17].

Mealey y Oates también plantean una propuesta parecida, en su trabajo indican que monocitos periféricos en sangre de pacientes diabéticos producen elevadas cantidades de TNF-α en respuesta a los antígenos presentes en *Porphyromonas gingivalis*, respuesta que no ocurre en monocitos de paciente sanos [18].

Otro estudio, de Naguib et al [19] realizado en ratones diabético expuesto a una cantidad exacta de *Porphyromonas gingivalis* contradice el propuesto por Mealey y Oates, argumentado que la sobreproducción de TNF-α y por ende la presencia de inflamación constante, es un proceso autónomo y no se debe al reconocimiento de antígenos bacterianos por parte de las células blancas, siendo independiente del tipo de microorganismo invasor [19].

Así mismo en el trabajo de Singh et al. [20] se estudió como la diabetes mellitus tipo 2 se relaciona con TNF-α salival, se descubrió que el promedio cuantitativo saliva de TNF-α en paciente diabéticos tipo 2 es mayor que en aquellos pacientes sanos y también individuos no diabéticos que a su vez padecen periodontitis crónica. Singh et al. explican que el TNF-α es una citoquina proinflamatoria que regula la transcripción de las metaloproteinasas de la matriz o MMP que se manifiestan clínicamente como destrucción en el tejido periodontal [20].

Se ha encontrado que no solo la periodontitis es una complicación derivada de la diabetes si no que padecer un desbalance en la salud gingival del paciente también tiene un efecto negativo sobre los niveles glucémicos del individuo. Según el artículo de Matthews [21] existen abundantes evidencias que apoyan esta relación bidireccional, se ha encontrado que un correcto control sobre la evolución de la enfermedad periodontal en pacientes diabéticos reduce significativamente niveles séricos de productos finales de glicación avanzada (AGEs, *advanced glycation end products*).

Nishimura [17], también comenta que un tratamiento periodontal exitoso reduce los niveles de TNF-α, y que a su vez una reducción de TNF-α se correlaciona con mejoras en el control metabólico de la diabetes. Nishimura et al desarrollan que esta citoquina producida por el tejido adiposo tiene la capacidad de reducir la sensibilidad a la insulina debido a que TNF-α estimula la lipolisis en adipocitos liberando ácidos grasos que a su vez inhiben la acción de la insulina [17].

El estudio de Grover [3] comenta esta dinámica, y añade que la unión entre productos finales de glicación avanzada y receptores de estos presentes en células de músculo liso, células endoteliales, neuronas, macrófagos y monocitos, ocasionan complicaciones a nivel vascular como el incremento en la permeabilidad vascular, estimulación de moléculas de adhesión, y aumento en la migración de monocitos al endotelio vascular. Según los autores, los monocitos activados se adhieren al endotelio de los vasos penetrando dentro del mismo donde se asocian a lipoproteínas de baja densidad y desencadenan una cascada de reacciones que elevan la producción de colágeno, obstruyendo la luz de los vasos [3].

Respecto a los estudios observados sobre el factor de necrosis tumoral alfa, se encuentra una limitación respecto al tipo de diabetes mellitus estudiada, en la mayoría de estos trabajos la evidencia se basa en la patogénesis únicamente de diabetes mellitus tipo 2, un tipo de diabetes que se desarrolla como consecuencia de los hábitos de vida del paciente y no posee una base puramente genética como la diabetes mellitus tipo 1. Sería necesario realizar más estudios en pacientes que padecen diabetes mellitus tipo 1 y comparar como ocurre en ellos la cascada de reacciones inflamatorias ante la exposición a un ente bacteriano.

Otra limitación que podemos encontrar consiste en que los mecanismos exactos mediante los cuales el factor de necrosis tumoral alfa afecta los niveles glucémicos no han sido bien detallados, según Nishimura y colaboradores existen varias teorías de como la elevación de Factor de necrosis tumoral alfa impide el correcto funcionamiento de la insulina [17] la mayoría de ellos mencionan afectaciones sobre una molécula llamada sustrato 1 del receptor de insulina, pero todavía no existe un consenso entre los expertos.

b) Células Polimorfonucleares

Según el trabajo de Rajkumar y colaboradores [22], en el caso de pacientes diabéticos existe un defecto en la función neutrófila que incrementa la susceptibilidad a desarrollar patologías periodontales. El autor comenta que esto se debe al constante estado hiperglucémico de los individuos diabéticos, junto con un incremento en la lipidemia característico de este tipo de pacientes, que reduce el poder de quimiotaxis y fagocitosis. Rajkumar explica que células polimorfonucleares aisladas en pacientes diabéticos con cetoacidosis evidencian poca actividad fagocita contra especies *staphylococcos*. Los autores comentan, además, que esta inactividad es atribuida a una reducción en la capacidad hidrofóbica en neutrófilos [22].

Esta teoría concuerda con lo publicado por Nishimura et al. [17] donde Nishimura aclara que aquellos pacientes con defectos tanto cualitativos como cuantitativos de neutrófilos son más propensos a desarrollar periodontitis o gingivitis severa, y con el estudio de Grover y Luthra, donde se habla de defectos cualitativos en neutrófilos y además habla de defectos de colágeno [3]. Grover y Luthra proponen que los monocitos en pacientes diabéticos sufren hiperreactividad derivada no de un estado hiperglucémico si no por la presencia de una hiperlipidemia sostenida. Además, argumentan a diferencia de Rajkumar, que los impedimentos funcionales neutrófilos en pacientes diabéticos no se asocian a la hiperglucemia si no a defectos en la producción de nicotinamida adenina dinucleótido fosfato, según ellos un componente esencial en el mantenimiento de neutrófilos [3].

Mealey y Oates [18] también confirman estas alteraciones en monocitos y neutrófilos, afirmando que en los neutrófilos se ven afectadas tres capacidades: capacidad quimiotática, capacidad adhesiva y capacidad fagocítica. De este modo se inhibe la reducción de bacterias dentro de la bolsa periodontal y aumentando el grado de destrucción periodontal [18]. Concuerdan con las conclusiones de Grover y Luthra, quienes señalan la existencia de un híper funcionamiento de monocitos y que esto a su vez desencadena sobreproducción de citoquinas proinflamatorias [3].

En su estudio, Grover y Luthra, a diferencia de Rajkumar, conceden más importancia a los efectos de la hiperlipidemia en el funcionamiento de células polimorfonucleares, explicando que las células adiposas o adipocitos tiene la capacidad de producir una molécula llamada proteína C reactiva (PCR), ésta aumenta la respuesta inflamatoria mediante llamamiento de otros mediadores de inflamación [3].

c) **Interleuquina-1 (IL-1)**

Salvi y colaboradores proponen que aquellos pacientes insulino-dependientes presentan una alteración de carácter autoinmune en genes asociado al antígeno leucocitario humano (HLA, *human leukocyte antigen*) HLA-DR3/4 y DQ [23], estas moléculas forman parte del complejo mayor de histocompatibilidad clase II (MHC II, *major histocompatibility complex*), su función principal es reconocer péptidos antigénicos es la superficie de otras moléculas y activar el sistema inmune [24]. Los autores explican que estas anomalías genéticas a su vez se asocian a la híper secreción de mediadores de inflamación, entre los cuales encontramos la inteleuquina-1b [23].

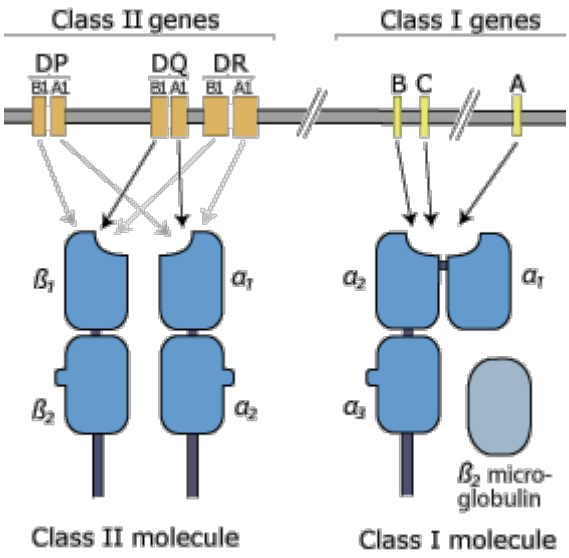

Figura 1. Composición de MHC II
(HLA genes and molecules. Faculté de médecine. Université de Genève; 2015)

Según Salvi et al. aquellos pacientes diabéticos presentan niveles de IL-1b significativamente mayores en el fluido gingival crevicular cuando estos fueron comparados con pacientes no diabéticos con un estado periodontal similar [23].

Desarrollando sobre este concepto Salvi et al. comentan que existen polimorfismos genéticos asociados a la interleuquina-1 que resultan en liberación exacerbada de esta molécula, aumentando el riesgo de sufrir variantes más agresivas de enfermedad periodontal. Uno de estos polimorfismos según los autores, ocurren en el cromosoma 2q13 [23].

Según Guzman et al. en su estudio evalúan la presencia de polimorfismos en genes asociados a IL-1 en pacientes diabéticos, y comenta que únicamente las variantes polimórficas de la interleuquina-1, IL-1b-511 y IL-1b+3954 han demostrado que aumentan la incidencia de la enfermedad periodontal [25].

Otros autores, Grover et al. resaltan el papel de IL-1b sobre la respuesta inflamatoria en paciente hiperglucémicos, mencionan que IL-1b tiene el poder de reclutar moléculas inflamatorias, facilita la degranulación de células polimorfonucleares, incrementa la síntesis de prostaglandinas y metaloproteinasas de la matriz extracelular, inhibe la síntesis de colágeno y activa ambos linfocitos T y B. Todos estos procesos convergen en la destrucción del tejido de soporte dentario [3].

En el artículo de Taylor señala que también existe una relación bidireccional entre IL-1 y los niveles glucémicos de los pacientes, comentando que esta molécula también tiene la capacidad de antagonizar la acción de la insulina [26]. Otros autores como Fève y Bastard [27], hablan también de esta relación en pacientes que sufren de diabetes mellitus tipo 2, ellos señalan que IL-1a y IL-1b ambos impiden el funcionamiento de la insulina alterando los receptores de esta hormona mediante fosforilación y obstruyendo la expresión de diferentes componentes involucrados en el transporte de glucosa. Fève y Bastard comentan que existe evidencia de que la producción de la interlequina-1 está asociada a un mayor riesgo de diabetes mellitus tipo 2 [27].

d) PEG-2

Kardeşler et al. en su estudio sobre pacientes diabéticos tipo 2, explican que la prostaglandina E2 es un metabolito del sistema de ciclooxigenasa y el mediador más potente en la pérdida de hueso alveolar durante la periodontitis [28]. Estos autores comentan que existe evidencia que indica que esta molécula tiene la capacidad de activar fibroblastos y osteoclastos que inducen la síntesis de metaloproteinasas de la matriz, interleuquina-1b y

otras citoquinas. Igualmente, mencionan que esta prostaglandina E2 está presente en el fluido gingival crevicular a niveles proporcionales a la severidad de la enfermedad periodontal [28]. Kardeşler et al. encontraron una correlación positiva entre profundidad de sondaje, sangrado al sondaje, nivel de inserción y fluido gingival crevicular total entre el grupo de estudio diabético [28].

Dentro de las limitaciones de este estudio encontramos una discrepancia en cuanto a la severidad de la enfermedad periodontal de ambos grupos de estudio: diabéticos cursando con enfermedad periodontal y no diabéticos cursando con enfermedad periodontal, en comparación con otros trabajos. Se requiere la realización de estudios a mayor escalar para realmente entender la raíz de los procesos que se activan ante la periodontitis en paciente diabéticos.

Navarro et al. de acuerdo con lo comentado anteriormente por Kardeşler, señalan que la gran mayoría de destrucción del tejido de soporte conectivo dental es causada por la producción de mediadores de inflamación interleuquina-1, prostaglandina E2, factor de necrosis tumoral e interleuquina-6, secretados por las células inmunológicas ante un ataque de microorganismos [29].

Araya et al. [30] en su estudio *ex vivo* realizado compararon la expresión de prostaglandina E2, entre otros marcadores, a nivel sanguíneo en pacientes diabéticos tipo 1 con y sin periodontitis agresiva expuestos a lipopolisacáridos de bacterias Gram negativas. Araya y colaboradores señalan que los niveles de prostaglandina E2 son particularmente

mayores en aquellos pacientes diabéticos indiferentemente de la presencia o no de periodontitis agresiva [30]. La limitación en este trabajo se evidencia en el tipo de estudio realizado, siendo *ex vivo* existe la posibilidad que este estudio no represente verdaderamente las interacciones que ocurren *in vivo* donde muchos otros factores propios del individuo influyen sobre la respuesta inmunológica.

Ebersole et al. [31] realizaron un trabajo que concuerdan con los autores previamente mencionados, este artículo sobre sujetos diabéticos tipo 1 demuestran que éstos presentan mayores niveles de prostaglandina E2, además de otros marcadores de inflamación, en el fluido gingival crevicular comparados con sujetos sanos con afectación periodontal similar [31].

Ebersole et al. así mismo indican que existe una asociación entre diabetes y presencia de monocitos hiperactivo que secretan prostaglandina E2 a un ritmo acelerado en comparación con no diabéticos; además, estos autores explican que la presencia prostaglandina E2 también se asocia a estados más graves de enfermedad periodontal [31].

En su estudio clínico Peruzzo Lopes et al., compararon los efectos del tratamiento periodontal básico sobre los niveles glicémicos en pacientes diabéticos tipo 1 y tipo 2. En este artículo Peruzzo Lopes et al. confirman lo presentado por los otros autores, pacientes con periodontitis presentan niveles dominantes de citoquinas proinflamatorias entre las cuales destaca la prostaglandina E2 [32]. Peruzzo Lopes y colaboradores comentan respecto a la expresión de prostaglandina E2 que, en paciente diabéticos con signos de periodontitis, el

tratamiento periodontal básico muestra una reducción importante en la cantidad de prostaglandina E2 presentes y también de los niveles glicémicos [32].

O'Connell et al. muestran en su trabajo que la terapia periodontal compuesta de raspador y alisado radicular y doxicilina mejorar notablemente el balance de la glucemia en paciente diabéticos tipo 2 y reduce también la expresión de mediadores de inflamación [33].

Estos autores comentan como posible limitación que los cambios observados pueden estar influenciados por factores dietéticos que no fueron monitorizados durante el curso del estudio [33]. Así como también hemos comentado previamente, es necesario la confección de estudios que abarquen ambos tipos de diabetes mellitus para observar si existen coincidencias en la respuesta inflamatoria o destacar las diferencias que se puedan presentar.

Se podría deducir que la reducción de prostaglandina E2 beneficia el equilibrio glicémico en pacientes diabéticos con complicaciones periodontales, demostrando la presencia de una relación bidireccional, como se ha comentado con otros mediadores de inflamación, pero más información se necesita para llegar a una conclusión aceptada por todos los expertos.

Respuesta inmunológica de pacientes VIH positivos frente a la enfermedad periodontal

a) Células T4 y T8

Según Yeung et al. en su estudio realizado sobre el estatus periodontal de hombres VIH positivos encontraron que en todos los sujetos se exhibía un descenso en los niveles de linfocitos CD4 y en general se observó un incremento en la aparición de sintomatología oral característica de paciente VIH positivos [(5)]. Respecto a su salud periodontal, se encontró que los pacientes enfermos mostraban mayor pérdida de inserción clínica en comparación a pacientes sanos [(5)].

Yeung y colaboradores también señalan existe evidencia para sugerir que estos cambios en el tejido periodontal de paciente VIH positivos probablemente se debe a un defecto inmunológico y no a la acumulación de placa bacteriana [(5)]. Yeung et al., comentan que en este tipo de infección la población de linfocitos T se encuentra severamente afectada [(5)].

En la publicación previamente mencionada, se encuentra como limitación la alta tasa de abandono de sujetos a lo largo del tiempo lo cual podría afectar los resultados obtenidos. Además, este estudio se conformó con pacientes que ya presentaban patología periodontal previa por lo cual es difícil determinar si las alteraciones inmunológicas son en sí parte de la etiología en la periodontitis o si su rol se limita a la acción agravante.

En el artículo publicado por Lucht et al. se estudió la prevalencia de gingivitis y periodontitis en pacientes VIH positivos según las concentraciones sanguíneas de linfocitos T4

inductores y T8 supresores [4]. Lo escrito por Lucht et al. se encuentra en la misma línea que lo presentado por Yeung et al.; Lucht y colaboradores confirman que pacientes VIH positivos presentan anomalías cuantitativas y cualitativas de linfocitos T4 en sangre, esta condición según los autores muestra una relación inversamente proporcional a la severidad de la gingivitis [4]; proponiendo que este desbalance posee mayor efecto sobre la agresividad de la enfermedad periodontal que la acumulación de placa por sí misma.

Perea et al. exponen que existe gran correlación entre la aparición de variantes necrosantes en afectaciones periodontales e infección por VIH [34]. Este artículo señala que la reducción de linfocitos T4 periféricos está detrás de la aparición de ciertas formas de gingivitis avanzada como gingivitis y periodontitis necrosantes [34].

Sin embargo, en otro estudio Gonçalves et al. comentan que no es posible establecer la existencia de una relación directa entre el nivel de células T4 y estatus periodontal [35], y afirman que la prevalencia de enfermedad periodontal en paciente VIH positivos no varía respecto a la de la población sana, y que igualmente en aquellos pacientes VIH positivos, incluso aquellos que ya habían desarrollado SIDA, no se encontró gran discrepancia en la severidad de la enfermedad respecto a la población inmunológicamente competente e incluso se evidenció salud periodontal. En 40% de los casos de inmunosupresión la condición periodontal era aceptable [35]. Es importante destacar que el estudio de Gonçalves et al. fue enfocado únicamente en sujetos VIH positivos de la población de Brasil y que, por otra parte, estos autores excluyeron de su estudio aquellas manifestaciones necrosantes de enfermedad

periodontal que otros autores si consideraron, esto podría justificar la similitud en prevalencia de los grupos de control sanos y grupos de estudio.

Martinez-Canut et al. [36] comparten las ideas de Gonçalves et al. explicando que en pacientes VIH positivos, si son comparados con individuos sin patologías, no hay un aumento significativo en la incidencia de gingivitis o periodontitis agravada como periodontitis úlcero-necrosante o gingivitis úlcero-necrosante y argumentan que tanto en pacientes sanos como inmunodeprimidos estas formas de padecimiento periodontal son igual de inusuales, por lo cual no se pueden atribuir al descenso en cantidad de células linfocitarias [36].

Steidley et al. [37] en su estudio que compara el ratio de linfocitos T4 y T8 en el tejido gingival de pacientes sanos y enfermos, afirman, que para que la respuesta inmune del huésped ante microorganismos sea adecuada, es necesario que haya una proporción mayor de células T4 que T8 mientras que si esta proporción se acerca a la igualdad el individuo exhibe mayor inhabilidad defensiva, y que este declive se evidencia en el tejido gingival de adultos VIH positivos con trastornos periodontales, sugiriendo que las complicaciones periodontales en pacientes VIH positivos están reguladas específicamente por especímenes T4 [37].

b) Células Polimorfonucleares

Lamster et al. manifiestan que en pacientes VIH positivos existe una respuesta inflamatoria exuberante que incluye la activación de células polimorfonucleares y macrófagos, detrás de la destrucción de tejidos. En este artículo se menciona que la actividad de este tipo de marcadores inmunológicos muestra una acentuación en su potencial fagocítico [38].

Lamster señala que las células polimorfonucleares en paciente VIH positivos presentan alteraciones en sus competencias fagocíticas [38]; de la misma forma comenta que estas células producen metaloproteinasas de la matriz, en su forma activa, las cuales se observan en el fluido gingival crevicular de paciente VIH positivos, comentando que estas enzimas podrían ser responsables del deterioro periodontal en pacientes contaminados por el virus [38].

No obstante, un artículo publicado por Estevez et al. indica lo contrario, afirmando que no existe varianza respecto al funcionamiento fagocítico en paciente enfermos y pacientes sanos [39].

Respuesta inmunológica de pacientes con Síndrome de Down frente a la enfermedad periodontal

a) **Células Polimorfonucleares**

Según lo publicado por Izumi et al., los pacientes que padecen este síndrome presentan una población neutrófila con bajo porcentaje de fagocitosis, resultados negativos en el examen de azul de nitro-tetrazolio [(6)], una prueba que mide la capacidad de estas células de convertir el compuesto nitro-tetrazolio, inicialmente incoloro, en una sustancia de color azul [(40)]. Estas carencias, y específicamente aquellas de la quimiotaxis de neutrófilos, según los escritores, acelera la progresión de la enfermedad periodontal en pacientes trisómicos.

Izumi et al. notaron que este tipo de migración celular guiada esta encarecida en este tipo de ejemplares, no obstante, no encontraron diferencia entre el grupo control y el grupo de estudio con respecto a la migración celular aleatoria [(6)]. Al mismo tiempo Izumi y colaboradores relacionan la pérdida de hueso y avance de la enfermedad con el índice quimiotático del paciente, a menor índice quimiotático mayor progresión en la enfermedad [(6)].

Izumi y colaboradores aluden que existen diferentes teorías sobre el origen de esta modificación en la respuesta defensora, destacando que existe una asociación directa entre el grado de quimiotaxis y la cantidad de receptores quimiotácticos; por otro lado, otro posible factor causal mencionado en este artículo habla de niveles séricos de zinc insuficientes observado en paciente con síndrome de Down con quimiotaxis afectada, dando a entender

que deficiencias en este oligoelemento tiene efecto en la regulación inmunológica [6]. Sin embargo, se encuentra una limitación en esta teoría ya que los autores son incapaces de explicar que dispositivos bioquímicos establecen esta relación.

