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TRABAJO DE FIN DE GRADO

Grado en Odontología

SALIVA AND SERUM BIOMARKERS IN PERIODONTITIS AND CORONARY ARTERY DISEASE

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Abstract

Hypothesis and Objectives: Periodontitis is one of the most common inflammatory diseases in the world, affecting more than 50% of the population. Its inflammatory capacity has been shown to increase the risk of coronary heart disease, thus linking both diseases. Metalloproteinases (MMPs) are zinc-dependent enzymes involved in the breakdown of the extracellular matrix in both periodontitis and atherosclerotic plaque in coronary heart disease. This literature review aims to analyze the diagnostic potential of MMPs (MMP-8, MMP-9) and the tissue inhibitor of matrix metalloproteinase (TIMP-1) in saliva and serum for the detection of periodontal and/or coronary artery disease.

Methodology: Research was conducted through PubMed and Wiley Online Library platforms. A total of 36 articles were read and analyzed, and eight were analyzed in depth to describe the results of this project.

Results: MMP-8, MMP-9 in saliva show an elevated expression in patients with periodontal diseases while TIMP-1 is reduced in periodontal patients. MMP-8 is also found in high levels in other fluids such as gingival crevicular fluid (GCF). On the other hand, serum MMP-8 and MMP-9 show a high expression in patients with coronary heart disease. However, the level of TIMP-1 in blood is shown to be of no significance for the diagnosis of coronary heart disease.

Conclusion: MMP-8, MMP-9 are potential biomarkers for the diagnosis of periodontal disease and coronary heart disease. However, sampling of biological fluids is essential

for diagnostic value. Thus, MMP-8 and MMP-9 in the serum are considered less relevant for the diagnosis of periodontal disease. Likewise, the use of saliva biomarkers is not considered useful for the diagnosis of coronary heart disease. TIMP-1 levels in saliva and serum does not show conclusive results and therefore more research should be carried out.

Resumen

Objetivos: La periodontitis es una de las enfermedades inflamatorias más comunes en el mundo, que afecta a más del 50% de la población. Se ha demostrado que su capacidad inflamatoria aumenta el riesgo de sufrir una cardiopatía coronaria, lo que relaciona ambas enfermedades. Las metaloproteinasas (MMP) son enzimas dependientes del zinc que participan en la descomposición de la matriz extracelular tanto en la periodontitis como en la placa aterosclerótica de la enfermedad coronaria. Esta revisión bibliográfica tiene como objetivo analizar el potencial diagnóstico de las MMP (MMP-8, MMP-9) y del inhibidor tisular de la metaloproteinasa de la matriz (TIMP-1) en saliva y suero para la detección de la enfermedad periodontal y/o coronaria.

Metodología: La investigación se realizó a través de las plataformas Pubmed y Wiley Online Library. Se consultaron y se analizaron un total de 36 artículos, ocho de estos estudios se analizaron para describir los resultados.

Resultados: Las MMP-8, MMP-9 en saliva muestran un resultado elevado para las enfermedades periodontales mientras que el TIMP-1 está reducido en los pacientes

periodontales. La MMP-8 también se refleja elevada en otros fluidos como el líquido crevicular gingival (GCF). Por otro lado, la expresión de MMP-8, MMP-9 en suero es elevada en paciente con enfermedad coronaria. Sin embargo, el nivel de TIMP-1 en sangre se muestra sin importancia para el diagnóstico de la cardiopatía coronaria.

Conclusión: Las MMP-8, MMP-9 son potenciales biomarcadores para el diagnóstico de la enfermedad periodontal y la enfermedad coronaria. Sin embargo, la toma de muestras de fluidos biológicos es esencial para el valor diagnóstico. Los biomarcadores MMP-8 and MMP-9 en suero son considerados menos relevantes para el diagnóstico de la enfermedad periodontal. Asimismo, el uso de biomarcadores de saliva no se considera útil para el diagnóstico de la enfermedad coronaria. El TIMP-1 no muestra resultados concluyentes, de modo que hace falta una mayor investigación de este biomarcador.

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1. Introduction

The increase in non-communicable diseases (NCD) worldwide causes the death of about 70% of global mortality or 41 million deaths of individuals per year. The greatest NCD worldwide is cardiovascular disease, which in Europe alone causes the death of more than 3.9 million patients.[1] Every year cardiovascular diseases, which include stroke, rheumatic heart disease, cardiomyopathy, myocardiopathy and coronary heart disease, represent the leading cause of death worldwide.[2] Coronary heart disease is the leading cause of cardiovascular mortality, claiming more than 4.5 million lives annually worldwide.[3] On the other hand, periodontitis is also considered a highly prevalent non-communicable disease. Around 40-50% of the world' s population suffers from periodontitis, and up to 11.2% of them experience severe periodontitis (Fig 1).[1] And although it does not cause deaths, in 2016 it was considered one of the diseases that caused YLD (years of disability) of those of 3.5 million people around the world.[4]