Amano et al. por otra parte, discuten otra hipótesis para justificar esta disfunción. Ellos explican que las anomalías asociadas a neutrófilos en pacientes trisómicos se relaciona con la inmadurez en el desarrollo de estas unidades. Conforme a los autores, en este caso los neutrófilos presentan reducida segmentación nucleica, evidencia para sugerir que al predominar las formas inmaduras de los neutrófilos existe un acortamiento en la vida media de las mismas [41].

b) Modificaciones en el cromosoma 21

Debido a la naturaleza de la afección, el cromosoma 21 en paciente con síndrome de Down presenta varias alteraciones asociadas a la respuesta inmune de los sujetos. Entre estas modificaciones encontramos, alteraciones en el metabolismo oxidativo [41]. Conforme a Amano et al. el análisis genético de linfocitos T revela una sobre expresión del gen codificante para la enzima superóxido dismutasa, localizado en el cromosoma trisómico 21q.16 [41]. El superóxido dismutasa en una enzima importante en la conversión de superóxidos derivados del oxígeno en peróxido de hidrógeno, de esta manera se sugiere que la abundancia de esta enzima y por ende incremento en concentración de peróxido de hidrogeno desencadenan reacciones con metales como el hierro para formar hidroxilos radicales que pueden inducir peroxidación de lípidos presentes en las membranas celulares y causar daño en los tejidos [41].

Además, el aumento de la enzima anteriormente mencionada a su vez implicaría una reducción en las concentraciones de oxígeno desembocando en una reducción en la actividad bactericida de células con capacidades fagocíticas como las células polimorfonucleares [41]. Esta teoría aún no ha sido completamente esclarecida por los autores por lo que es necesario la elaboración de estudios específicos

En segundo lugar, Amano et al. hacen referencia a cambios asociado en el gen codificante para la molécula de adhesión celular del síndrome de Down, ubicada en la sección 21q22.2-22.3, del cromosoma 21. Estas moléculas de adhesión son parte de una nueva familia de inmunoglobulinas y se asocian a conexiones neuronales [41], y según el artículo se ha encontrado que alteraciones de estas moléculas afecta negativamente la fagocitosis de bacterias debido a la reducción de glicoproteínas superficiales necesarias para adherir y fagocitar bacterias [41].

Cabe destacar que en el artículo de Amano et al., este concepto se pretende aplicar al entorno periodontal en humanos, pero no menciona bases científicas que justifiquen esta extrapolación.

c) Células T4 y T8

Según Morgan [1] en linfocitos T de paciente trisómicos se encuentran impedimentos en la capacidad de reconocer y responder ante antígenos específicos. Además, el autor comenta que el número de células tipo T con receptores funcionales es menor en este tipo de pacientes, y que estas discapacidades celulares tienen que ver con el proceso de maduración

de los linfocitos, donde se observa baja actividad mitótica y debido a ello un incremento de formas inmaduras linfocitarias

d) PGE-2

Morgan [1] también comenta que el desgaste de tejidos periodontales en paciente trisómicos se debe la presencia de altos niveles de prostaglandina E2 en el fluido gingival crevicular en comparación a pacientes euploides. En su trabajo el autor también menciona que la prostaglandina E2 es un fuerte indicador de inflamación y de reabsorción ósea en el medio oral y que una posible teoría detrás de estas alteraciones es la composición de la microflora subgingival, ya que, según lo expuesto, especies *Actinobacillus actinomycetemcomitans* son conocidas por estimular la superproducción de prostaglandina E2 en monocitos.

e) Infra expresión de la interleuquina-10 (IL-10)

Según Cavalcante et al. [42] en individuos sanos ante un ataque bacteriano por periodontitis, se activan los sistemas inmunológicos, específicamente aquellos que incrementa los niveles de mRNA para la interleuquina-10, mientras que en individuos trisómicos estos mismos niveles se ven significativamente rebajados. La interleuquina-10 es un mediador antiinflamatorio que se encuentra atenuado en pacientes con síndrome de Down [42].

Como limitación podemos mencionar que en este estudio no se incluyeron pacientes con síndrome de Down sin afectación periodontal, la inclusión de este grupo a las

observaciones podría ayudar a los investigadores a aclarar si la infra expresión de interleuquina-10 es un resultado de las interacciones de las bacterias periodontales con el medio oral, o si es debida a las características propias de la trisomía.

Propuestas terapéuticas para tratar la enfermedad periodontal. Enfoque sistémico

a) **Terapia fotodinámica como coadyuvante antibacteriano**

Según Larrea-Oyarbide et al. [9] la terapia fotodinámica sería de gran ayuda en el tratamiento periodontal a nivel bacteriano ya que ayuda en la destrucción de los contenido de las bolsas periodontales y en su descontaminación por medio de la eliminación de bacterias anaerobias, argumentando que si se utiliza un láser de diodo de 805nm de longitud de onda a una potencia de 2,5W para la limpieza de bolsas periodontales durante máximo 4 segundos, se consigue la eliminación de especies *Actinobacillus actinomycetemcomitans* en más del 70 % y de especímenes *Prevotella intermedia* en más del 80%.

Larrea-Oyarbide et al. [9] comentan que la potencia mínima para obtener un efecto bactericida es de 1W y que si se sobrepasa ese límite se corre el riesgo de carbonización irreversible de los tejidos.

Otro trabajo de Escudero-Castaño et al. [8] concuerda con lo dicho anteriormente, el uso de láser de diodo como coadyuvante antibacteriano en el tratamiento periodontal básico tiene gran potencial ya que puede eliminar en gran porcentaje las bacterias del tipo *Actinobacillus actinomycetemcomitans*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia* y *Streptococcus sanguis*. Aunque, según comenta Escudero-Castaño et al. no se encontraron en sus resultados suficiente evidencia estadística que justifique estas afirmaciones [8].

Las discrepancias entre estos autores pueden deberse a que, en el estudio de Escudero-Castaño et al. la muestra del estudio es demasiado pequeña para realizar injerencias estadísticas. Asimismo, debe tenerse en cuenta que la flora oral si bien presenta organismos que pueden identificarse en numerosas poblaciones, suele ser un factor muy específico del huésped, y lejos de ser un factor estático presenta dinamismo frente a los estímulos endógenos y exógenos que aparezcan.

b) **Melatonina como herramienta de regeneración ósea**

Acikan et al. [11] mencionan que la melatonina podría inducir formación ósea mandibular, y también tendría el poder de inducir la diferenciación de osteoblastos inmaduros para ayudar en la formación de hueso. Además, en este artículo se destaca la capacidad de la melatonina para promover la expresión de sialoproteinas, osteocalcina y osteopontina, todos componentes claves en la formación de la matriz ósea. Acikan et al. indica que la melatonina puede inhibir la reabsorción ósea e incrementar la densidad de hueso inactivando el receptor del ligando kappa-B que juega un rol importante en la formación de osteoclastos. De la misma manera, en este artículo se indica que dosis farmacológicas de melatonina incrementan la cantidad de masa ósea, densidad mineral del mismo y el volumen de hueso trabecular [11].

Es importante notar que este estudio basa sus argumentos en interacciones ocurridas en ratones y no seres humanos, por lo que el mecanismo de acción de la melatonina podría verse afectado si se estudiase en modelos humanos, ya que en estos también existen múltiples factores genéticos y no genéticos que afectan la remodelación ósea.

Sifat y Witt-Enderby [10] argumentan por su parte, que la melatonina posee una habilidad antioxidante, y por ello puede eliminar radicales libres que, según los autores, son causantes del agravamiento de la enfermedad periodontal.

c) **Administración de péptidos antimicrobianos para reducir la carga bacteriana dentro de la cavidad oral.**

Gorr et al. [12] explican que la administración de péptidos microbianos específicos para un microorganismo son una alternativa al tratamiento antibiótico regular ya que, ayudan a preservar aquellas bacterias comensales que son beneficiosas para el equilibrio de la flora oral. Se ha demostrado que estos péptidos antimicrobianos hechos a medida, poseen una capacidad bactericida ante la presencia de *Pseudomonas aeruginosa, Streptococcus mutan, Escherichia coli* y *Staphylococcus epidermis.*

Según lo escrito por Gorr et al. comentan que se pueden obtener péptidos antimicrobianos "de diseño" mediante la síntesis de moléculas miméticas. Una de las que mencionan, llamada mPE, muestra una baja toxicidad, correcta especificidad contra diferentes tipos de bacterias, incluso bacterias resistentes a la terapia antibiótica, y disminuye el riesgo de provocar resistencia en *Staphylococcus aureus* [12]. En el artículo se explica, además, que mPE es eficaz contra bacterias Gram positivas y negativas que se pueden encontrar en el biofilm. Otro ejemplo, es el compuesto XOMA 629 desarrollado por la Universidad de Berkeley, en el que se observa capacidad bactericida y antifúngica [12].

De los ejemplos mencionados por Gorr et al. es importante destacar que estos compuestos aún no se han probados en humanos, si no en cultivos independientes y estudios preclínicos por lo que se desconoce los resultados de su aplicación clínica.

d) **Ingesta de suplementos de vitamina D**

Garcia et al. [15] sugieren que la ingesta de vitamina D no influye en la mejora de la enfermedad periodontal si el paciente recibe tratamiento regular. Sin embargo, sí afirman que la ingesta de suplementos de calcio y vitamina D está asociada a una mejora en la salud periodontal comparado a la no ingesta. Garcia et al. argumenta que en los pacientes periodontales que toman suplementos de este tipo hay evidencia de menor sangrado al sondaje y reducción de la inflamación de los tejidos. En este estudio, los autores determinaron que una ingesta mayor a 400 IU diarias es suficiente para observar mejoras en la salud periodontal [15].

Se debe notar que este estudio comenta los efectos beneficiosos del calcio como tratamiento a largo plazo, resultados favorables fueron observador después de un año de ingesta de suplementos en paciente con periodontitis moderada. Es difícil predecir qué efectos tendría una ingesta de calcio a igual concentración en paciente con déficits inmunológicos que agravan su situación periodontal, como lo son los analizados en este trabajo.

e) Inyecciones en papila interdental de inhibidores de la IL-1 (interleuquina-1) y TNF (factor tumor necrosante)

Delima et al. [16] presentaron un estudio donde cometan la eficacia del tratamiento periodontal con inyecciones intrapapilares de inhibidores solubles de interleuquina-1 y factor tumor necrosante. En su estudio remarcan, que la aplicación local de receptores solubles de estos dos mediadores de inflamación *in vivo* es eficaz en la inhibición de la pérdida de tejido conectivo evidenciaba por menor pérdida de inserción clínica, menor distancia del límite amelo-cementario al hueso alveolar.

En este estudio, encontramos diversos factores limitantes, primero que la metodología de replicación de la enfermedad periodontal no refleja las variantes progresivas de la enfermedad, su forma más común, si no que representa un modelo híper agudo que es difícil de evidenciar a efectos reales en humanos. De igual forma, este es un estudio realizado en animales en el cual es posible dudar si refleja con exactitud las respuestas del medio oral humano.

5. CONCLUSIÓN

- Se establece mediante la lectura de artículos, la importancia de la asociación entre la condición periodontal y tres enfermedades sistémicas: diabetes, síndrome de Down y VIH.
- Gracias al análisis de la literatura, es posible identificar los procesos celulares a través de los cuales se manifiesta la enfermedad periodontal en los tres tipos de pacientes mencionados.
    - En el caso de pacientes diabéticos, según la recopilación de archivos, destaca el papel que juegan los marcadores PGE-2, IL-1 junto con el TNF-α en la reacción inflamatoria y su relación bidireccional con la afección.
    - En aquellos pacientes portadores del VIH, la reacción inflamatoria la domina el déficit cuantitativo de linfocitos, especialmente los linfocitos T4, siendo esta carencia una característica propia de la enfermedad.
    - En los pacientes trisómicos, se destacan las modificaciones genéticas en el cromosoma 21 específicas de esta patología.
- Respecto a las opciones terapéuticas, se han desarrollado seis terapias alternativas al tratamiento periodontal convencional.
- Para el correcto tratamiento de las manifestaciones orales de la enfermedad periodontal es importante tener en cuenta no solo los factores relacionados con la higiene y hábitos de vida del paciente, si no también estudiar en profundidad la respuesta inmune del huésped y personalizar las técnicas terapéuticas a los

requerimientos del paciente. Estos métodos innovadores funcionan mejor en conjunto con un tratamiento periodontal estándar.

- Es importante, no solo la labor del odontólogo en la práctica si no también la cooperación con otros profesionales como, médicos, microbiólogos o genetistas que trabajen en conjunto para transformar estas terapias, a veces desconocidas por los aquejados, en terapias de acceso universal.

6. RESPONSABILIDAD

Sostenibilidad Medioambiental

Es importante que los expertos tanto generales como odontólogos aprendan a diferenciar formas prevalentes de enfermedad periodontal de aquellas derivadas sistémicas graves y de interés en salud pública como lo son la diabetes mellitus y la infección por virus de inmunodeficiencia humana. La educación de la población general también es de gran relevancia para que puedan identificar el momento de aparición de los síntomas y signos de dichas afectaciones. Esta convergencia entre pacientes y profesionales deriva en un tratamiento odontológico completo donde se tengan en cuenta todas las variables que puedan influenciar en su éxito.

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ANEXOS

Morgan J. Why is periodontal disease more prevalent and more severe in people with Down syndrome? Special Care in Dentistry. 2007;27(5):196–201

ARTICLE

ABSTRACT

Periodontal disease has been found to be significantly more prevalent and more severe in people with Down syndrome. A series of studies have reported a prevalence of between 58% and 96% for persons younger than 35 years of age. This phenomenon cannot simply be attributed to poor oral hygiene. The etiology of periodontal disease in persons with Down syndrome is complex. In recent years, much focus has been placed on the altered immune response resulting from the underlying genetic disorder. This paper presents an overview of contemporary knowledge on periodontal disease in patients with Down syndrome.

KEY WORDS: Down syndrome, periodontal disease, preventive care

Why is periodontal disease more prevalent and more severe in people with Down syndrome?

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Introduction

Down syndrome (DS) is an autosomal chromosomal disorder resulting from trisomy of all or part of chromosome 21.[1] Approximately 95% of people with DS have an extra complete chromosome 21. The remaining 5% result from other chromosomal abnormalities including translocation in 3% of people and mosaicism in 2% of people.[2,3] The incidence of DS is generally cited as being between 1 in 600 to 1 in 1,000 live births.[4] In Ireland, this condition affects approximately 1 in 580 live births, which is the highest incidence in Europe.[4]

Periodontal disease is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both."[5]

The pathogenesis of periodontal disease is complex. In response to microbial substances released from plaque bacteria in the gingival sulcus, epithelial and connective tissue cells are stimulated to produce inflammatory mediators, leading to infiltration of the connective tissue by numerous defense cells. In the early stages of the immune response, neutrophils predominate. As further microbial substances enter the systemic circulation, committed lymphocytes return to the site of infection, and antibodies specific to bacterial antigens are produced by plasma cells. This essentially protective response is enough to control the infection in people who are not susceptible to periodontitis.[6]

In susceptible individuals, however, the primary host defenses are unable to control the microbial challenge, leading to the epithelium becoming increasingly permeable and ulcerated. There is increased migration of neutrophils into the tissues, which secrete a variety of inflammatory mediators and proteolytic enzymes. Once the concentration of these inflammatory mediators and enzymes becomes pathologically high, histological destruction of the collagen fibers, periodontal ligament, and alveolar bone occurs.[6] Preshaw *et al.*[6] noted that the majority of periodontal destruction is the result of "collateral damage arising from the activation of the host defenses against the presence of bacteria".

In 2005, the World Health Organization provided an overview of periodontal disease worldwide and reported that 10% to 15% of adults suffered from periodontal disease.[7] Brown *et al.*[8] reported that the prevalence of periodontal disease among the general population in the United States ranged from 29% for persons aged 19 to 45 years, to 50% for persons aged 45 years and older. An increased prevalence and severity of periodontal disease has been reported in people with DS compared with age-matched subjects of similar levels of intellectual impairment and compared with the general population.[9,10] Prevalence varies between 58% and 96% for those under 35 years of age.[11,12]

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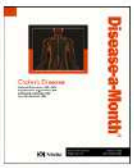

Effects of periodontal disease on systemic health

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ABSTRACT

About one in two adults in the United States has periodontal disease. Chronic periodontitis is an oral disease affecting the supporting structures of the teeth leading to progressive loss of the attachment apparatus and bone around teeth. It is characterized by gingival pocket formation and/or gingival recession. The disease is initiated by bacteria and their components like lipopolysaccharide and causes a heightened host inflammatory response. This cascade of inflammatory response ultimately leads to an increased osteoclastic activity and bone loss. Individuals with periodontitis have increased systemic levels of acute phase proteins, plasma antibody levels, coagulation factor, total white blood cell count, neutrophils, C reactive protein (CRP), and cytokines such as INF- gamma (Interferon gamma), TNF-α (Tumor necrosis Factor- Alpha), IL (Interleukin)-1β, IL-2 and IL-6. As periodontitis works on the same chronic inflammation model seen in systemic diseases, there is sufficient evidence to suggest a bi-directional link between the two. This article summarizes the established associations between periodontal disease and systemic health.

Introduction

Periodontitis is a chronic inflammatory disease that affects the gums and the bone surrounding teeth caused by an organized community of bacteria called dental plaque. The bacteria

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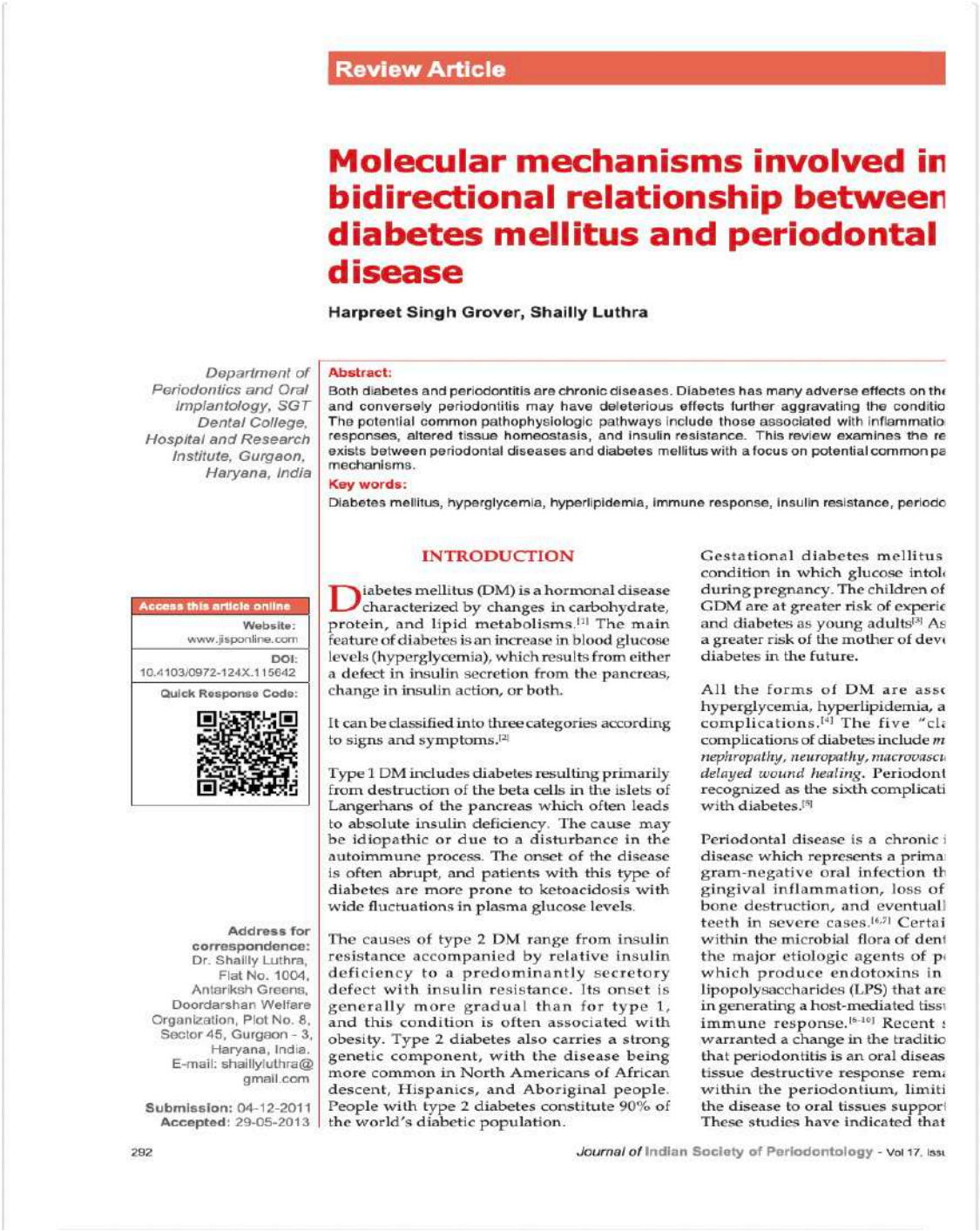

Review Article

Molecular mechanisms involved in bidirectional relationship between diabetes mellitus and periodontal disease

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Abstract:

Both diabetes and periodontitis are chronic diseases. Diabetes has many adverse effects on the and conversely periodontitis may have deleterious effects further aggravating the conditio The potential common pathophysiologic pathways include those associated with inflammatio responses, altered tissue homeostasis, and insulin resistance. This review examines the re exists between periodontal diseases and diabetes mellitus with a focus on potential common pa mechanisms.

Key words:

Diabetes mellitus, hyperglycemia, hyperlipidemia, immune response, insulin resistance, periodc

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INTRODUCTION

Diabetes mellitus (DM) is a hormonal disease characterized by changes in carbohydrate, protein, and lipid metabolisms.[1] The main feature of diabetes is an increase in blood glucose levels (hyperglycemia), which results from either a defect in insulin secretion from the pancreas, change in insulin action, or both.

It can be classified into three categories according to signs and symptoms.[2]

Type 1 DM includes diabetes resulting primarily from destruction of the beta cells in the islets of Langerhans of the pancreas which often leads to absolute insulin deficiency. The cause may be idiopathic or due to a disturbance in the autoimmune process. The onset of the disease is often abrupt, and patients with this type of diabetes are more prone to ketoacidosis with wide fluctuations in plasma glucose levels.

The causes of type 2 DM range from insulin resistance accompanied by relative insulin deficiency to a predominantly secretory defect with insulin resistance. Its onset is generally more gradual than for type 1, and this condition is often associated with obesity. Type 2 diabetes also carries a strong genetic component, with the disease being more common in North Americans of African descent, Hispanics, and Aboriginal people. People with type 2 diabetes constitute 90% of the world's diabetic population.

Gestational diabetes mellitus condition in which glucose intol during pregnancy. The children of GDM are at greater risk of experic and diabetes as young adults[3] As a greater risk of the mother of dev diabetes in the future.

All the forms of DM are assc hyperglycemia, hyperlipidemia, a complications.[4] The five "cl complications of diabetes include *m nephropathy, neuropathy, macrovascu delayed wound healing*. Periodont recognized as the sixth complicati with diabetes.[5]

Periodontal disease is a chronic disease which represents a prima gram-negative oral infection th gingival inflammation, loss of bone destruction, and eventuall teeth in severe cases.[6,7] Certai within the microbial flora of dent the major etiologic agents of p which produce endotoxins in lipopolysaccharides (LPS) that are in generating a host-mediated tiss immune response.[8-10] Recent warranted a change in the traditio that periodontitis is an oral diseas tissue destructive response rema within the periodontium, limiti the disease to oral tissues support These studies have indicated that

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Lucht E, Heimdahp A, Nord CE. Periodontal disease in HIV-infected patients in relation to lymphocyte subsets and specific micro-organisms

Periodontal disease in HIV-infected patients in relation to lymphocyte subsets and specific micro-organisms

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Lucht E, Heimdahl A and Nord CE: Periodontal disease in HIV-infected patients in relation to lymphocyte subsets and specific micro-organisms. J Clin Periodontol 1991: 18: 252–256.

Abstract. Visible plaque index (VPI), gingival bleeding index (GBI) and pocket depth (PD) were analyzed in relation to potential periodontal pathogenic micro-organisms and peripheral numbers of T4+ and T8+ lymphocyte subsets in 10 patients with human immunodeficiency virus (HIV) infection, 10 patients with AIDS related complex (ARC) and 10 patients with acquired immune deficiency syndrome (AIDS). 10 healthy persons served as controls. Periodontal disease in patients with more advanced stages of HIV infection were related to the severity of the systemic disease, and to decreasing numbers of T4+ lymphocytes in peripheral blood, but not to VPI or the occurrence of periodontal pathogenic micro-organisms.

Key words: periodontal disease; HIV-infections; lymphocyte subsets; immune deficiency; micro-organisms.

Accepted for publication 8 May 1990

Periodontal complications and symptoms related to infection with human immunodeficiency virus (HIV) have been observed and described during recent years (Kenrad et al. 1987, Reichart et al. 1987). Necrotizing gingivitis is observed in up to 9% of patients and rapidly progressive periodontitis is another frequent finding in HIV-positive individuals (Reichart et al. 1987, Winkler & Murray 1987). Different hypotheses have been proposed with regard to the etiology of gingivitis and periodontitis in HIV-patients. Thus, a shift in the microflora, changes in the host's defense mechanisms as well as a direct effect of HIV have been postulated (Gornitsky & Pekovic 1987, Winkler & Murray 1987).

In this paper, we report on the occurrence of gingivitis and progressive periodontitis in patients with different stages of HIV-infection in relation to dental plaque, microbiological findings and peripheral blood concentrations of T4+ and T8+ helper/suppressor cells.

Material and Methods

Patients

30 patients with different stages of HIV-infection participated in the study. 10 of the patients were HIV-positive without clinical signs of infection. 10 patients had clinical symptoms corresponding to the AIDS-related complex (ARC) and 10 patients had the full acquired immune deficiency syndrome (AIDS) according to the CDC-definition (1986). 2 HIV-positive subjects without clinical symptoms were heterosexually infected females. 27 patients were male homosexuals and 1 person was a male intravenous drug abuser. An age-matched group of 10 heterosexual HIV-negative men served as control. The mean age in the 4 groups were: controls: 37.7 years, HIV-grop: 35.5, ARC-group: 42.3 years, AIDS-group: 38.1.

Medication

Any medication for HIV infection or HIV related problems as well as other drugs was registered.

Clinical registration of periodontal disease

The occurrence and distribution of dental plaque was recorded and a visible plaque-index (VPI) was calculated for each individual (Ainamo & Bay 1975). The number as well as the extent of necrotized gingival papillas were recorded and the distribution of gingivitis was estimated by a gingival bleeding index (GBI) (Ainamo & Bay 1975). Periodontal disease was estimated by probing 4 sites of each tooth (Ainamo et al. 1982). From these values, the mean pocket depth was calculated as well as the number of periodontal pockets >4 mm.

Microbiological investigations

From the 3 deepest periodontal pockets in each quadrant, samples for microbiological investigations were obtained as described by Slots & Rosling (1983) 3 coal paperpoints (Johnson Fine Absorbent Point, Johnson & Johnson, East Windsor, NJ) were subsequently inserted into the periodontal site until resistance was met. The points were kept in place for 10 seconds and then transferred to 2 ml transport medium VMG II (Möller 1966).

The total counts of the predominant cultivable microorganisms (numbers of colony forming units (CFU)/ml transport medium) were estimated from serial 10-fold dilutions of aerobically and anaerobically incubated supplemented blood-agar plates. The subgingival microflora was monitored for total counts of *Actinobacillus actinomycetemcomit-*

Yeung SCH, Stewart GJ, Cooper DA, Sindhusake D. Progression of Periodontal Disease in HIV Seropositive Patients. Journal of Periodontology. 1993;64(7):651–7

Progression of Periodontal Disease in HIV Seropositive Patients

Stephen C. H. Yeung, Graeme J. Stewart,† David A. Cooper,‡ and Doungkamol Sindhusake§*

DATA FROM CROSS-SECTIONAL STUDIES suggest that periodontitis in HIV-infected patients is a more destructive form of disease in contrast to the slowly progressing form of adult periodontitis in the general population. We studied prospectively over an 18-month period 30 HIV infected, but asymptomatic, patients and compared the rate of periodontal attachment loss with that of a healthy control group (n = 10) matched for age and plaque index. Every 6 months, each subject was assessed for their clinical status by a physician and CD4+ cell count determined. The proliferative response of peripheral blood lymphocytes was determined by in vitro cultures with PHA and Con A. The periodontal health status was assessed by scoring with plaque index (PI), gingival index (GI), and periodontal disease index (PDI). The control subjects were assessed for periodontal status only. Of the 30 HIV-positive patients whose data were analyzed 14 received Zidovudine (AZT) while the remaining 16 did not. There was no correlation between any clinical parameter measured and periodontal status as determined by PI or GI. However, a significant difference in the change of periodontal disease index (PDI) was observed between the HIV-infected and control groups ($P = 0.005$). We concluded that HIV-infected patients with pre-existing periodontitis tend to experience a greater rate of attachment loss over time compared with controls. *J Periodontol 1993; 64:651–657.*

Key Words: Periodontal index; periodontitis; HIV infections/physiology; periodontal attachment; disease progression.

Human immunodeficiency virus (HIV) infection is a major interest and concern to dentists and other oral health care workers because of the many varieties of oral lesions often associated with an HIV infection. Most of these lesions are considered opportunistic infections. For example, oral candidiasis caused by *Candida albicans*,[1,2] ulcers caused by herpes simple virus,[3] and oral warts by papillomavirus[4] are a few of the commonly occurring oral lesions. Furthermore, Epstein Barr virus (EBV) is thought to be associated with hairy leukoplakia,[5] while cytomegalovirus has been implicated in Kaposi's sarcoma.[6,7] An aggressive form of gingivitis and periodontitis has also been reported in the literature.[8–10] The incidence of gingivitis and periodontitis among HIV-infected persons is reported to be high.[11–12] This clinical observation has important implication for the management of HIV-infected and AIDS patients. Typically, the lesion resembles that of acute necrotizing ulcerative gingivitis (ANUG) and is characterized by rapid loss of attachment and alveolar bone as well as being extremely painful.[11] Unfortunately, the mechanism for this rapid tissue destruction is not known.

Data from cross-sectional studies suggest that periodontitis in HIV-infected persons is a more destructive form of periodontal disease in contrast to the slowly progressing form of adult periodontitis in the general population.[11] We studied the periodontal status of a cohort of HIV-infected, but asymptomatic, males for a minimum period of 18 months. The change of their periodontal status was then compared with a smaller cohort of healthy individuals (HIV negative) matched for age and sex, plaque index, gingival index, and periodontal disease index. The aim of this study was to determine the difference, if any, in the rate of progression of periodontal disease over time between a group of HIV-seropositive men and a control group.

MATERIALS AND METHODS

Patients

After obtaining informed consent, 45 HIV-infected but asymptomatic patients who were enrolled for a placebo-controlled clinical trial of Zidovudine (AZT) at St. Vincents' Hospital, Sydney, were recruited into the present study. Of the 45 patients, 15 were excluded from the data

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Izumi Y, Sugiyama S, Shinozuka O, Yamazaki T, Ohyama T, Ishikawa I. Defective Neutrophil Chemotaxis in Down's Syndrome Patients and Its Relationship to Periodontal Destruction. Journal of Periodontology. 1989;60(5):238–42

Defective Neutrophil Chemotaxis in Down's Syndrome Patients and Its Relationship to Periodontal Destruction

Y. Izumi*, S. Sugiyama,* O. Shinozuka† T. Yamazaki,† T. Ohyama,† and I. Ishikawa*

THE DEGREE OF DEFECTIVE NEUTROPHIL chemotaxis in patients with Down's syndrome (DS) and its relationship to the severity of periodontal disease were studied. Fourteen patients with DS and 14 healthy controls were examined. Oral hygiene, gingival inflammation, and pocket depths were measured in clinical surveys. Bone loss was evaluated on the oral radiographs. Neutrophil chemotaxis was measured by the agarose plate method and the Boyden chamber method. The chemotactic index of the agarose plate method and the mean numbers of migrated cells of the Boyden chamber method were correlated with statistical significance ($r_s = 0.066$, $P < 0.01$). DS patients showed significantly lower chemotaxis than healthy volunteers with both methods. No difference was shown between the two groups in the random migration of the neutrophils. From the oral radiographic analysis, the DS patients exhibited various prevalence of bone loss which was inversely proportional to the chemotactic index and a significant correlation between them was shown ($r_s = -0.612$ $P < 0.05$). A significant correlation was also found between the age of the patient and the prevalence of bone loss ($r_s = 0.591$ $P < 0.05$). These results indicate that defective neutrophil chemotaxis influences the progression of periodontal disease in DS patients.

Down's syndrome, or trisomy 21, was first described as the "Mongolian type of idiocy" in 1866 by Down.[1] Lejeune et al.[2] discovered that Down's syndrome was caused by a chromosomal aberration. The unusual genetic background of these subjects is responsible for the gross physical and mental abnormalities which are characteristics of this syndrome. Increased susceptibility to infection has been found in patients with the syndrome. The high prevalence of advanced periodontal disease in patients with DS has been emphasized repeatedly in several studies. Prevalence rates of from 60% to 100% in young adults under 30 years of age have been reported.[3–9] It is suspected that the increased progression of periodontal disease is caused by both endogenous and exogenous factors.[10] Leukocytes have been shown to be an important host defense in the periodontal barrier. Defects or dysfunctions of bactericidal capacities have been described in the leukocytes of DS patients. Gregory et al.[11] found partial phagocytosis of the leukocytes against staphylococus in 10 out of 63 DS children. Kretschmer et al[12] reported that about 50% of DS patients had defects in the capacities of the leukocytes to reduce NBT and to kill staphylococci. Defective neutrophil function was related to the rapid progress of the disease as is seen in juvenile periodontitis. Recently, defective neutrophil chemotaxis has also been reported in DS patients.[13,14] The purpose of this investigation was to clarify the relationship of defective neutrophil chemotaxis in DS patients to the severity of periodontal disease.

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MATERIALS AND METHODS

Fourteen patients with DS (9 males and 5 females, 12 to 34 years of age with a median of 17.7 years of age) were examined. The diagnosis of DS was confirmed as trisomy 21 by cytogenetic examinations. Clinical examinations, surveys of dental radiographs for bone loss, and analysis of neutrophil chemotaxis were performed on the patients. The control group consisted of 14 healthy subjects with no deepened periodontal pockets (12 males and 2 females, 23 to 26 years of age with a median 24.0 years of age). The same clinical and laboratory examinations were carried out on both groups.

At the clinical examinations, oral hygiene was assessed using the Plaque Control Records of O'Leary et al.[15] after disclosing the whole dentition. The amount of gingival inflammation was measured by the Gingival Index of Löe and Silness[16] on teeth numbers 16, 21, 24, 36, 41, and 44.[17] Pocket depth was measured with a periodontal probe on the above mentioned teeth.

Axelsson P, Lindhe J. The significance of maintenance care in the treatment of periodontal disease. Vol. 8, Journal of Clinical Periodoniology. 1981

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The significance of maintenance care in the treatment of periodontal disease

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Abstract. The present investigation was performed to assess the efficacy of a maintenance care program to prevent recurrence of disease in patients subjected to treatment of advanced periodontitis. In addition, the periodontal status was monitored of a group of patients who following the end of active treatment were referred back to general practitioners for maintenance care. The material consisted of 90 patients who in 1972 were referred for specialist treatment of advanced periodontal disease. The patients were first subjected to an initial examination including assessment of oral hygiene, gingivitis, probing depths and attachment levels. They were on an individual basis given case presentation, instructed how to practice proper tooth-cleaning methods, their teeth were scaled and eventually the periodontal pockets were treated using the modified Widman technique. During the first 2 months following surgery the patients were recalled once every 2 weeks for professional tooth cleaning. Two months after the end of surgical treatment, the patients were reexamined to provide baseline data. Every third patient was thereafter referred back to the general dentist for maintenance care. Two out of three patients were maintained in a carefully designed and controlled maintenance care program at the university clinic. This program involved recalls once every 2–3 months and included instruction and practice in oral hygiene, meticulous scaling and professional tooth cleaning. The patients were reexamined 3 and 6 years after the baseline examination.

The results demonstrated that in patients suffering from destructive periodontitis, a treatment program that involved oral hygiene instruction, scaling, root planing and modified Widman flap procedures resulted in the establishment of clinically healthy gingiva and shallow pockets. Patients who were placed on a carefully designed recall program were over a 6-year period able to maintain excellent oral hygiene standards and unaltered attachment levels. In contrast patients who subsequent to active treatment were not maintained in a supervised program showed obvious signs of recurrent periodontitis at the follow-up examinations.

It is obvious from a number of long- and short-term studies that treatment of periodontal disease including oral hygiene instruction, scaling, root planing and surgery – in order to get access to the root surfaces for proper debridement – can not only arrest the gradual breakdown of the supporting apparatus but, indeed, also result in gain of clinical attachment and regrowth of alveolar bone (e.g. Ramfjord et al. 1973, Lindhe & Nyman 1975, Rosling et al. 1976, Polson & Heijl 1978, Knowles et al. 1979). It has also become apparent, however, that the long-term success of periodontal treatment is dependent upon the effectiveness of the maintenance care program's subsequent active treatment. Hence, in patients who following completion of surgical treatment are placed on maintenance care which includes recalls every 3 months for prophylaxis and instruction in home care techniques, the long-term result of treatment seems to be successful. On the other hand in patients who are recalled for maintenance care at a less frequent interval (6–12 months) there is an obvious risk for recurrence of periodontitis (Nyman et al. 1975, 1977).

Studies by Suomi et al. (1971), Björn (1974),

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Una terapia innovadora en el tratamiento de la enfermedad periodontal. La terapia fotoactiva

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ESCUDERO-CASTAÑO, N.; PEREA-GARCÍA, M.A.; GARCÍA-GARCÍA, V.; BASCONES-MARTÍNEZ, A. *Una terapia innovadora en el tratamiento de la enfermedad periodontal. La terapia fotoactiva.* Cient Dent 2009;6;1:9-19.

RESUMEN

INTRODUCCIÓN: A pesar de que las terapias mecánicas y químicas han demostrado una gran efectividad clínica en estudios longitudinales, el tratamiento con las mismas no se halla exento de una serie de limitaciones, como la incapacidad de eliminar de forma predecible determinados patógenos periodontales, o la capacidad de recolonización de dichos patógenos persistentes en otros nichos orales, así como el gran problema que supone el uso abusivo de los antibióticos: las resistencias. Estas limitaciones de la terapia convencional nos sirven de justificación en la búsqueda de tratamientos alternativos, como es el caso de la terapia fotoactiva. Así, en este estudio, el objetivo fundamental es comprobar si la terapia fotoactiva podría combatir estas adversidades junto con una mejora en los parámetros microbiológicos. MATERIAL: Estudio piloto con 15 pacientes divididos en 3 grupos de tratamiento. MÉTODO: Ensayo clínico randomizado, paralelo y a doble ciego en pacientes seleccionados a través de un muestreo no probabilístico de casos consecutivos. RESULTADOS: No existen diferencias estadísticamente significativas entre los tratamientos empleados. CONCLUSIONES: No se demuestra la superioridad de ningún tratamiento frente al resto, a la hora de valorar los parámetros microbiológicos.

PALABRAS CLAVE

Terapia fotodinámica; Terapia fotoactiva; Láser diodo; Azul de metileno.

An innovator therapy for the periodontal disease. The photoactive therapy

SUMMARY

INTRODUCTION: Although longitudinal studies have shown the clinical efficacy of both mechanical and chemical therapies, there are still some inconvenient such as the ability to suppress in a predictable manner specific periodontal pathogens; the regrowth capacity of such pathogens and their ability to persist in other oral niches, plus the big antibiotic problem caused by resistance. In this context the aim of this study was to test that photoactive therapy can be used in order to avoid these adversal effects and improve microbiological parameters. MATERIAL: Pilot study with 15 patients divided into 3 treatment groups. METHOD: Randomized parallel double blind study, with a non-probabilistic consecutive patients selection. RESULTS: There are no SS differences between therapies tested. CONCLUSION: No treatment has shown to be better tan another regarding microbiological parameters.

KEY WORDS

Photodynamic therapy; Photoactive therapy; Methylene blue; Diode laser.

Larrea-Oyarbide N, España-Tost A, Berini-Aytés L, Gay- Escoda C. Aplicaciones del láser de diodo en Odontología. Rev del Ilus Cons Gen Colegios Odontólogos y Estomatólogos España [Internet]. 2004;9(5):529–34. Available from: http://www.gayescoda.com

Aplicaciones del láser de diodo en Odontología


Larrea-Oyarbide, Nerea

Applications of diode laser in dentistry

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Resumen: El láser de diodo tiene numerosas aplicaciones en la especialidad de Cirugía Bucal siendo utilizado preferentemente para realizar intervenciones quirúrgicas sobre los tejidos blandos siempre que no impliquen un excesivo sangrado. En Endodoncia, Implantología Bucofacial y Periodoncia se emplea por su importante efecto bactericida. También se utiliza en procedimientos de blanqueamiento dentario. Es importante controlar adecuadamente el tiempo de aplicación y la potencia de trabajo para evitar el sobrecalentamiento de los tejidos vecinos, lo que produciría su necrosis. Siempre que se utilice el láser de diodo se debe efectuar la protección ocular recomendada tanto para el profesional, sus ayudantes y personal auxiliar, como para el paciente.

Palabras clave: Láser de Diodo, Láser en Odontología.

Abstract: The diode laser has numerous applications in the specialty of Oral Surgery, being preferentially used for surgical interventions on soft tissues as long as they do not imply an excessive bleeding. In endodontics, implantology and periodontics it is used because of its important bactericidal effect. It is also used for dental bleaching procedures. It is important to appropriately control the time of application and the working power in order to avoid the overheating of the neighbouring tissues and the subsequent necrosis. Whenever the diode laser is used, all the participating persons – clinician, assistants, auxiliary personnel and patient – have to wear the recommended eye protection.

Key words: Diode laser, Laser in Dentistry.

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Sifat A, Witt-Enderby PA. Melatonin effects on bone: Potential use for the prevention and treatment for osteopenia, osteoporosis, and periodontal disease and for use in bone-grafting procedures. Journal of Pineal Research. 2014;56(2):115–25

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Journal of Pineal Research

Journal of Pineal Research — Molecular, Biological, Physiological and Clinical Aspects of Melatonin

REVIEW ARTICLE

Melatonin effects on bone: potential use for the prevention and treatment for osteopenia, osteoporosis, and periodontal disease and for use in bone-grafting procedures

Abstract: An important role for melatonin in bone formation and restructuring has emerged, and studies demonstrate the multiple mechanisms for these beneficial actions. Statistical analysis shows that even with existing osteoporotic therapies, bone-related disease, and mortality are on the rise, creating a huge financial burden for societies worldwide. These findings suggest that novel alternatives need to be developed to either prevent or reverse bone loss to combat osteoporosis-related fractures. The focus of this review describes melatonin's role in bone physiology and discusses how disruption of melatonin rhythms by light exposure at night, shift work, and disease can adversely impact on bone. The signal transduction mechanisms underlying osteoblast and osteoclast differentiation and coupling with one another are discussed with a focus on how melatonin, through the regulation of RANKL and osteoprotegerin synthesis and release from osteoblasts, can induce osteoblastogenesis while inhibiting osteoclastogenesis. Also, melatonin's free-radical scavenging and antioxidant properties of this indoleamine are discussed as yet an additional mechanism by which melatonin can maintain one's bone health, especially oral health. The clinical use for melatonin in bone-grafting procedures, in reversing bone loss due to osteopenia and osteoporosis, and in managing periodontal disease is discussed.

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Key words: melatonin, menopause, osteoblasts, osteoclasts, osteopenia, osteoporosis, Per2

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Worldwide, 8.9 million osteoporosis-related fractures occur every year, amounting to about one osteoporosis-related fracture every 3 s [1]. According to the International Osteoporosis Foundation, more than 200 million women worldwide have osteoporosis where most of them are age 60 or over [2]; the female-to-male ratio for fracture is 1.6 [1]. In the European Union, approximately 22 million women and 5.5 million men (between 50 and 84 yr) are projected to have osteoporosis; this number will rise by 23% by 2025 [3]. In the United States, nearly 57 million adults over age 50 are affected by bone disease, 48 million adults have osteopenia, and 9 million adults have osteoporosis, which places these individuals at risk for developing bone fracture. If left unchanged, by 2030, the prevalence of osteoporosis will increase to 11.9 million and 64.3 million with osteopenia [4].

In the United States, the annual fracture rate is 1.5 million per year (300,000 hip and 700,000 vertebral fractures), which is expected to increase by 3 million by 2025 [5, 6]. In the United Kingdom, although it was expected that the 12-month survival rate after hip fracture would be 90–91%, the actual numbers were less than expected with 63.3% of men and 74.9% of women surviving [7]. In the United States, hip fracture is responsible for approximately 31,000 excess deaths within 6 months, which can start as early as age 50; this is significant, considering that one in every three women and one in five men in the United States will experience an osteoporosis-related fracture in their lifetime [6]. In addition to increasing morbidity and mortality rates, osteoporosis-related fractures are also creating huge economical burdens to societies worldwide. For example, osteoporosis treatment and related fracture cost in the United States (per year) is $19 billion, which is expected to increase to $25.3 billion by 2025 [6]. In 2010, osteoporosis-related costs amounted to about €37 billion in the European Union where fracture treatment (66%) and long-term fracture care (29%) accounted for a majority of these costs [1, 8].

A greater prevalence of bone loss and related fractures occurs in an aging population, especially in postmenopausal women, where 30% of all postmenopausal women have osteoporosis and 40% of them are anticipated to have one or more fractures during their lifetime [9]. The hormonal imbalances that occur during the menopausal transition that contribute to vasomotor symptoms are also involved in bone loss [10]. Interestingly, a study comprised of 149,524 white postmenopausal women (mean age 64.5 yr) showed that among 2259 women in whom a new fracture occurred after 1 yr, 82% of them were osteopenic [11]; a 5.6-yr study on postmenopausal women found similar results [12]. These studies suggest that attention should be given to those with osteopenia as well as osteoporosis

Acikan I, Mehmet G, Artas G, Yaman F, Deniz G, Bulmus O, et al. Systemic melatonin application increases bone formation in mandibular distraction osteogenesis. Brazilian oral research. 2018 Sep 21;32:e85

ORIGINAL RESEARCH
Mouth and Jaw Surgery

Systemic melatonin application increases bone formation in mandibular distraction osteogenesis

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Abstract: This study aimed to investigate the effects of different doses of systemic melatonin application on new bone formation during mandibular distraction osteogenesis (DO) in rats. Mandibular DO was performed on 30 adult female Sprague-Dawley rats, which were randomly divided into three groups: control group (CNT), melatonin dose 1 (MLT-D1), and melatonin dose 2 (MLT-D2). A five-day latent waiting period and a ten-day distraction phase followed the surgery. After the surgery, rats from the MLT-D1 and MLT-D2 groups received 25 and 50 mg/kg melatonin, respectively, at 7, 14, 21, 28, and 35 days. The animals were euthanised 28 days after distraction, *i.e.* at 43 days after surgery. Histological and histomorphometric analyses revealed that the distracted bone area was completely filled with new bone formation in all three groups. The MLT-D2 group exhibited the most new bone formation, followed by MLT-D1 and CNT. The melatonin groups had more osteoclasts than the CNT ($p < 0.05$). The number of osteoblasts was higher in the melatonin groups than in the CNT group, and the MLT-D2 had more osteoclasts than the MLT-D1 group ($p < 0.05$). Finally, the osteopontin (OPN) and vascular endothelial growth factor (VEGF) levels were higher in the melatonin groups than in the CNT group, and the MLT-D2 had higher OPN and VEGF levels than the MLT-D1 ($p < 0.05$). This study suggests that systemic melatonin application could increase new bone formation in DO.

Keywords: Melatonin; Pineal Gland; Osteogenesis, Distraction; Bone and Bones.

Introduction

Distraction osteogenesis (DO) is a reasonable treatment option for the reconstruction of maxillar and mandibular bone deficiencies and craniofacial anomalies, as it prevents the onset of donor site morbidity while generating both hard (jaw bone) and soft tissues.[1,2] During the DO procedure, transduction of bone osteotomies using mechanical force at the bone fracture site stimulates a potent osteogenic and vasculogenic response in newly regenerated bone tissues, resulting in anisotropically oriented bone.[3] Although DO is a reliable method for treating jaw bone and soft tissue abnormalities, there are some limitations, particularly connected to long-term consolidation periods and the stability of regenerated bone.

Gorr SU, Abdolhosseini M. Antimicrobial peptides and periodontal disease. Journal of Clinical Periodontology. 2011;38(SUPPL. 11):126–41

J Clin Periodontol 2011; 38 (Suppl. 11): 126–141 doi: 10.1111/j.1600-051X.2010.01664.x

Journal of Clinical Periodontology

Antimicrobial peptides and periodontal disease

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Gorr S-U, Abdolhosseini M. Antimicrobial peptides and periodontal disease. J Clin Periodontol 2011; 38 (Suppl. 11): 126–141. doi: 10.1111/j.1600-051X.2010.01664.x.

Abstract

Aims: The goal of this review is to identify the antimicrobial proteins in the oral fluids, saliva and gingival crevicular fluid and identify functional families and candidates for antibacterial treatment.

Results: Periodontal biofilms initiate a cascade of inflammatory and immune processes that lead to the destruction of gingival tissues and ultimately alveolar bone loss and tooth loss. Treatment of periodontal disease with conventional antibiotics does not appear to be effective in the absence of mechanical debridement. An alternative treatment may be found in antimicrobial peptides and proteins, which can be bactericidal and anti-inflammatory and block the inflammatory effects of bacterial toxins. The peptides have co-evolved with oral bacteria, which have not developed significant peptide resistance. Over 45 antibacterial proteins are found in human saliva and gingival crevicular fluid. The proteins and peptides belong to several different functional families and offer broad protection from invading microbes. Several antimicrobial peptides and proteins (AMPs) serve as templates for the development of therapeutic peptides and peptide mimetics, although to date none have demonstrated efficacy in human trials.

Conclusions: Existing and newly identified AMPs may be developed for therapeutic use in periodontal disease or can serve as templates for peptide and peptide mimetics with improved therapeutic indices.

Key words: antibacterial; antibiotics; antimicrobial peptides; cathelicidin; defensin; lipopolysaccharide; peptide mimetics

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Periodontitis is an inflammatory disease that affects approximately half of US adults over 30 years of age. Similarly, 54% of subjects examined in the 1998 UK Adult Dental Health survey exhibited at least moderate pocketing on one or more teeth (Morris et al. 2001). A systematic review of periodontal health in Europe indicates that, on average, 60% of the adult population has clinical attachment loss of >3 mm (König et al. 2010). Periodontal disease is characterized by the formation of mixed biofilms on the teeth and gingival tissues. The oral cavity is an environment exposed to a multitude of bacteria with over 700 possible resident species of which 150–200 are typically found in most individuals. It is thought that this bacterial flora is controlled initially by the innate immune system of oral epithelia, saliva and gingival crevicular fluid, which is rich in antimicrobial proteins and peptides (AMPs) (Table 1). These AMPs constitute a diverse class of host-defense molecules that act early to combat invasion and infection by bacteria and other microorganisms, with over 45 identified to date (Table 2). This group of proteins and peptides has engendered considerable interest in the past decade as a biological paradigm in innate immunity and as a potential source of novel antibiotics (e.g., Brogden 2005, Ganz 2005, Gordon et al. 2005, Wheeler and Hood 2005, Dale et al. 2006, Peschel and Sahl 2006, Schroder and Harder 2006, Talbot et al. 2006, Kinane et al. 2007, Hirsch et al. 2008, Kinane et al. 2008, Sorensen et al. 2008, Gorr 2009). These AMPs presumably protect oral tissues from infection as minor cuts and abrasions or even tooth extractions, which create large lesions in the oral epithelium, typically resolve without major infection or inflammation (Zasloff 2002b). On the other hand, the normal oral flora is in a balance between pathogens and commensals that requires regular cleaning to be maintained. A decrease in oral hygiene is quickly followed by the build-up of oral biofilms on tooth surfaces and, if left untreated, will progress to gingival inflammation and possibly

Conflict of interest and source of funding statement

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ESSENTIAL DENTAL KNOWLEDGE

The Relation Between Periodontal Disease and Vitamin D

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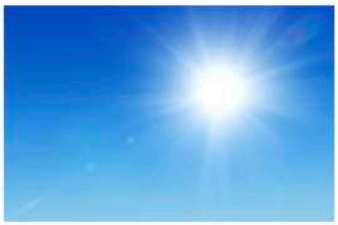

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Abstract

Background: There is conflicting evidence regarding the association between vitamin D and periodontal disease. The purpose of this study was to explore that relation.

Methods: This cross-sectional study used data from the Canadian Health Measures Survey for respondents 13–79 years of age. Vitamin D status was determined by measuring plasma 25-hydroxyvitamin D (25(OH)D) concentrations. Periodontal disease was defined by gingival index (GI) and calculated loss of attachment (LOA). Statistical analyses included bivariate tests and multiple logistic regression.

Results: At the bivariate level, 25(OH)D concentrations below the cutoff levels of 50 nmol/L and 75 nmol/L were associated with GI. However, multiple regression analyses for GI revealed no association with mean 25(OH)D level or either concentration. Although no significant association between LOA and 25(OH)D status was identified at the bivariate level, a statistically significant association was observed between LOA and 25(OH)D levels < 75 nmol/L on multiple regression analysis. However, mean 25(OH)D concentrations and those < 50 nmol/L were not associated with LOA on multiple regression analysis.

Conclusion: Vitamin D status was inversely associated with GI at the bivariate level, but not at the multivariate level. Conversely, vitamin D status was not associated with LOA at the bivariate level, but it was inversely associated with LOA at the multivariate level. These results provide modest evidence supporting a relation between low plasma 25(OH)D concentrations and periodontal disease as measured by GI and LOA.

Bikle DD. Vitamin D and the immune system: Role in protection against bacterial infection. Current Opinion in Nephrology and Hypertension. 2008;17(4):348–52

Vitamin D and the immune system: role in protection against bacterial infection

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Purpose of review

The role of vitamin D extends well beyond that of regulating calcium homeostasis. One of these areas is immune function. Immunity is both adaptive and innate, and vitamin D signaling is operative in both. This review will examine these actions of vitamin D, in particular the role of vitamin D in host defense against infection.

Recent findings

This review will consider two examples of vitamin D-regulated innate immunity that have been recently explored: the role of vitamin D signaling within macrophages to enable them to respond to and kill *Mycobacterium tuberculosis* organisms, and the role of vitamin D signaling in the keratinocytes of the epidermis to enable them to respond to disruption of their barrier function. Potential application to periodontal disease will then be considered.

Summary

Both adaptive and innate immune processes are two edged: beneficial and harmful. Although suppression of adaptive immunity may be beneficial in a number of self-destructive diseases, such suppression may predispose to infection. Enhancement of innate immunity is clearly beneficial in diseases like tuberculosis, but potentiation of proinflammatory processes can increase tissue destruction as in bone loss in periodontal disease. The balance, however, favors adequate vitamin D nutrition in host defense against infection.

Keywords

adaptive immunity, innate immunity, keratinocyte, macrophage, periodontium, vitamin D

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1062-4821

Introduction

The potential role for vitamin D and its active metabolite $1,25(OH)_2D_3$ in modulating the immune response was first appreciated 25 years ago with three important discoveries: the presence of vitamin D receptors (VDRs) in activated human inflammatory cells [1], the ability of $1,25(OH)_2D_3$ to inhibit T cell proliferation [2], and the ability of disease-activated macrophages to produce $1,25(OH)_2D_3$ [3]. The enzyme responsible for $1,25(OH)_2D_3$ production in macrophages and subsequently also identified in dendritic cells is the same enzyme as exists for that purpose in the kidney (CYP27B1). Unlike that in the kidney, however, this enzyme in macrophages and dendritic cells like that in keratinocytes [4,5] is stimulated by cytokines but not by parathyroid hormone (PTH) and is not directly feedback-inhibited by its product [6,7]. We now know that vitamin D and CYP27B1 play important roles in both innate and adaptive immunity.

The adaptive immune response is generally defined by T and B lymphocytes and their ability to produce cytokines and immunoglobulins, respectively, to specifically combat the source of the antigen presented to them by cells such as macrophages and dendritic cells. Vitamin D exerts an inhibitory action on the adaptive immune system. In particular, $1,25(OH)_2D_3$ suppresses proliferation and immunoglobulin production and retards the differentiation of B cell precursors into plasma cells [8•]. As noted above $1,25(OH)_2D_3$ inhibits T cell proliferation [2], in particular the Th1 cells capable of producing interferon (IFN)-γ and interleukin (IL)-2 and activating macrophages [9]. These actions prevent further antigen presentation to and recruitment of T lymphocytes (role of IFN-γ), and T lymphocyte proliferation (role of IL-2). In contrast IL-4, IL-5, and IL-10 production can be increased [10], shifting the balance to a Th2 cell phenotype. T regulatory (Treg) cells are also increased by $1,25(OH)_2D_3$ [11] as shown by increased FoxP3 expression and IL-10 production [12•]. The IL-10 so produced is one means by which CD4+/CD25+ Treg cells block Th1 development. At least in part these actions on T cell differentiation stem from actions of $1,25(OH)_2D_3$ on dendritic cells. $1,25(OH)_2D_3$ decreases expression of the costimulatory molecules CD40, CD80, CD86 in dendritic cells and decreases their secretion of IL-12, a

Garcia MN, Hildebolt CF, Miley DD, Dixon DA, Couture RA, Anderson Spearie CL, et al. One-Year Effects of Vitamin D and Calcium Supplementation on Chronic Periodontitis. Journal of Periodontology. 2011;82(1):25–32

One-Year Effects of Vitamin D and Calcium Supplementation on Chronic Periodontitis

M. Nathalia Garcia,*† Charles F. Hildebolt,† D. Douglas Miley,*† Debra A. Dixon,§ Rex A. Couture,‡ Catherine L. Anderson Spearie,‖ Eric M. Langenwalter,¶ William D. Shannon,# Elena Deych,# Cheryl Mueller,** and Roberto Civitelli**

Background: A previous study reported by this group found that patients in periodontal maintenance programs taking vitamin D and calcium supplementation had a trend for better periodontal health compared to patients not taking supplementation. The objective of the present study is to determine, for the same cohort of subjects, whether such differences persist over a 1-year period.

Methods: Fifty-one patients enrolled in maintenance programs from two dental clinics were recruited. Of these, 23 were taking vitamin D (≥400 IU/day) and calcium (≥1,000 mg/day) supplementation, and 28 were not. All subjects had at least two interproximal sites with ≥3 mm clinical attachment loss. For mandibular-posterior teeth, gingival index, plaque index, probing depth, attachment loss, bleeding on probing, calculus index, and furcation involvement were evaluated. Photostimulable-phosphor, posterior bitewing radiographs were taken to assess alveolar bone. Daily vitamin D and calcium intakes were estimated by nutritional analysis. Data were collected at baseline, 6 months, and 12 months.

Results: Total daily calcium and vitamin D intakes were 1,769 mg (95% confidence interval, 1,606 to 1,933) and 1,049 IU (781 to 1,317) in the taker group, and 642 mg (505 to 779) and 156 IU (117 to 195) in the non-taker group, respectively ($P<0.001$ for both). Clinical parameters of periodontal health improved with time in both groups ($P<0.001$). When clinical measures were considered collectively, the differences between supplement takers and non-takers had the following P values: baseline ($P = 0.061$); 6 months ($P = 0.049$); and 12 months ($P = 0.114$). After adjusting for covariates, the P values for the effect of supplementation were as follows: baseline ($P = 0.028$); 6 months ($P = 0.034$); and 12 months ($P = 0.058$).

Conclusions: Calcium and vitamin D supplementation (≤1,000 IU/day) had a modest positive effect on periodontal health, and consistent dental care improved clinical parameters of periodontal disease regardless of such supplements. Our findings support the possibility that vitamin D may positively impact periodontal health and confirm the need for randomized clinical trials on the effects of vitamin D on periodontitis. *J Periodontol 2011;82:25-32.*

KEY WORDS

Alveolar bone loss; calcium; chronic periodontitis; vitamin D.

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Vitamin D and calcium are fundamental for bone mineralization and the prevention of osteoporosis. Vitamin D plays an important role in calcium homeostasis, promoting calcium absorption in the intestine and stimulating osteoblasts to enable normal bone growth and preservation. Severe vitamin D deficiency causes mineralization defects (osteomalacia), but chronically low intake of vitamin D and calcium leads to a negative calcium balance and bone loss, and it is reasonable to expect this effect to occur in alveolar bone as it does in other bones of the body. A number of epidemiologic studies have reported a positive association between low bone mass or osteoporosis and alveolar bone loss and tooth loss.[1-9] This suggests that low bone mass is a risk factor for the development and progression of periodontal disease.[4,6]

Besides its role in bone and calcium homeostasis, the biologically active form of vitamin D, 1α,25-dihydroxyvitamin, has been demonstrated to function as an immunomodulator

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Delima AJ, Oates T, Assuma R, Schwartz Z, Cochran D, Amar S, et al. Soluble antagonists to interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibits loss of tissue attachment in experimental periodontitis. J Clin Periodontol. 2001;28:233–40

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Soluble antagonists to interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibits loss of tissue attachment in experimental periodontitis

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Abstract

Background, aims: Periodontal disease is a significant cause of tooth loss among adults and is characterized by the alteration and permanent destruction of the deeper periodontal tissues. Although the presence of pathologic microbes is required to trigger this process, the amplification and progression of the diseased state is believed to rely heavily on the production of host mediators in response to bacteria or their metabolic products. The inflammatory response is effective in preventing large-scale colonization of the gingival tissues by bacteria that lie in close proximity to the tooth surface or within the gingival sulcus. It has been postulated that the host-response in some individuals may lead to an over-reaction to invading oral pathogens resulting in the destruction of periodontal tissues.
Methods: Several host-derived mediators are believed to contribute to this response. Two agents considered to be essential in periodontal destruction are interleukin-1 (IL-1) and tumor necrosis factor (TNF). We investigated the role of IL-1 and TNF in the loss of connective tissue attachment in a *Macaca fascicularis* primate model of experimental periodontitis. Silk ligatures impregnated with the periodontal pathogen, *Porphyromonas gingivalis* were wrapped around the posterior teeth and the activity of IL-1 and TNF were inhibited by soluble receptors to these proinflammatory cytokines via local injection into interdental papillae.
Results: Histomorphometric analysis indicates that IL-1 and TNF antagonists significantly reduced the loss of connective tissue attachment by approximately 51% and the loss of alveolar bone height by almost 91%, both of which were statistically significant.
Conclusion: This investigation demonstrates that the loss of connective tissue attachment and progression of periodontal disease can be retarded by antagonists to specific host mediators such as IL-1 and TNF and may provide a potential treatment modality to combat the disease process.

Key words: periodontal disease; inflammatory mediators; cytokine; bone; inflammation; osteoclast; cytokine antagonist; soluble receptors

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Resorption of alveolar bone, lysis of PDL fibers, alterations in the quality and quantity of collagen in the gingival connective tissues, and apical migration of the epithelial attachment are all hallmarks of advanced periodontal disease. Although bacteria are required to initiate this process, it is widely held that the host response to these microbes plays a central role in periodontal disease. The interplay between the periodontal pathogens and the host is responsible for the amplification and progression of the inflammatory response and is believed to require the produc-

Nishimura F, Iwamoto Y, Mineshiba J, Shimizu A, Soga Y, Murayama Y. Periodontal Disease and Diabetes Mellitus: The Role of Tumor Necrosis Factor-α in a 2-Way Relationship. J Periodontol. 2003;74(1):97–102

J Periodontol • January 2003

Periodontal Disease and Diabetes Mellitus: The Role of Tumor Necrosis Factor-α in a 2-Way Relationship

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It is generally accepted that obesity is associated with many other multiple-risk factor syndromes such as hypertension, hyperlipidemia, type 2 diabetes mellitus, and periodontal disease. The number of obese people is increasing rapidly in both western and eastern countries. Adipocytes in the adipose tissues of obese people produce large quantities of biologically active molecules such as leptin, an important molecule regulating energy expenditure and body weight. Therefore, adipocyte-derived active molecules, named adipocytokines, are candidate molecules accounting for the close association between obesity and other multiple-risk factor syndromes. The proinflammatory cytokine tumor necrosis factor-α (TNF-α) is produced by adipocytes, and its blood concentration is elevated in obese patients and declines with weight loss. Studies have demonstrated that TNF-α suppresses insulin action via its specific receptor; hence, it exacerbates insulin resistance. In addition to adipocytes, monocytes/macrophages produce large quantities of TNF-α. Thus, TNF-α, produced from monocytic cells due to inflammatory diseases, may have an additive influence on insulin sensitivity to adipocyte-derived TNF-α. Here, we hypothesized that 1) TNF-α produced by the adipose tissues of obese patients acts as a risk factor for periodontal inflammation, and 2) TNF-α produced due to periodontal inflammation may be an additional important factor influencing insulin sensitivity in both obese and type 2 diabetic patients. We believe that this interaction is a possible mechanism accounting for a 2-way relationship between type 2 diabetes and periodontal disease. *J Periodontol 2003;74:97-102.*

KEY WORDS

Diabetes mellitus, type 2; insulin resistance; obesity; periodontal diseases/etiology; risk factors; tumor necrosis factor.

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The number of people with type 2 diabetes mellitus is increasing in both western and eastern societies.[1] This increase is considered to be due largely to an increase in the overweight (obese) population, which is strongly associated with rapid changes in our lifestyle such as increased sugar/lipid consumption and motorization.[1] Type 2 diabetes mellitus has long been known to act as a risk factor for periodontal disease.[2] Additionally, obesity has been reported to be associated with periodontal disease.[3] Furthermore, successful periodontal treatment appears to have a beneficial role in the metabolic control of type 2 diabetes,[4,5] indicating that type 2 diabetes/obesity not only influences the pathophysiology of periodontal disease in a "1-way" fashion, but periodontal disease in turn influences the disease status of type 2 diabetes/obesity in a reciprocal fashion. Since understanding this "2-way" relationship between obesity/type 2 diabetes mellitus and periodontal disease is an important step in establishing effective therapeutic strategies for these patients, we present our hypothesis on the underlying mechanisms behind this "2-way relationship."

OBESITY AND INSULIN RESISTANCE

Obesity is the most important risk factor for type 2 diabetes mellitus. It is characterized by low insulin sensitivity, a state known as insulin resistance. The proinflammatory cytokine tumor necrosis factor-α

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AAP-Commissioned Review

Diabetes Mellitus and Periodontal Diseases

Brian L. Mealey* and Thomas W. Oates*

Background: The purpose of this review is to provide the reader with practical knowledge concerning the relationship between diabetes mellitus and periodontal diseases. Over 200 articles have been published in the English literature over the past 50 years examining the relationship between these two chronic diseases. Data interpretation is often confounded by varying definitions of diabetes and periodontitis and different clinical criteria applied to prevalence, extent, and severity of periodontal diseases, levels of glycemic control, and complications associated with diabetes.

Methods: This article provides a broad overview of the predominant findings from research published in English over the past 20 years, with reference to certain "classic" articles published prior to that time.

Results: This article describes current diagnostic and classification criteria for diabetes and answers the following questions: 1) Does diabetes affect the risk of periodontitis, and does the level of metabolic control of diabetes have an impact on this relationship? 2) Do periodontal diseases affect the pathophysiology of diabetes mellitus or the metabolic control of diabetes? 3) What are the mechanisms by which these two diseases interrelate? and 4) How do people with diabetes and periodontal disease respond to periodontal treatment?

Conclusions: Diabetes increases the risk of periodontal diseases, and biologically plausible mechanisms have been demonstrated in abundance. Less clear is the impact of periodontal diseases on glycemic control of diabetes and the mechanisms through which this occurs. Inflammatory periodontal diseases may increase insulin resistance in a way similar to obesity, thereby aggravating glycemic control. Further research is needed to clarify this aspect of the relationship between periodontal diseases and diabetes. *J Periodontol 2006;77:1289-1303.*

KEY WORDS

Diabetes mellitus; inflammation; insulin resistance; obesity; periodontal diseases.

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Periodically, the Board of Trustees of the American Academy of Periodontology identifies the need for review of the literature on a specific topic and requests the Editor-in-Chief of the Journal of Periodontology *to commission such a review. The selected author is solely responsible for the content, and the manuscript is peer reviewed, like all other* Journal *articles. The Academy's Board of Trustees does not review or approve the manuscript prior to publication, and the content of the review should not be construed as Academy policy.*

METHODS

The information presented in this review is based on a survey of English language literature primarily over the last 20 years, although certain "classic" articles are referenced from before the 1980s. The literature search was conducted using the National Library of Medicine's Entrez PubMed search engine. The article does not contain an exhaustive article-by-article review of the literature but, instead, provides a broad overview of the predominant findings from research. The article does not seek to analyze statistically any of the data from the reviewed articles, but relies on the original data analysis and author interpretation. Several references are cited from the medical literature and are not meant to be inclusive of all or even a substantial part of the medical literature available on the subject of diabetes mellitus. Diabetes mellitus is a clinically and genetically

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Diabetes Prolongs the Inflammatory Response to a Bacterial Stimulus Through Cytokine Dysregulation

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Diabetes has been identified as an important risk factor for infection. But relatively little is known about how diabetes alters the inflammatory response to bacteria. The objective of this study was to investigate how diabetes affects host–bacteria interactions by focusing on the inflammatory response in a connective tissue setting. Diabetic (db/db) and control (db/+) mice were inoculated with *Porphyromonas gingivalis*, a pathogen associated with bite wounds and periodontal disease. The response was measured histologically or by the expression of inflammatory cytokines. By quantitative histologic analysis, there was little difference between the diabetic and control mice on day 1. On day 3, however, the inflammatory infiltrate had subsided in the control group, whereas it had not in the diabetic group ($p < 0.05$). Similar results were noted at the molecular level by the persistent expression of tumor necrosis factor-α (TNF-α) and the chemokines MCP-1 and MIP-2. The importance of TNF in this process was demonstrated by reversal of the prolonged chemokine expression by specific inhibition of TNF with Enbrel. These results indicate that cytokine dysregulation associated with prolonged TNF expression represents a mechanism through which bacteria may induce a more damaging inflammatory response in diabetic individuals.

Key words: chemokine/cytokine/diabetes/hyperglycemia/inflammation/obesity/TNF
J Invest Dermatol 123:87–92, 2004

Diabetes mellitus affects over 15 million Americans and has a dramatic impact on health, causing a high degree of morbidity and mortality in affected individuals as well as placing an economic burden on the health care system (Edelman, 1998; Zimmet *et al*, 2001) Although type 1 and type 2 diabetes have different etiologies, they share common symptoms of glucose intolerance, hyperglycemia, hyperlipidemia, and many of the same complications. (Kahn and Flier, 2000). As the course of diabetes progresses, complications develop, which include a number of vascular abnormalities, nephropathy, poor wound healing, and enhanced risk of infection (Jensen and Deckert, 1992; Libman *et al*, 1993; Loe, 1993; Elner *et al*, 1995; Patterson and Andriole, 1997; Vlassara and Palace, 2002).

Several mechanisms have been suggested for increased susceptibility to infection in diabetics including impaired chemotactic, phagocytic, and bacterial killing by cells of the innate immune response (Drachman *et al*, 1966; Mowat and Baum, 1971; Sima *et al*, 1988; Pickup and Crook, 1998). Interestingly, diabetics are not more susceptible to all infections but seem to be particularly more vulnerable to Gram-negative infections (Joshi *et al*, 1999). These may include urinary tract infections, soft-tissue infections, and periodontal disease (Loe, 1993; Patterson and Andriole, 1997; Cutler *et al*, 1999; Joshi *et al*, 1999). Soft-tissue infections, especially those associated with human or animal bites may involve Gram-negative oral pathogens, as does periodontitis (Williams, 1990; Goldstein, 1992; Brook, 2003). Anaerobic bacteria are present in approximately one-third of bite wounds and are associated with the formation of abscesses and with relatively serious infections (Goldstein, 1992; Brook, 2003). In addition, enhanced susceptibility to periodontal pathogens is one of the significant and characteristic complications of diabetes (Loe, 1993; Nishimura *et al*, 1998).

Type 2 diabetes is associated with higher serum levels of inflammatory cytokines (tumor necrosis factor, TNF) (Desfaits *et al*, 1998; Katsuki *et al*, 1998; Fernanadez-Real *et al*, 2001; Mishima *et al*, 2001). This may be due to the production of TNF in adipose tissue (Hotamisligil *et al*, 1995) (Hotamisligil, 1994), the activity of advanced glycation end products or enhanced cytokine production caused by indirect effects of hyperinsulinemia or hyperglycemia (Soop *et al*, 2002; Vlassara and Palace, 2002). *In vitro* studies have been carried out to examine the effect of diabetes on the response of leukocytes to inflammatory stimuli such as lipopolysaccharide (LPS). The results, however, have been inconsistent with some studies showing decreased expression of inflammatory cytokines, whereas others have shown significantly enhanced expression (Kulseng *et al*, 1996; Salvi *et al*, 1997; Desfaits *et al*, 1998; Geerlings *et al*, 2000; Zykova *et al*, 2000).

Despite the high societal cost of diabetes, relatively little is know about how type 2 diabetes alters the inflammatory response to bacteria, particularly in dermal connective tissue. To investigate this matter, we tested the response of normal and diabetic (db/db) mice using a scalp model that is well suited to study host–bacteria interactions in a connective tissue setting (Zubery *et al*, 1998; Graves *et al*,

Abbreviations: TNF, tumor necrosis factor

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Original Article

Salivary TNF-alpha: A potential marker of periodontal destruction

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Abstract:

Aims and Objectives: (1) To evaluate the effect of type 2 diabetes mellitus on salivary TNF-α level in chronic periodontitis. (2) To evaluate the effect of smoking on salivary TNF-α level in chronic periodontitis. (3) To compare and correlate TNF-α level with the healthy individuals. **Materials and Methods:** Subjects aged 30-35 years were included for the study and divided into four groups as a group of 20 systemically and periodontally healthy individuals (group I), a group of 20 subjects with pocket probing depth (PPD) ≥5 mm and clinical attachment loss (CAL) of ≥2 mm (group II), a group of 20 diabetic subjects (of more than 5 years) with periodontal parameters as of group II as (group III) and a group of 20 subjects smoking (≥10 cigarettes a day) with periodontal parameters of group II as (group IV). Periodontal parameters of PPD, CAL, gingival index (GI), and plaque index (PI) were measured using standard indices and criteria. Three milliliter of unstimulated saliva was taken and salivary TNF-α determined by using ELISA technique (Quantikine Human total TNF-A immunoassay kit). **Results:** Data revealed highest mean TNF-α in group III followed by group IV, group II, and group I. Mean TNF-α of both group III (76.1%) and group IV (48.8%) was significantly higher as compared to group I ($P < 0.001$). Mean TNF-α of group III was also found to be significantly different and higher (68.1%) as compared to group II ($P < 0.001$). Although higher mean TNF-α (31.5%) was found in group IV in comparison to group II, the difference was not statistically significant. Besides above, TNF-α also showed a direct positive correlation with PPD in group II ($r = 0.30$, $P > 0.05$) and a significant negative correlation was observed between CAL and TNF-α in group IV. **Conclusion:** Our study clearly underlines a profound impact of diabetes and smoking on salivary TNF-α in chronic periodontitis subjects in comparison to healthy subjects. Moreover, diabetes status increased TNF-α significantly in comparison to smoking in chronic periodontitis patients.

Key words:

Biomarker, chronic periodontitis, diabetes mellitus, smoking, TNF-alpha

INTRODUCTION

Oral health is indispensable to overall healthy being. Man has been suffering from ailments of oral cavity since time immemorial. Oral diseases especially caries and periodontitis are known for their high prevalence and rapid morbidity. Periodontal diseases are a group of chronic, progressive bacterial infections resulting in inflammation and destruction of tooth supporting tissues.[1] The periodontal disease is known to have a complex pathogenesis with both bacterial and host factors contributing to the destruction of periodontium. Role of host immune response is most important factor in periodontitis as it determines both disease progression and severity.[2] Diabetes mellitus is one such widely prevalent endocrine disorder which is known to alter this delicate balance thereby causing exaggerated tissue destruction when challenged with chronic diseases like periodontitis.[3] In smokers too, a suppressed immune response favor increased periodontal destruction.[4,5] Hence, immune function in periodontitis is a specialized function where every single molecule can have ramifications on the resultant tissue protective and destructive response.

Difficulty in determining active disease and ongoing destruction in periodontal tissue by traditional diagnostic aids like probing depth and attachment loss has proved them to be inadequate in modern era of periodontal therapeutics.[6] Search for a biomarker for periodontitis has resulted in researchers trying out and finding new molecules that can guide a clinician in many a decision regarding the patient's condition.

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine released by macrophages is known for its substantial role in periodontitis mediated bone loss.[7] This can be detected in saliva and gingival crevicular fluid (GCF) in both health and periodontitis.[8] Increased concentration observed in periodontitis correlate closely with the tissue destruction and immune response.[9] TNF-α also inhibits insulin transduction and contributes to insulin resistance in diabetes mellitus.[10] Enhanced expressions of serum TNF-α have been observed in smokers in rheumatoid arthritis and chronic obstructive pulmonary disease (COPD). Also, up-regulation of its expression in keratinocytes in chronic inflammatory skin diseases like psoriasis has also been observed.[11] This clearly indicates the

Matthews DC. The relationship between diabetes and periodontal disease. Journal (Canadian Dental Association). 2002

The Relationship Between Diabetes and Periodontal Disease

• Debora C. Matthews, DDS, Dip Perio, MSc •

Abstract

There is good evidence to support the claim that periodontitis may be more prevalent among diabetic patients than nondiabetic people. Similarly, studies have shown that periodontal therapy influences glycemic control in people with diabetes mellitus. Given that nearly 10% of Canadians are affected by either type 1 or type 2 diabetes (including those in whom the disease is undiagnosed), all dentists will encounter patients with diabetes. Dental practitioners must be aware of the implications of this relationship and manage their patients' periodontal care accordingly.

MeSH Key Words: *diabetes mellitus/complications; periodontal diseases/complications; risk factors*

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By the year 2010, it is expected that 3 million Canadians will be afflicted with diabetes mellitus.[1] It has been reported that for every person known to have diabetes, there is someone else in whom the disease remains undiagnosed.[2] In other words, up to 10% of Canadian adults may currently have diabetes. This means that dentists will regularly encounter diabetic patients. This paper discusses the possible impact of diabetes on the periodontal patient and the ways in which untreated periodontitis may influence the course of diabetes.

What Is Diabetes?

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to defective secretion or activity of insulin.[1] In the current classification of this condition, the terms "insulin-dependent diabetes mellitus" and "non-insulin-dependent diabetes mellitus" are not used, in part because they relate to treatment rather than to the diagnosis. A conclusive diagnosis of diabetes mellitus is made by assessing glycated hemoglobin levels; in those people with diabetes, sequential fasting plasma glucose levels will be 7 mmol/L or more.

Diabetes mellitus can be classified into 1 of 4 broad categories according to signs and symptoms.

Type 1 diabetes mellitus encompasses diabetes resulting primarily from destruction of the beta-cells in the islets of Langerhans of the pancreas. This condition often leads to absolute insulin deficiency. The cause may be idiopathic or due to a disturbance in the autoimmune process. The onset of the disease is often abrupt, and patients with this type of diabetes are more prone to ketoacidosis and wide fluctuations in plasma glucose levels. If untreated, these patients are likely to manifest the classic signs and symptoms of diabetes: polyuria (excessive urine output), polydipsia (excessive thirst) and polyphagia (excessive appetite), as well as pruritis, weakness and fatigue. These patients are more likely to suffer severe systemic complications as a result of the disease.

The causes of type 2 diabetes mellitus range from insulin resistance with relative insulin deficiency to a predominantly secretory defect accompanied by insulin resistance. The onset is generally more gradual than for type 1, and this condition is often associated with obesity. In addition, the risk of type 2 diabetes increases with age and lack of physical activity, and this form of diabetes is more prevalent among people with hypertension or dyslipidemia. Type 2 diabetes has a strong genetic component, with the disease being more common in North Americans of African descent, Hispanics and Aboriginal people. People with type 2 diabetes constitute 90% of the diabetic population.

Gestational diabetes mellitus (GDM) is glucose intolerance that begins during pregnancy. The children of mothers with GDM are at greater risk of experiencing obesity and diabetes as young adults.[3] As well, there is a greater risk to the mother of developing type 2 diabetes in the future.

Rajkumar D, Gokulanathan S, Natarajan S, Mahalingam L, Thangavelu K. Diabetes and periodontal diseases. Eur J Mol Clin Med. 2020;7(2):6633–7

Dental Science - Short Communication

Diabetes and periodontal disease

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ABSTRACT

Diabetes mellitus is a systemic disease characterized by increased blood glucose levels and abnormalities of lipid metabolism due to absence or decreased level of insulin. It affects all the body organs and their functions either directly or indirectly. Every dentist should have a basic understanding of the etiopathogenesis, oral and systemic manifestations of this disease. The periodontal diseases are a consequence of extension of the gingival inflammation into the underlying supporting structures of the periodontium, initiated by the presence of plaque and its products on the surfaces of the teeth and the adjoining structures. The progression of periodontal disease is influenced by variety of factors like microorganisms, host response, systemic background, and genetic makeup of the host. Amongst them, diabetes mellitus tops the list. Diabetes and periodontitis influence the clinical outcome of each other and control of both influences the clinical improvement of each.

KEY WORDS: Diabetes mellitus, periodontitis, vascular changes

Diabetes mellitus (DM) is a term applied to a heterogeneous group of disorders that share the characteristic of altered glucose tolerance (or) impaired lipid and carbohydrate metabolism. It develops as a result of either deficient production of insulin or impaired use of insulin. It can be divided into two types: Type I or insulin-dependent DM and Type II or non–insulin-dependent DM. Type I is caused by the destruction of insulin producing B-cells of pancreas. Type II is due to impaired insulin function rather than deficiency.[1]

Type I usually develops before the age of 30 and the patient is totally dependent on the supply of insulin. Type II has its onset later in life and is usually managed through diet modification in combination with hypoglycemic agents. The general signs and symptoms of diabetes are a direct result of hyperglycemia, and the signs and symptoms are polyuria, polydipsia, and polyphagia, weakness, and fatigue with pruritus. The signs and symptoms may be reversible with early diagnosis and therapy.

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History

Description of DM dates back to 1500 years BC by the Egyptians. In 400 BC, Sushrutha described it as honey urine. In 1869, Langerhans discovered the islets in pancreatic tissue. In 1921, Banting and Best described hypoglycemic substances isolated from pancreas. In 1955, oral hypoglycemic agents were introduced. Gruner first reported the association between diabetes and periodontal disease. In 1928, Williams stated that gingivitis and periodontitis among diabetic patients are modified. He termed it "diabetic periodontoclasia." Glickman in 1946 found in an experimental animal study that periodontal disease in diabetic animals was not different histologically and was thus not a unique clinical entity.

Relationship of Diabetes and Periodontitis

Periodontitis is stated to be the sixth complication of diabetes.[2] Prevalence of severe periodontitis in diabetics as compared to non-diabetics has been found to be 59.6%:39%.[3] Majority of well-controlled studies show a higher prevalence and severity of periodontal disease in diabetics than in non-diabetics with similar local irritation including greater loss of attachment, greater alveolar bone loss, increased bleeding on probing, and increased tooth mobility resulting in tooth loss.

The probable influence of diabetes on the onset and development of periodontal disease has been studied by

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PGE_2, IL-1β, and TNF-α Responses in Diabetics as Modifiers of Periodontal Disease Expression

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Abstract

Diabetes mellitus is a systemic disease that affects more than 12 million people in the United States and represents a risk factor for periodontitis with odds ratios of 2.1 to 3.0. New data support the concept that in diabetes-associated periodontitis, the altered host inflammatory response plays a critical role. We have recently examined the gingival crevicular fluid (GCF) mediator level, monocytic secretion, and clinical presentation of 39 insulin-dependent diabetes mellitus (IDDM) patients and 64 non-diabetic patients with various degrees of periodontal health and disease. First, we found that there was an unexpected high level of GCF mediators among the IDDM subjects, even in the gingivitis and mild periodontitis patients. Furthermore, the GCF and monocytic mediator responses were obviously bimodal in distribution with respect to periodontal status. Gingivitis patients and mild periodontitis patients represented one low response group, and the moderate and severe periodontitis subjects the high response group. Accordingly, these 4 periodontal subgroups were pooled to form 2 main groups for analyses—group A (AAP Types I–II) and group B (AAP Types III–IV). Diabetics had significantly higher GCF levels of both PGE_2 and IL-1β when compared to non-diabetic controls with similar periodontal status. Within the diabetic group, the GCF levels of these inflammatory mediators were almost 2-fold higher in group B subjects when compared to diabetics from group A. Among diabetics, GCF TNF-α levels were only marginally detectable and no significant difference was found between group A and group B patients. Insulin-dependent diabetic patients with gingivitis or mild periodontitis (group A) and moderate to severe periodontitis (group B) have abnormal monocytic inflammatory secretion in response to LPS challenge from Porphyromonas gingivalis (P. gingivalis) *as compared to non-diabetic periodontal patients. Data suggest that the diabetic state results in a significantly upregulated monocytic secretion of PGE_2 (4.2-fold), IL-1β (4.4-fold), and TNF-α (4.6-fold) when compared to non-diabetic controls. Within diabetics, LPS dose-response curves demonstrated that monocytes from group B patients secreted approximately 3 times more PGE_2 and 6.2 times more TNF-α than those from group A; however, there was no significant difference in monocytic IL-1β secretion between the 2 diabetic groups. This upregulated monocytic trait is thought to exist independently of the presence of severe periodontal disease since, in non-diabetic patients with adult periodontitis, Gram-negative bacterial infections alone are not sufficient to elicit a systemic hyperresponsive monocytic trait. Between group A and group B diabetics, there was no significant difference in metabolic control as expressed by mean level of glycosylated hemoglobin (HbA_{1c}). In conclusion, our data suggest that diabetic patients have exaggerated inflammatory responses when compared to non-diabetic controls. Fur-*

Choo S. The HLA System: Genetics, Immunology, Clinical Testing, and Clinical Implications. Yonsei Medical Journal. 2007;48(1):11–23

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The HLA System: Genetics, Immunology, Clinical Testing, and Clinical Implications

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The human major histocompatibility complex HLA is located on the short arm of chromosome 6. It is known to be the most polymorphic genetic system in humans. The biological role of the HLA class I and class II molecules is to present processed peptide antigens. The HLA system is clinically important as transplantation antigens. Molecular HLA allele typing is routinely performed to provide HLA class I and class II allele matching in unrelated donor hematopoietic stem cell transplantation. Prospective lymphocyte crossmatching is critical in solid organ transplantation to prevent allograft rejection. HLA alloimmunization causes various problems in transfusion therapy. The HLA system is associated with certain diseases, but its underlying mechanisms are not yet fully explained.

Key Words: Major histocompatibility complex, HLA, histocompatibility testing, transplantation

THE HLA SYSTEM

The genetic loci involved in the rejection of foreign organs are known as the major histocompatibility complex (MHC), and highly polymorphic cell surface molecules are encoded by the MHC. The human MHC is called the HLA (Human Leukocyte Antigen) system because these antigens were first identified and characterized using alloantibodies against leukocytes.[1] Leukocyte-agglutinating antibodies (leukoagglutinins) were observed in sera from multiparous women and previously transfused patients. Graft rejection was found to be associated with the development of antibodies against allogeneic leukocytes.

The HLA system has been well known as transplantation antigens, but the primary biological role of HLA molecules is in the regulation of immune response.[2]

Genomic organization of the HLA system

The human MHC maps to the short arm of chromosome 6 (6p21) and spans approximately 3,600 kilobases of DNA.[3] The human MHC is divided into three regions (Fig. 1).

The class I region contains the classical *HLA-A*, *HLA-B*, and *HLA-C* genes that encode the heavy chains of class I molecules.

The class II region consists of a series of subregions, each containing *A* and *B* genes encoding α and β chains, respectively.[4] The *DR* gene family consists of a single *DRA* gene and up to nine *DRB* genes (*DRB1* to *DRB9*). The *DRA* gene encodes an invariable α chain and it binds various β chains encoded by the *DRB* genes. HLA-DR antigen specificities (i.e., DR1 to DR18) are determined by the polymorphic DRβ1 chains encoded by *DRB1* alleles. HLA haplotypes of certain *DRB1* alleles contain specifically linked *DRB3*, *DRB4*, or *DRB5* locus. The *DP* and *DQ* families each have one expressed gene for α and β chains and additional unexpressed pseudogenes. The *DQA1* and *DQB1* gene products associate to form *DQ* molecules,

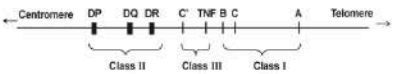

Fig. 1. The human MHC on the short arm of chromosome 6. The HLA-DR, DP, and DQ regions consist of one or more *A* and *B* genes, respectively. TNF (tumor necrosis factors); C' (complement genes).

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Association Between Interleukin-1 Genotype and Periodontal Disease in a Diabetic Population

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Background: Recently, it has become evident that for many common chronic diseases, modifying factors amplify disease mechanisms to make the clinical condition more severe. The aims of this report were 1) to investigate the prevalence of periodontitis in a diabetic population, 2) to evaluate the association of periodontitis with metabolic control, and 3) to evaluate periodontitis in diabetics with different interleukin (IL)-1 genotypes.

Methods: One hundred diabetic patients were screened. Type and duration of diabetes, level of control (glycosylated hemoglobin), and demographic data were recorded. Periodontal disease was defined as two or more teeth with clinical attachment loss (CAL) ≥5 mm. Poorly controlled diabetes was defined as glycosylated hemoglobin values >8%. Finger-stick blood samples were collected and analyzed for genotyping of IL-1A (+4845), IL-1B (+3954), IL-1B (–511), and IL-1RN (+2018) polymorphisms.

Results: Among the diabetic patients in the study, 66% showed periodontal destruction, and 43% of those could be characterized as severe. The prevalence of severe attachment loss increased with decreasing control of diabetes. Only the IL-1B (–511) genotype was found to be associated with periodontal disease in the African American patients ($P < 0.05$). The frequency of allele 1 was 0.77 in periodontitis affected versus 0.33 in healthy African American diabetics. A borderline significant association between IL-1B (+3954) and periodontal disease also was noted in Caribbean periodontal patients ($P = 0.06$); however, the allele 2 frequency in this population was only 10%.

Conclusions: These data confirm the high prevalence and severity of periodontitis in the diabetic population, and support the association between poor glycemic control and periodontal disease. The low prevalence of some of the IL-1 gene polymorphisms in the ethnic groups included in this study limits the validity of conclusions on genotype associations with clinical findings, but there was a trend suggesting that allele 1 at IL-1B (–511) and IL-1B (+3954) was overrepresented among diabetics with periodontal disease. *J Periodontol 2003;74:1183-1190.*

KEY WORDS

Alleles; diabetes mellitus/complications; genotype; interleukin-1; metabolic control; periodontal diseases/complications; polymorphism.

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Diabetes mellitus (DM) encompasses a heterogeneous group of disorders with the common characteristic of altered glucose tolerance or impaired lipid and carbohydrate metabolism. DM affects approximately 17 million people in the United States and is increasing at an annual rate of 6%.[1] This increase is probably due to an increased awareness by the public in response to awareness campaigns, an increase in the elderly population, and an increase in the accuracy of diagnosis. The disease is clearly a public health problem.

The relationship between diabetes mellitus and periodontal health status was determined in Pima Indians of the Gila River Indian community in Arizona by Emrich et al.[2] This tribe of Native Americans has the world's highest reported incidence and prevalence of non–insulin-dependent diabetes mellitus. Subjects with type 2 diabetes had an increased risk of destructive periodontitis when attachment loss was used to measure the disease. These findings demonstrated that diabetes increases the risk of developing destructive periodontal disease about three-fold.[2]

It also has been suggested that the variation in severity of periodontitis among diabetics is related to metabolic control. Some studies have reported an association between poor glycemic control and increased occurrence of periodontitis,[3-6] although a number also have reported no association.[7,8] The extensive variations in the design, conduct, and analysis of this set of studies contribute to inconsistencies

Taylor GW. Bidirectional interrelationships between diabetes and periodontal diseases: an epidemiologic perspective. Ann Periodontol. 2001;6(1):99–112.

Ann Periodontol

Bidirectional Interrelationships Between Diabetes and Periodontal Diseases: An Epidemiologic Perspective

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This review evaluates evidence for a bidirectional relationship between diabetes and periodontal diseases. A comprehensive Medline search of the post-1960 English language literature was employed to identify primary research reports of relationships between diabetes and periodontal diseases. Reports included in the review on the adverse effects of diabetes on periodontal health (DM→PD) were restricted to those comparing periodontal health in subjects with and without diabetes. Review of adverse affects of periodontal infection on glycemic control included reports of periodontal treatment studies and follow-up observational studies in which changes in glycemic control could be assessed. Observational studies reporting DM→PD provided consistent evidence of greater prevalence, severity, extent, or progression of at least one manifestation of periodontal diseases in the large majority of reports (supportive evidence in 44/48 total reviewed; 37/41 cross-sectional and 7/7 cohort). Additionally, there were no studies reviewed with superior design features to refute this association. Treatment studies provided direct evidence to support periodontal infection having an adverse, yet modifiable, effect on glycemic control. However, not all investigations reported an improvement in glycemic control after periodontal treatment. Additional evidence to support the effect of severe periodontitis on increased risk for poorer glycemic control comes from 2 follow-up observational studies. The evidence reviewed supports viewing the relationship between diabetes and periodontal diseases as bidirectional. Further rigorous, systematic study is warranted to establish that treating periodontal infections can be influential in contributing to glycemic control management and possibly to the reduction of the burden of complications of diabetes mellitus. *Ann Periodontol 2001;6:99-112.*

KEY WORDS

Diabetes mellitus/prevention and control; periodontitis/complications; risk factors; literature review.

Diabetes mellitus and chronic periodontitis are common chronic diseases in adults in the U.S. population. Diabetes mellitus is disease of metabolic dysregulation characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both. Dysregulation of protein and lipid metabolism also occurs. Particularly susceptible individuals or those with chronic poor metabolic control may experience one or more commonly recognized complications in the eyes, heart, blood vessels, kidney, and nervous system. These complications are associated with a significant burden for the individual and society in terms of increased morbidity and premature mortality. This increased burden includes direct costs of medical care and indirect costs such as lost productivity.[1]

There are 2 major types of overt diabetes in the U.S., Type 1 (formerly classified as insulin-dependent) and Type 2 (formerly classified as non-insulin-dependent).[2] Additional types of diabetes include gestational diabetes mellitus, which affects approximately 3% to 5% of all pregnancies, and diabetes associated with or secondary to other conditions, comprising 1% to 2% of individuals with diabetes in the U.S.[1,2] Type 2 diabetes is most prevalent; approximately 90% to 95% of people diagnosed with diabetes in the U.S. have Type 2, and almost all people ages 45 years and older diagnosed with diabetes have Type 2. Over

Fève B, Bastard JP. The role of interleukins in insulin resistance and type 2 diabetes mellitus. Nat Rev Endocrinol [Internet]. 2009;5(6):305–11. Available from: http://dx.doi.org/10.1038/nrendo.2009.62

The role of interleukins in insulin resistance and type 2 diabetes mellitus

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Abstract | In the past few years, several interleukins (ILs) attracted considerable attention as potential effectors in the pathology and physiology of insulin resistance associated with type 2 diabetes mellitus (T2DM) and obesity. IL-1, a major proinflammatory cytokine, is present at increased levels in patients with diabetes mellitus, and could promote β-cell destruction and alter insulin sensitivity. The effects of IL-1 are likely to be counteracted by IL-1 receptor antagonist protein (IL-1ra), as suggested by interventional studies in patients with T2DM who were treated with a recombinant form of this protein. However, studies in IL-1ra-deficient mice provided controversial results on the exact effect of the IL-1 signaling pathway on insulin secretion, insulin sensitivity and accumulation of adipose tissue. Likewise, IL-6 has been suggested to be involved in the development of obesity-related and T2DM-related insulin resistance. The action of IL-6 on glucose homeostasis is also complex and integrates central and peripheral mechanisms. Both experimental and clinical studies now converge to show that several ILs contribute to the pathology and physiology of T2DM through their interaction with insulin signaling pathways and β-cell function.

Fève, B. & Bastard, J.-P. *Nat. Rev. Endocrinol.* **5**, 305–311 (2009); published online 28 April 2009; doi:10.1038/nrendo.2009.62

Introduction

In the past decades, type 2 diabetes mellitus (T2DM) has rapidly emerged as a worldwide health challenge, with an estimation that over 350 million people will be affected by the disease in 2030.[1] Progress in understanding the pathogenesis of T2DM thus represents a major goal to improve T2DM treatment and prevention.

T2DM results from a combination of insulin resistance and impaired insulin secretion.[2] Although the molecular mechanisms that lead to insulin resistance are not fully understood, excess accumulation of adipose tissue, especially in visceral depots, is clearly related to the development of insulin resistance. In the past few years, obesity and insulin resistance have been recognized to be associated with a low-grade, systemic inflammation of adipose tissue.[3] However, we must point out that adiposity is also associated with ectopic lipid accumulation in nonadipose tissues, including muscle (in the form of intramyocellular lipids) and the liver (which potentially causes hepatic steatosis). Thus, the pathogenesis of insulin resistance is now considered to involve disorders in both lipid metabolism and abnormal adipokine or cytokine production associated with the inflammatory state.

After fatty acids are taken up by muscles and the liver, they are transformed to acyl-coenzyme A (acyl-CoA), then oxidized in the mitochondria to generate ATP. When present in excess, acyl-CoA molecules are metabolized to diacylglycerols and ceramides, which promote insulin resistance. These lipid compounds induce the phosphorylation of serine residues of insulin-responsive substrate (IRS), which thus prevents its activation by tyrosine phosphorylation and subsequent interaction with PI3K (Figure 1). Decreased activity of IRS results in reduced glucose uptake and glycogen synthesis in the muscles, and increased glucose production in the liver.[4] Several kinases could be involved in lipid-induced IRS phosphorylation of serine residues, such as protein kinase C-ε in the liver,[5,6] protein kinase C-θ in skeletal muscle,[7,8] and c-jun N-terminal kinases (JNK 1 and JNK 2) that are activated by endoplasmic reticulum stress secondary to lipid excess.[3]

As mentioned above, a potential link between obesity and insulin resistance is ectopic lipid accumulation. However, obesity is also associated with a systemic, chronic, inflammatory response characterized by altered cytokine production and activation of inflammatory signaling pathways. A large number of studies have linked this inflammation to the development of insulin resistance, and showed that it involves the production of inflammatory cytokines, such as tumor necrosis factor (TNF), interleukins (ILs), and cytokine-like proteins known as adipokines. Some of these molecules seem to be secreted by adipocytes themselves, whereas others are mainly produced by cells in the stromal vascular fraction,[9] particularly by macrophages. The role of TNF and adipokines is out of the scope of this Review, and consequently we will not discuss it in detail here; instead, we provide insights into recent findings on the implication of ILs in the pathology and physiology of insulin resistance and T2DM.

Competing interests
The authors declare no competing interests.

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Kardeşler L, Buduneli N, Biyikoğlu B, Çetinkalp Ş, Kütükçüler N. Gingival crevicular fluid PGE2, IL-1ß, t-PA, PAI-2 levels in type 2 diabetes and relationship with periodontal disease. Clin Biochem. 2008 Jul;41(10–11):863–8

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CLINICAL BIOCHEMISTRY

Gingival crevicular fluid PGE_2, IL-1ß, t-PA, PAI-2 levels in type 2 diabetes and relationship with periodontal disease

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Abstract

Objectives: To evaluate if type 2 diabetes mellitus increase gingival crevicular fluid (GCF) levels of prostaglandin E_2 (PGE_2), interleukin-1beta (IL-1ß), tissue-type plasminogen activator (t-PA), and plasminogen activator inhibitor-2 (PAI-2).

Design and methods: Seventeen type 2 diabetic patients with periodontal disease (DM), 17 otherwise healthy periodontally diseased patients (PD) and 17 systemically and periodontally healthy control subjects (H) were enrolled. Clinical periodontal measurements were recorded at six sites/tooth. GCF samples were analyzed by ELISA. Data were tested by statistical tests.

Results: DM group revealed lower IL-1ß levels than PD group ($p<0.01$). PGE_2, t-PA and PAI-2 levels were similar in DM and PD groups ($p>0.05$). PGE_2, t-PA levels were higher in DM and PD groups than H group ($p<0.05$). PAI-2 level was higher in DM group than H group ($p<0.05$). GCF total amount of PGE_2 in DM group exhibited significant correlations with all clinical periodontal measurements ($p<0.05$).

Conclusion: Type 2 diabetes in this study seems not to increase GCF levels of the evaluated inflammatory mediators.

Keywords: Diabetes; ELISA; Gingival crevicular fluid; IL-1beta; Periodontal disease; PGE_2; PAI-2; t-PA

Introduction

Type 2 diabetes mellitus (DM) describes a metabolic disorder of multiple aetiology, characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion (β-cell dysfunction), insulin action (insulin resistance) or both [1]. A progressive deterioration of β-cell function coupled with the addition of acquired insulin resistance for which the β-cell cannot compensate causes this chronic metabolic disease. Fifty-four percent of type 2 DM patients present both insulin resistance and low insulin secretion [1]. Type 2 DM patients were 2.8 times more likely to have destructive periodontal disease [2] and 4.2 times more likely to have alveolar bone loss progression [3]. Effects of diabetes on the periodontium have been discussed recently in a review paper [4]. In fact periodontal disease has been considered to be another complication of DM [5] and evidence also supports poor glycaemic control contributing to poor periodontal health [6–8].

Impaired fibrinolysis is found in type 2 DM and high tissue/blood vessel type plasminogen activator (t-PA) level is predictive of future diabetes [9]. Plasminogen activator inhibitor-2 (PAI-2) produced by cells like macrophages and epithelial cells regulate the activities of t-PA [10,11]. Elevated concentrations of t-PA and PAI-2 in gingival crevicular fluid (GCF) have been reported suggesting their involvement in the aggravation of gingival inflammation [12]. Xiao et al. [13] have stated that t-PA and PAI-2 may play a significant role in periodontal tissue destruction and remodelling and that t-PA and PAI-2 in GCF may be used as disease markers.

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Navarro A, Faria R, Bascones A. Relación entre diabetes mellitus y enfermedad periodontal.

Relación entre diabetes mellitus y enfermedad periodontal

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Navarro Sánchez AB, Faria Almeida R, Bascones Martínez A. Relación entre diabetes mellitus y enfermedad periodontal. Av Periodon Implantol. 2002; 14, 1: 9-19.

RESUMEN

La asociación entre diabetes mellitus y la enfermedad periodontal ha sido motivo de estudio durante mucho tiempo. Son varias las hipótesis que se barajan a la hora de explicar dicha relación. El propósito de este artículo es revisar los estudios publicados en la literatura periodontal hasta la fecha.

PALABRAS CLAVE

Diabetes mellitus, hiperglucemia, periodontitis

INTRODUCCIÓN

La diabetes mellitus (DM) es la enfermedad endocrina más frecuente e incluye un grupo de trastornos metabólicos caracterizados por la elevación de los niveles de glucosa en sangre acompañados de complicaciones a largo plazo.

Puede ser clasificada en dos categorías principales:
- Diabetes mellitus insulino-dependiente o tipo I.
- Diabetes mellitus no-insulino dependiente o tipo II.

La **diabetes mellitus tipo I** se debe a la destrucción probablemente de etiología autoinmune, de las células beta de los islotes del páncreas dando como resultado niveles plasmáticos de insulina bajos o indetectables. El inicio es normalmente antes de los 40 años de edad, puede ser agudo, con sed, poliuria, polifagia y pérdida de peso. La enfermedad se controla mediante inyecciones diarias de insulina y es característicamente inestable en episodios de cetoacidosis.

La **diabetes mellitus tipo II** es de inicio insidioso, apareciendo en individuos de edad media como resultado de una utilización defectuosa de la insulina, siendo los niveles plasmáticos de insulina en valores absolutos, normales o altos. Estos pacientes no presentan episodios de cetoacidosis y controlan la hiperglucemia mediante dieta y/o hipoglucemiantes orales. Un elevado porcentaje de estos pacientes presenta problemas de obesidad.

ASPECTOS EPIDEMIOLÓGICOS

La asociación entre diabetes mellitus y la enfermedad periodontal ha sido motivo de estudio durante mucho tiempo.

Clásicamente se ha atribuido una relación directa entre la diabetes mellitus y la incidencia y severidad de la enfermedad periodontal, sin embargo, los diversos estudios publicados en la literatura muestran resultados aparentemente contradictorios.

Existen 5 razones que podrían explicar estas discrepancias:
1. La existencia de 2 tipos clínicos de DM bien diferenciados, los cuales han sido, a menudo, indistintamente tratados en los estudios.
2. Los grupos control se han considerado como "no diabéticos" simplemente por determinación de glucemia basal, sin tener en cuenta medidas analíticas más precisas.
3. Se han utilizado diferentes índices de destrucción periodontal.

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Araya AV, Pavez V, Perez C, Gonzalez F, Colombo A, Aguirre A, et al. Ex vivo lipopolysaccharide (LPS)-induced TNF-a, IL-1b, IL-6 and PGE 2 secretion in whole blood from Type 1 diabetes mellitus patients with or without aggressive periodontitis.

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Ex vivo lipopolysaccharide (LPS)-induced TNF-α, IL-1β, IL-6 and PGE_2 secretion in whole blood from Type 1 diabetes mellitus patients with or without aggressive periodontitis

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ABSTRACT. Several studies have demonstrated that diabetes is a risk factor for developing periodontal disease, increasing its prevalence and severity. Furthermore, periodontitis may impair the metabolic control and adequate treatment of diabetic patients. LPS from Gram-negative bacteria penetrates the periodontal tissues and subsequently recruits and activates immune cells. Progression to severe periodontitis with loss of supporting structures is mediated by several factors, including secretion of a broad spectrum of inflammatory and destructive mediators such as cytokines (TNF-α, IL-1β and IL-6), chemokines (IL-8) and prostaglandin E_2 (PGE_2).

The aim of this work is to investigate differences in the TNF-α, IL-1β and IL-6 expression and prostaglandin E_2 (PGE_2) release in blood from diabetic patients with and without aggressive periodontitis (AP) stimulated with lipopolysaccharide (LPS). For this purpose we recruited 29 Type 1 diabetes mellitus (DM) patients, 14 with AP and 15 without AP. Fourteen healthy individuals formed the control group. For cytokine expression and PGE_2 secretion, an ex vivo whole blood culture system was used . Cytokines and PGE_2 were detected by commercial immunometric assays. A wide range of inter-individual variability in spontaneous and LPS-induced TNF-α, IL-1β and IL-6 levels in patient groups and controls was found. The mean of spontaneous and LPS-induced TNF-α and IL-1β levels did not differ significantly ($p > 0.5$) when patients were compared to control individuals. Although not significant, the spontaneous TNF-α, IL-1β and IL-6 levels in the group of Type 1 DM with AP were higher than in controls, while in diabetic patients without AP, these values were depressed in comparison with controls. In both groups of patients, the means of LPS-induced IL-6 levels were higher than the controls but the differences observed were not significant ($p = 0.07$).

However, the LPS-induced PGE_2 levels varied significantly when all groups were compared ($p = 0.007$). The means of LPS-induced PGE_2 levels for Type 1 diabetic patients with AP ($p = 0.0009$) and without AP ($p = 0.024$) were significantly higher than the levels observed for healthy controls. Finally, we conclude that Type 1 diabetic patients with or without AP did not express higher LPS-induced TNF-α, IL-1β and IL-6 levels than controls. However, the PGE_2 levels released were significantly higher than those detected in controls.

Keywords: TNF-α, IL-1β, IL-6, PGE_2, diabetes

INTRODUCTION

Diverse studies have demonstrated that diabetes is a risk factor for developing periodontal disease, increasing its prevalence and severity [1-5]. According to previous reports, the prevalence of periodontitis in Type 1 diabetic patients between the ages of 13 and 18 is approximately 9.8% [6], while in the 20-29-year-old age group, the rate rises to 40.0% [2, 7].

Since Type 1 diabetes mellitus (Type 1 DM) generally develops at a very early stage of life, there may be a high probability of a severe, early onset periodontitis, resulting in tooth loss if not detected sufficiently quickly.

Furthermore, periodontitis may impair the metabolic control and adequate treatment of diabetic patients, being associated with a reduction in the glycosylated haemoglobin levels. There may also be an additional potential risk of bacteraemia leading to systemic inflammatory response syndrome [8, 9].

Ebersole JL, Holt SC, Hansard R, Novak MJ. Microbiologic and Immunologic Characteristics of Periodontal Disease in Hispanic Americans With Type 2 Diabetes. J Periodontol. 2008 Apr;79(4):637–46

J Periodontol • April 2008

Microbiologic and Immunologic Characteristics of Periodontal Disease in Hispanic Americans With Type 2 Diabetes

Jeffrey L. Ebersole,* Stanley C. Holt,† Richard Hansard,‡ and M. John Novak*

Background: The microbiology of periodontitis in type 1 diabetes has been reported, but less is known about type 2 diabetes. Moreover, these data have not linked microbial colonization, host response, and clinical presentation in type 1 or type 2 diabetes. The objectives of this study were to relate periodontal status, periodontal microorganisms, and host-response characteristics in Hispanic Americans with type 2 diabetes.

Methods: Plaque and serum samples were obtained from 63 Hispanic American subjects with and without type 2 diabetes. The microbiology of subgingival plaque samples was evaluated using DNA checkerboard hybridization, and serum antibody to a battery of oral microorganisms was determined using an enzyme-linked immunosorbent assay.

Results: In general, similar pathogens were present in periodontitis sites from subjects with and without type 2 diabetes, although the periodontitis sites in diabetes showed a higher frequency of *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*), and *Campylobacter* spp. Serum antibody to *Campylobacter rectus* was elevated in type 2 diabetes, whereas antibody to *P. gingivalis* and *C. rectus* were elevated in subjects with periodontitis, irrespective of diabetes status. Stratification of the population based upon antibody to *P. gingivalis* or *C. rectus* suggested a linkage between elevated antibody to *P. gingivalis*, increased frequency of diabetes, and significantly worse periodontitis.

Conclusion: The increased severity of periodontal disease with type 2 diabetes may reflect an alteration of the pathogenic potential of periodontal bacteria and/or a modification of the characteristics of the host's inflammatory response that may contribute to a breakdown in the homeostasis of the periodontium. *J Periodontol 2008;79:637-646.*

KEY WORDS

Diabetes; Hispanic Americans; immunology; microbiology; periodontitis.

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Studies[1-4] of the microbial progression from periodontal health through gingivitis to periodontitis have indicated a progressive change from a predominantly Gram-positive to an anaerobic Gram-negative biofilm. Various reports[5-7] described the predominant microorganisms in periodontitis sites from subjects with type 1 diabetes. The amount of glycemic control seemed to have minimal impact on the characteristics of the pathogens present at diseased sites. Although less is known of the bacterial specificity of type 2 diabetes–associated periodontal disease, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Campylobacter rectus*, *Fusobacterium nucleatum*, and *Eikenella corrodens* have been identified at diseased sites in these subjects, with no effect of diabetes control on the distribution of these bacteria.[8,9] A study[8] of type 2 diabetes in the Pima Indians suggested that *P. gingivalis* from periodontally diseased sites in this "high-risk" group was a different antigenic type than in nondiabetic subjects. Recently, a benzoyl-DL-arginine-naphthylamine (BANA) test was used to characterize the potential pathogenic microbiota in subjects with and without type 2 diabetes.[10] No differences were noted between these groups; however, stratification of the subjects with diabetes, based upon metabolic control, demonstrated higher BANA reactions in

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Peruzzo Lopes CC, do Monte Ribeiro Busato P, Michelin Mânica MF, de Araújo MC, Marquez Zampiva MM, Bortolini BM, et al. Effect of basic periodontal treatment on glycemic control and inflammation in patients with diabetes mellitus type 1 and type 2: controlled clinical trial. J Public Heal. 2017 Aug 1;25(4):443–9

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ORIGINAL ARTICLE

Effect of basic periodontal treatment on glycemic control and inflammation in patients with diabetes mellitus type 1 and type 2: controlled clinical trial

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Abstract
Objective Compare the response of basic periodontal therapy in diabetes patients with diabetes type 1 and type 2.
Materials and methods We selected 70 patients with periodontitis; these were divided into three groups: the control group (n = 11), systemically healthy patients; test group 1 (n = 14), patients with type 1 diabetes mellitus; test group 2 (n = 27), patients with type 2 diabetes mellitus. The groups received basic periodontal treatment after clinical examination. The analyses were performed at 0, 3 and 6 months; clinical parameters included the amount of periodontal and gingival crevicular fluid. Glycated hemoglobin (HbA1c) levels and prostaglandin E2 (PGE2) expression were measured.
Results All clinical periodontal parameters evaluated improved in both groups, as did the amount of gingival crevicular fluid. A more significant decrease in HbA1c and PGE2 expression ($p < 0.05$) occurred in test group 1 after 6 months.
Conclusion The basic periodontal treatment was more effective for glycemic control in patients with type 1 diabetes mellitus.

Keywords Type 1 diabetes mellitus · Type 2 diabetes mellitus · Inflammation · Basic periodontal treatment · Glycemic control

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Introduction

Diabetes mellitus (DM) is an endocrine and metabolic disorder caused by uncontrolled levels of glucose in the blood due to a deficiency in insulin production or activity (Llambés et al. 2005). Generally, there are two types of DM, which are characterized as: diabetes mellitus type 1 (DM1), which, in most cases, breaks out during childhood and adolescence and represents only 5–10% of patients with diabetes; diabetes mellitus type 2 (DM2), the common form of the disease, which prevails among older adults (American Diabetes Association 2004; Graves et al. 2007).

DM1 is associated with several complications of the patient's homeostasis, including reduced resistance to infections due to a jeopardized immune reaction, a decrease of the

O'Connell PAA, Taba M, Nomizo A, Foss Freitas MC, Suaid FA, Uyemura SA, et al. Effects of Periodontal Therapy on Glycemic Control and Inflammatory Markers. J Periodontol. 2008 May;79(5):774–83

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Effects of Periodontal Therapy on Glycemic Control and Inflammatory Markers

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Background: Periodontitis, a complication of diabetes mellitus (DM), can induce or perpetuate systemic conditions. This double-masked, placebo-controlled study evaluated the effects of periodontal therapy (scaling and root planing [SRP]) on the serum levels of glycated hemoglobin (HbA1c) and on inflammatory biomarkers.

Methods: Thirty subjects with type 2 DM and periodontitis were treated with SRP + placebo (SRP; N = 15) or with SRP + doxycycline (SRP+Doxy; N = 15), 100 mg/day, for 14 days. Clinical and laboratory data were recorded at baseline and at 3 months after treatment.

Results: After 3 months, the reduction in probing depth was 0.8 mm for the SRP group (P <0.01) and 1.1 mm for the SRP+Doxy group (P<0.01) followed by a 0.9% (SRP; P = 0.17) and 1.5% (SRP+Doxy; P<0.01) reduction in HbA1c levels. A significant reduction in interleukin (IL)-6; interferon-inducible protein 10; soluble fas ligand; granulocyte colony-stimulating factor; RANTES; and IL-12 p70 serum levels were also verified (N = 30). To our knowledge, this is the first report on the effects of periodontal therapy on multiple systemic inflammatory markers in DM.

Conclusions: Periodontal therapy may influence the systemic conditions of patients with type 2 DM, but no statistical difference was observed with the adjunctive systemic doxycycline therapy. Moreover, it is possible that the observed improvement in glycemic control and in the reduction of inflammatory markers could also be due to diet, which was not controlled in our study. Therefore, a confirmatory study with a larger sample size and controlled diet is necessary. *J Periodontol 2008;79:774-783.*

KEY WORDS

Biomarkers; diabetes; inflammation; periodontitis.

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Diabetes mellitus (DM) and periodontitis are common chronic diseases in adults. Both diseases are highly prevalent in the world population. Approximately 21 million children and adults in the United States (7% of the population) have diabetes,[1] and this incidence is increasing annually. By the year 2025, it is estimated that 300 million people will have diabetes and that more than one in three people >30 years of age will have periodontitis. It is also estimated that ≥35.7 million people in the United States have periodontitis.[2]

DM is one of a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Based on these conditions, DM can be classified into two main types: type 1 DM is caused by destruction of the pancreatic β cells that are known to produce insulin; type 2 DM results from defects in insulin molecules or from defective cell receptors for insulin. This defect indicates impaired insulin function (insulin resistance) rather than deficiency or lack of production.[3] The chronic hyperglycemic condition of diabetes is associated with long-term damage to, dysfunction, or failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Periodontitis is also considered to be one of these complications. It is generally accepted that periodontal disease is more

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Perea MA, Campo J, Charlén L, Bascones A. Enfermedad periodontal e infección por VIH: estado actual. Av en Periodoncia e Implantol Oral. 2006;18(3):135–47

Enfermedad periodontal e infección por VIH: estado actual

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Perea MA, Campo J, Charlén L, Bascones A. *Enfermedad periodontal e infección por VIH: estado actual.* Av Periodon Implantol. 2006; 18, 3: 135-147.

RESUMEN

La infección por el virus de la inmunodeficiencia humana (VIH) puede tener influencia a nivel periodontal. El deterioro del sistema inmune por una disminución de los linfocitos TCD4+ puede comprometer las defensas del huésped a nivel sistémico por lo que se puede aumentar la susceptibilidad a padecer diferentes patologías en la cavidad oral. En este trabajo de revisión se recoge el estado actual de la enfermedad periodontal en pacientes VIH+ y trata de abordar como el VIH puede influir en la microbiota subgingival aumentando el riesgo de padecer periodontitis. La presencia de otros factores coadyuvantes podría favorecer la aparición de patología o incluso agravarla independiente de la presencia del VIH.

PALABRAS CLAVE

VIH, enfermedad periodontal, SIDA, situación inmunológica, higiene oral.

Aceptado para publicación: Enero 2006.

INTRODUCCIÓN

Las infecciones periodontales son un conjunto de enfermedades que, localizadas en la encía y en las estructuras de soporte del diente (ligamento y hueso alveolar), están provocadas por ciertas bacterias provenientes de la placa subgingival. Estas bacterias tienen un importante papel en el comienzo y posterior desarrollo de la periodontitis participando, en la formación de la bolsa periodontal con destrucción del tejido conectivo y reabsorción del hueso alveolar a través de un mecanismo inmunopatogénico. Al actuar sobre el tejido conectivo, las bacterias provocan una serie de reacciones inflamatorias e inmunológicas en el hospedador que se traducen en un acúmulo de células asociadas a la activación de los procesos de destrucción periodontal. Estos periodos de destrucción periodontal están asociados a distintos cambios en la población celular que confirman el infiltrado inflamatorio localizado en el tejido conectivo subepitelial (neutrófilos, macrófagos, linfocitos, células plasmáticas, etc.) (1). La enfermedad periodontal es una patología multifactorial dependiente de las características del hospedador, de los factores ambientales y de los agentes microbiológicos por lo que es probable que en un ambiente específico y con la influencia de factores genéticos determinen la susceptibilidad del individuo a padecer la enfermedad (2, 3).

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Gonçalves LDS, Maria S, Ferreira S, Jr AS, Villoria GE, Costinha LH, et al. Association of T CD4 Lymphocyte Levels and Chronic Periodontitis in HIV-Infected Brazilian Patients Undergoing Highly Active Anti-Retroviral Therapy: Clinical Results. 2005;(June):915–22

J Periodontol • June 2005

Association of T CD4 Lymphocyte Levels and Chronic Periodontitis in HIV-Infected Brazilian Patients Undergoing Highly Active Anti-Retroviral Therapy: Clinical Results

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German Eduardo Villoria,*† Lúcia Helena Costinha,*† and Ana Paula Colombo‡

Background: Controversial data regarding the association between immunosuppression and prevalence/severity of periodontal diseases in HIV infection have been reported. Thus, the aim of this study was to test the hypothesis that lower T CD4 lymphocyte levels are not related to a higher prevalence of chronic periodontitis in HIV-infected Brazilians undergoing highly active anti-retroviral therapy (HAART).

Methods: Sixty-four HIV-infected patients under HAART were classified as having chronic periodontitis; i.e., ≥three sites with probing depth (PD) and/or clinical attachment level (CAL) ≥5 mm or periodontal healthy (no sites with PD >3 mm and/or CAL >4 mm). All subjects received conventional periodontal therapy. Bleeding on probing, plaque accumulation, PD, and CAL were registered at six sites/tooth at baseline and 4 months after therapy. Epidemiological features and levels of T CD4 lymphocytes were obtained from medical records. Significance of differences in periodontal clinical parameters within and between groups were determined using Wilcoxon signed-rank and Mann-Whitney or independent sample *t* tests. Associations between T CD4 levels and clinical parameters were determined using the chi square test.

Results: Sixty-one percent of the HIV-infected patients represented AIDS cases, although 69% of them were periodontally healthy. The overall T CD4 lymphocyte mean levels was 333 ± 254 cells/mm^3 and viral load was 12,815 ± 24,607 copies/mm^3. Yet the prevalence of chronic periodontitis was relatively low (36%). In addition, patients with periodontitis presented a moderate disease (mean PD = 2.2 ± 0.10; mean CAL = 2.6 ± 0.13) and responded successfully to periodontal therapy. These subjects showed higher levels of T CD4 cells, but lower counts of neutrophils than periodontally healthy patients. Among periodontally healthy and chronic periodontitis patients, 41.7% and 22.9%, respectively, had low levels of T CD4 lymphocytes. No significant differences between periodontal status and epidemiological and immunological parameters were observed.

Conclusion: Based on these results, the hypothesis that lower T CD4 lymphocyte levels are not associated with higher prevalence of chronic periodontitis in HIV-infected Brazilians under HAART cannot be rejected. *J Periodontol 2005;76:915-922.*

KEY WORDS

Brazilians; highly active anti-retroviral therapy; HIV infections/therapy; periodontitis/epidemiology; T lymphocytes, CD4.

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Martínez-Canut P, Guarinos J, Bagán JV. Periodontal Disease in HIV Seropositive Patients and Its Relation to Lymphocyte Subsets. J Periodontol. 1996;67(1):33–6

Periodontal Disease in HIV Seropositive Patients and Its Relation to Lymphocyte Subsets

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THIS STUDY WAS PERFORMED to determine the type of periodontal pathology found in a group of HIV+ patients and its relation to serum levels of CD4. The sample consisted of 101 individuals: intravenous drug users (84%), homosexuals (7%), and heterosexuals (10%). Each patient was examined clinically and radiographically. Periodontal clinical parameters included gingival index and probing depth and loss of attachment on four sites per tooth. Severity of disease was defined as the most severe lesion found: gingivitis, or early, moderate, or advanced periodontitis. CD4 counts were determined on 64 of these patients. Associations between severity of the disease and gender and CD4 counts were analyzed using the Mantel Haenszel chi square test, while associations between severity and age and CD4/CD8 ratio were analyzed using the Kruskal-Wallis test. No disease was found in 14.8% of the sample, gingivitis was found in 21.8%, early periodontitis in 43.6%, moderate periodontitis in 10.9%, and advanced periodontitis in 8.9%. Linear gingival erythema (LGE) was seen in 17.8% of all patients and necrotizing periodontitis (NUP) in 4.9%. No statistically significant differences were observed between the severity of the disease and CD4 counts. *J Periodontol 1996;67:33–36.*

Key Words: CD4-CD8 ratio; antigens, CD4; HIV infections; gingivitis/epidemiology; periodontitis/epidemiology; T-lymphocyte subsets.

Since the earliest report on periodontal pathology related to HIV infection,[1] many attempts have been made to identify and classify the variety of oral diseases and periodontal diseases in particular associated with this infection.[2–6] These attempts, however, have faced several limitations, derived basically from diversity in the study methods, clinical criteria used to identify each periodontal disease, and differences due to the study group, mainly the staging level of the infection and the risk population studied.[7]

The influence of these variables may justify the lack of consistency of classifications and terminology utilized to define the variety of periodontal diseases related to HIV infection. This may also explain the wide variation of prevalence rates of these periodontal entities among studies, which makes comparing them unreliable.[8]

The need to develop standardized criteria to define periodontopathic entities taking place in HIV+ patients is evident. Three types of parameters are currently used for this purpose:[9] 1) conventional periodontal parameters (gingival index, attachment loss, etc.); 2) clinical parameters of specific forms of periodontal disease seen in HIV infection (tissue necrosis, marginal band of erythema); and 3) CD4 count grouping in concordance with the Centers for Disease Control (CDC) classification system.[10]

The purpose of this study was to determine the type of periodontal pathology found in a group of HIV+ patients, according to serum levels of CD4.

MATERIALS AND METHODS

A group of 101 HIV+ patients seeking dental treatment at the Dental School of the University of Valencia were selected for the study. These patients were examined between September 1988 and June 1992 and gave their consent after being informed about the purpose of the study.

HIV status had been previously tested by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot. Risk group for acquisition of HIV infection was elicited upon interview. In 64 of these individuals, 7 days prior to the periodontal examination, a determination was carried out of T-lymphocyte subsets in peripheral blood, by immunofluorescence, using conjugated antibod-

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Steidley KE, Thompson SH, McQuade MJ, Strong SL, Scheidt MJ, Van Dyke TE. A Comparison of T4:T8 Lymphocyte Ratio in the Periodontal Lesion of Healthy and HIV-Positive Patients. J Periodontol. 1992;63(9):753–6

A Comparison of T4:T8 Lymphocyte Ratio in the Periodontal Lesion of Healthy and HIV-Positive Patients

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PREVIOUS REPORTS DESCRIBE A CHARACTERISTIC, rapidly progressive, periodontitis that is unique to patients who are seropositive for HIV antibody (Western blot +). The purpose of this study was to compare the T4 and T8 lymphocyte subpopulations in the peripheral blood and periodontal lesions of these HIV patients with those of healthy controls. T-cell subsets in peripheral blood were quantified by flow cytometry. The values from this analysis were used to calculate the peripheral T4:T8 lymphocyte ratio for each patient. Gingival tissue (papilla) was obtained from 8 HIV + patients and from 6 healthy HIV − control patients during routine gingival surgery. The T-cell subpopulations in the gingival tissue were determined using serial cryostat sections that were labeled with monoclonal antibodies for T4 and T8 cells and developed using an avidin-biotin-peroxidase system. Six sections were taken from each of the 14 tissue specimens (one per patient). The sections were examined at 450 × and the mean number of T4 and T8 cells calculated for each section. These mean values were then used to determine the T4:T8 lymphocyte ratio for each tissue specimen. The peripheral blood analysis revealed a mean serum T4:T8 ratio of (2.07 ± 0.455) for the controls and (0.58 ± 0.26) for the HIV patients. The significantly lower T4:T8 ratio in HIV patients is consistent with their diagnosis. Although the results indicated that the mean T4:T8 lymphocyte ratio in the gingiva of controls was highly variable (2.70 ± 1.344), the gingiva of HIV patients consistently exhibited a complete absence of T-cells. The lack of locally present immune effector and regulatory cells in HIV seropositive patients with periodontal disease could in part explain the characteristic and rapidly progressive nature of their periodontal disease. *J Periodontol 1992; 63:753–756.*

Key Words: Periodontitis; HIV virus; T4 lymphocytes; T8 lymphocytes.

The human immunodeficiency virus (HIV) is a retrovirus that, by preferentially attacking and destroying the T4 lymphocyte, causes an immunocompromised state and its associated pathogenic sequelae (AIDS). In studying these patients, several oral diseases have been related to HIV infection and the development of AIDS.[1–3] Candidiasis, for example, has been used as a criterion in the Walter Reed and CDC Classifications.[4] Winkler and Murray[3] identified a unique HIV-associated periodontal condition that they named AIDS-virus-associated-periodontitis (AVAP). Winkler subsequently changed this term to the more specific HIV-associated gingivitis (HIV-G) or HIV-associated periodontitis (HIV-P).[5] Clinical features include: rapid progression, interproximal ulceration, marked edema, gingival erythema, and pain.

Since the HIV virus attacks the T4 lymphocyte and a rapidly progressive form of periodontitis has been related to HIV infection, it is possible that HIV infection affects local gingival immunoregulation. The purpose of this study was to evaluate the T4:T8 lymphocyte ratio in the gingiva and serum of both healthy (HIV −) and HIV + patients with periodontitis.

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The opinions of this article do not represent the views of the United States Department of Defense, the Department of Army, or the United States Army Dental Corps. Use of any commercial products in this project does not imply endorsement by the U.S. Government.

MATERIALS AND METHODS

Subjects

The participants in this study included 8 HIV + patients (3 white males and 5 black males) ages 18 to 31 years old with periodontal disease. The selection criteria, other than

Lamster IB, Grbic JT, Mitchell-Lewis DA, Begg MD, Mitchell A. New concepts regarding the pathogenesis of periodontal disease in HIV infection. Ann Periodontol. 1998;3(1):62–75

New Concepts Regarding the Pathogenesis of Periodontal Disease in HIV Infection

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Abstract

Periodontal manifestations of human immunodeficiency virus (HIV) infection were first described in 1987. Initially, the lesions receiving attention were HIV-associated gingivitis (now known as linear gingival erythema [LGE]) and HIV-associated periodontitis (now known as necrotizing ulcerative periodontitis [NUP]). The true prevalence of LGE was difficult to determine due to variable diagnostic criteria. Recently, LGE has been associated with intraoral Candida *infection. The prevalence of NUP is low (≤ 5%), and this lesion is associated with pronounced immunosuppression. Current focus on the periodontal manifestations of HIV infection centers on rapid progression of chronic adult periodontitis in HIV+ patients. Attempts to identify the pathogenesis of the increased progression of periodontitis have not proven successful. For example, analysis of subgingival plaque for the presence of bacterial pathogens has failed to detect differences between HIV+ and HIV− patients. Recently our laboratory has identified alterations in the host response in the gingival crevice of HIV+ patients. Comparing HIV+ and HIV− injecting drug users (IDU), levels of the proinflammatory cytokine interleukin-1β (IL-1β) in gingival crevicular fluid (GCF) were slightly elevated at sites with a probing depth of 1 to 3 mm. At deeper sites (≥ 4 mm), total IL-1β in GCF was significantly greater in HIV+ individuals. Using the lysosomal acid glycohydrolase β-glucuronidase (βG) as a measure of the influx of polymorphonuclear leukocytes (PMN) into the gingival crevice, our data indicated a significant correlation of total βG in GCF and probing depth in the HIV− IDU (r = 76; P = .02). This result was similar to what we have observed in other studies. In contrast, for HIV+ subjects, total βG was not associated with probing depth (r = .20; NS). These data suggest that HIV+ patients have altered regulation of PMN recruitment into the gingival crevice. We have begun to investigate the conditions under which subgingival* Candida *may contribute to periodontal lesions in HIV+ individuals.* Candida *from subgingival sites has been cultured in HIV+ individuals. Subgingival* Candida *was distinct from* Candida *isolated from tongue and buccal mucosal surfaces (as indicated by genomic fingerprinting). We hypothesize the absence of adequate priming of PMN by HIV+ patients. This may be due to a reduced Th_1 lymphocyte response. The inability of HIV+ individuals to adequately prime PMN may allow* Candida *to colonize the subgingival environment. In that milieu, it may act directly or in concert with subgingival bacterial pathogens, or as a cofactor (by inducing production of proinflammatory cytokines) to increase the occurrence of periodontal attachment loss.*
Ann Periodontol 1998;3:62–75.

Key Words: HIV seropositivity; HIV infection; periodontal diseases, rapidly progressive; gingival crevicular fluid; neutrophils; *Candida*; gingivitis/microbiology.

Estevez M, Ballart IJ, Diez RA, Planes N, Scaglione C, Sen L. Early Defect of Phagocytic Cell Function in Subjects at Risk for Acquired Immunodeficiency Syndrome. Scand J Immunol. 1986;24(2):215–21

Scand. J. Immunol. **24,** 215–221, 1986

Early Defect of Phagocytic Cell Function in Subjects at Risk for Acquired Immunodeficiency Syndrome

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Estevez, M.E., Ballart, I.J., Diez, R.A., Planes, N., Scaglione, C. & Sen, L. Early Defect of Phagocytic Cell Function in Subjects at Risk for Acquired Immunodeficiency Syndrome. *Scand. J. Immunol.* **24,** 215–221, 1986

We studied the functions of peripheral blood monocytes and polymorphonuclear cells in 15 apparently healthy homosexual men, eight homosexual or bisexual subjects with unexplained generalized lymphadenopathies (pre-AIDS), four homosexual men with acquired immunodeficiency syndrome (AIDS), and 15 heterosexual men. In comparison with normal controls, the homosexual groups studied presented a decreased monocyte candidacidal activity for *Candida pseudotropicalis* that gradually deteriorates as the clinical symptoms progress towards AIDS. The monocyte phagocytic function was retained. Although the phagocytic and candidacidal activities of the polymorphonuclear cells did not differ from those of the normal controls, the candidacidal activity in some of the cases studied was unusually enhanced, indicating that the cells were in an activated state. In addition, only two of nine sera tested from asymptomatic homosexual males were positive for antibodies to HTLV-III/LAV, while six out of eight pre-AIDS and both of the two AIDS patients tested had antibodies to AIDS-associated retrovirus. We suggest that in AIDS the phagocytic system is already involved, together with B and T lymphocyte abnormalities, during the early events of the syndrome, even without the detection of AIDS-associated retrovirus antibodies.

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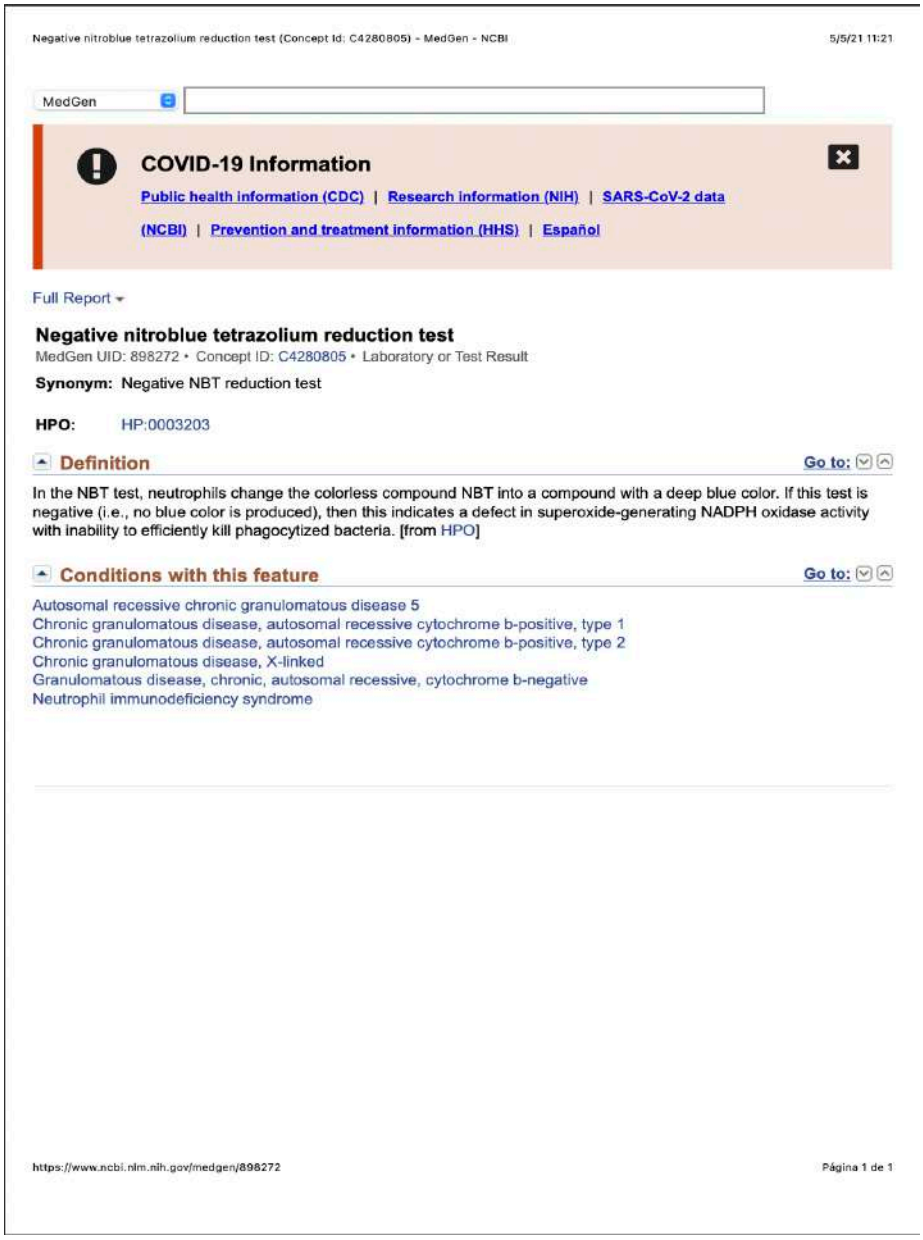
Over the past 5 years a new immunodeficiency syndrome has been described which was first recognized in men under 60 years old belonging to the homosexual community [14] and subsequently in intravenous drug addicts [21], Haitian immigrants [30], individuals who had received blood products [1], haemophiliacs [6], and in women and children related to patients with acquired immunodeficiency syndrome (AIDS) [12, 27]. This disease is characterized by a profound defect in the cellular immune responses [9, 13, 24], and the patients develop a high susceptibility to opportunistic infections, which are generally fatal [9, 13]. The opportunistic micro-organisms found in AIDS patients include protozoa (*Pneumocystis carinii, Toxoplasma gondii*), bacteria (mainly mycobacteria), fungi (*Candida albicans, Cryptococcus neoformans*), and virus (cytomegalovirus, *Herpes simplex)* [9, 13, 24]. The patients can also develop neoplasms such as Kaposi's sarcoma [9, 13, 24] and lymphomas [7, 31].

There are numerous reports indicating a progressive and irreversible impairment in lymphocyte functions, mainly attributed to alterations in the regulatory function of T-lymphocyte subsets in patients with AIDS [15, 16, 23] due to the progressive infection by a lymphocytopathic retrovirus (LAV, HTLV-III, or AIDS-associated retrovirus) [4, 10]. Multiple studies have demonstrated that apparently healthy individuals belonging to high-risk groups, can

Negative nitroblue tetrazolium reduction test (Concept Id: C4280805) - MedGen - NCBI [Internet]. Ncbi.nlm.nih.gov. 2021 [cited 23 February 2021]. Available from: https://www.ncbi.nlm.nih.gov/medgen/898272



Negative nitroblue tetrazolium reduction test (Concept Id: C4280805) - MedGen - NCBI 5/5/21 11:21

MedGen

COVID-19 Information

Public health information (CDC) | Research information (NIH) | SARS-CoV-2 data (NCBI) | Prevention and treatment information (HHS) | Español

Full Report

Negative nitroblue tetrazolium reduction test

MedGen UID: 898272 • Concept ID: C4280805 • Laboratory or Test Result

Synonym: Negative NBT reduction test

HPO: HP:0003203

Definition Go to:

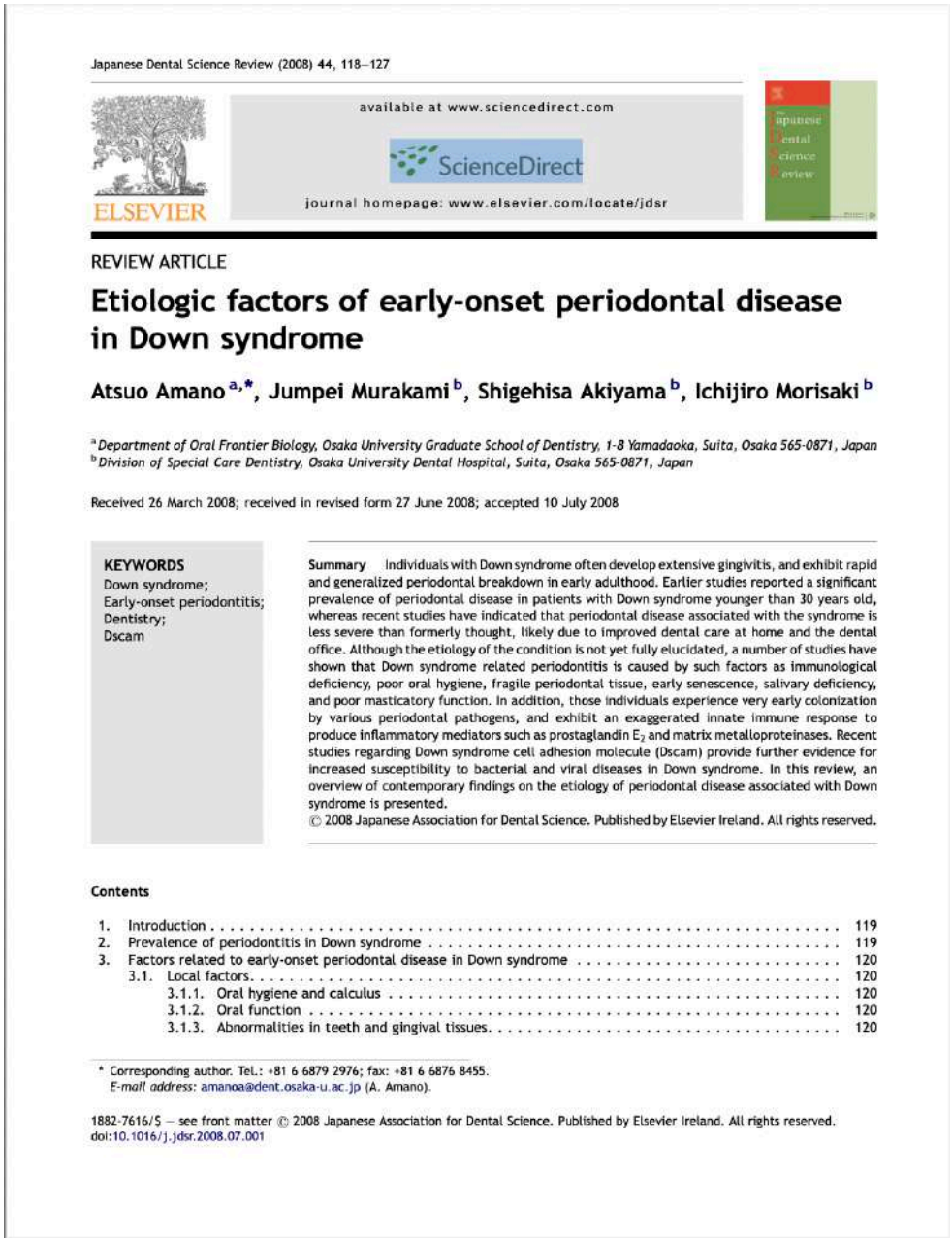
In the NBT test, neutrophils change the colorless compound NBT into a compound with a deep blue color. If this test is negative (i.e., no blue color is produced), then this indicates a defect in superoxide-generating NADPH oxidase activity with inability to efficiently kill phagocytized bacteria. [from HPO]

Conditions with this feature Go to:

Autosomal recessive chronic granulomatous disease 5
Chronic granulomatous disease, autosomal recessive cytochrome b-positive, type 1
Chronic granulomatous disease, autosomal recessive cytochrome b-positive, type 2
Chronic granulomatous disease, X-linked
Granulomatous disease, chronic, autosomal recessive, cytochrome b-negative
Neutrophil immunodeficiency syndrome

https://www.ncbi.nlm.nih.gov/medgen/898272 Página 1 de 1

Amano A, Murakami J, Akiyama S, Morisaki I. Etiologic factors of early-onset periodontal disease in Down syndrome. Jpn Dent Sci Rev [Internet]. 2008;44(2):118–27. Available from: http://dx.doi.org/10.1016/j.jdsr.2008.07.001



Japanese Dental Science Review (2008) 44, 118–127

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REVIEW ARTICLE

Etiologic factors of early-onset periodontal disease in Down syndrome

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KEYWORDS
Down syndrome;
Early-onset periodontitis;
Dentistry;
Dscam

Summary Individuals with Down syndrome often develop extensive gingivitis, and exhibit rapid and generalized periodontal breakdown in early adulthood. Earlier studies reported a significant prevalence of periodontal disease in patients with Down syndrome younger than 30 years old, whereas recent studies have indicated that periodontal disease associated with the syndrome is less severe than formerly thought, likely due to improved dental care at home and the dental office. Although the etiology of the condition is not yet fully elucidated, a number of studies have shown that Down syndrome related periodontitis is caused by such factors as immunological deficiency, poor oral hygiene, fragile periodontal tissue, early senescence, salivary deficiency, and poor masticatory function. In addition, those individuals experience very early colonization by various periodontal pathogens, and exhibit an exaggerated innate immune response to produce inflammatory mediators such as prostaglandin E_2 and matrix metalloproteinases. Recent studies regarding Down syndrome cell adhesion molecule (Dscam) provide further evidence for increased susceptibility to bacterial and viral diseases in Down syndrome. In this review, an overview of contemporary findings on the etiology of periodontal disease associated with Down syndrome is presented.

Contents

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Cavalcante LB, Tanaka MH, Pires JR, Henrique Apponi L, Aparecida Giro EM, Roberto Valentini S, et al. Expression of the Interleukin-10 Signaling Pathway Genes in Individuals With Down Syndrome and Periodontitis. J Periodontol. 2012;83(7):926–35

Volume 83 • Number 7

Expression of the Interleukin-10 Signaling Pathway Genes in Individuals With Down Syndrome and Periodontitis

Lícia Bezerra Cavalcante,* Marcia Hiromi Tanaka,* Juliana Rico Pires,† Luciano Henrique Apponi,† Elisa Maria Aparecida Giro,* Sandro Roberto Valentini,‡ Denise M. Palomari Spolidório,§ Marisa Veiga Capela,‖ Carlos Rossa Jr.,¶ and Raquel M. Scarel-Caminaga#

Background: Individuals with Down syndrome (DS) have a higher prevalence and severity of periodontal disease, which cannot be explained by poor oral hygiene alone and is related to changes in the immune response. The aim of this study is to evaluate whether DS was associated with differential modulation of expression of genes associated with proinflammatory and anti-inflammatory responses in periodontal disease.

Methods: A total of 51 individuals were evaluated: 19 individuals with DS and periodontal disease (group 1), 20 euploid individuals with periodontal disease (group 2; positive control), and 12 euploid individuals without periodontal disease (group 3; negative control). Clinical periodontal evaluation and gingival biopsies were performed. Quantitative reverse transcription-polymerase chain reaction was used to determine expression levels of interleukin-10 (IL-10), the receptors IL-10RA and IL-10RB, intracellular adhesion molecule 1 (ICAM-1), interferon-γ-inducible protein 10 (IP-10), and the signaling intermediates Janus kinase 1, signal transducer and activator of transcription 3 (STAT-3), and suppressor of cytokine signaling 3 (SOCS-3).

Results: Expression of *IL10, SOCS3, IP10,* and *ICAM1* mRNA in DS patients was significantly lower compared to euploid individuals with periodontal disease, whereas IL-10RB and STAT-3 mRNA levels were higher in individuals with DS.

Conclusion: Reduced expression of IL-10 coupled with a possible increase of *STAT3* activation (increase of *STAT3* and reduction of *SOCS3* mRNA) indicates an important modulation of the immune response, with attenuation of anti-inflammatory and increase of proinflammatory mediators. This modulation may be related to the increased prevalence and severity of periodontitis in individuals with DS. *J Periodontol 2012;83:926-935.*

KEY WORDS

Cytokines; Down syndrome; gene expression; inflammation; periodontitis.

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Down syndrome (DS) is a chromosomal disorder caused by an error in cell division that results in the presence of a third chromosome 21 or "trisomy 21."[1] The first observation that the oral conditions in young children with DS are markedly different from those in normal children was reported by Jones.[2] Since then, there have been at least two literature reviews examining the oral conditions of individuals with DS.[3,4]

Periodontal diseases, such as chronic periodontitis and aggressive periodontitis, are characterized by a progressive gingival inflammatory response to bacterial dental plaque, leading to destruction of the periodontium and eventually tooth loss.[5] Orner[6] observed an increased prevalence of periodontal disease in 89% of DS children compared to their age-matched and chromosomally normal siblings (58%). For individuals with DS who lived in institutions, a periodontal disease prevalence of 90% was observed in those ranging from 1 to 39 years, whereas 36% of DS children <6 years of age had periodontal pocket formation.[7]

Swallow[8] studied DS and mentally retarded (MR) patients in three different environments: institutions, day training centers, and special schools, and found that within these environments, the prevalence of periodontitis was higher in DS

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