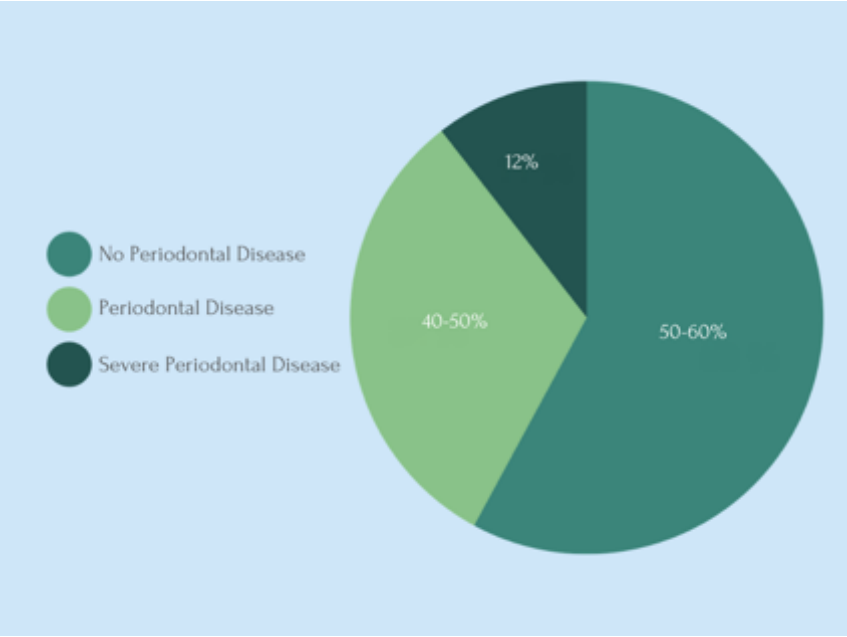

Fig 1. World population suffering periodontitis. Reference: Sanz M, Marco del Castillo A, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P. Own elaboration

Several studies have shown a correlation between periodontal disease and cardiovascular disease (e.g. stroke, myocardial infarction, vascular disease, coronary

artery disease (CAD)).[1] [5] It is crucial that dentists understand and identify the association between periodontal disease and cardiovascular disease. Important elements to take into account for a correct treatment of periodontitis and help to promote a healthy periodontium are crucial to reduce the overall inflammation in the organism and the prevention of cardiovascular disease. In addition, an early diagnosis of periodontitis is a key element in terms of the success of the treatment; thus, the progression of the inflammation could cause an irreversible loss of periodontal structures and potentially could facilitate the development of cardiovascular disease.

1.1 Periodontal Disease

Periodontitis, or periodontal disease, is a multifactorial inflammatory disease related to dental plaque and where its main victim is the destruction of the supporting tissues of the tooth.[6] There is evidence that there are different elements that influence periodontal diseases. Studies have suggested that there is a relationship between social income and periodontal diseases. It has been reported that people with a low socioeconomic index had 1.8 times more severe periodontitis than those with a high socioeconomic index.[4] Though, periodontal disease is produced by certain bacteria like, *Actinobacillus actinomycetemcomitans, Porphyro-monas gingivalis, Prevotella intermedia* and *Tannerella forsythensis*, which are essential for disease onset, the existence of predisposing factors will influence the pathogenesis of the disease. [7] Periodontitis can be chronic, also called continuous or aggressive, where bone loss and insertion is rapidly occurring. The periodontal disease is subdivided into localized, where less than 30% of the pieces are affected, or generalized, where more than 30% have pockets larger than 4mm. Periodontitis can be categorized as mild (1-2mm),

moderate (3-4mm) and severe with pockets deeper than 5mm. [7] The basic signs of periodontitis are the presence of periodontal pockets, gingival bleeding and bone loss from the alveolar bone.[6] The traditional methods for periodontal diagnosis are based on the patients' clinical history including intraoral and extra oral examination, presence or absence of BOP, periodontal pocket and radiographic images (Fig. 2):[8]

- Presence or absence of inflammation such as BOP (bleeding on probing). This indicator is used to monitor the inflammation present in gingival tissue. BOP is measured by inserting a probe into the sulcus with slight pressure. The presence of bleeding is often associated with the degree of bacteria present in the dental plaque, causing inflammation and therefore bleeding. [9] Absence of bleeding is a reliable indicator of periodontal health.[10]

- Probing depth: For the evaluation of probing depth, it is important to choose the correct periodontal probe, the most recommended, the CP12 probe. The probe is inserted at the base of the junctional tissue of 6 sites of each tooth (mid-buccal, mid-buccal, buccal, disto-buccal, mid-palatal, mid-palatal and disto-palatal. If probing depth, along with BOP persist over time, this can be considered a risk for progression of periodontal disease.[10]

- X-rays radiographic diagnosis is important for the diagnosis of periodontitis. A healthy periodontium would not exhibit changes in the lamina dura or shows no evidence of bone loss.[9] However, radiographs in periodontal patients show

bone loss and its pattern.[10] These radiographs cannot be used as the only diagnostic method, but as a complementary one to the rest of the tests.[9]

- Recession and clinical attachment loss: this method is considered as an additional method to radiographic tests, probing and BOP. Probing depth in mm added to recession equals the loss of attachment.[10]

- Dental mobility: the loss of attachment plus the loss of alveolar bone cause dental mobility. The degrees of mobility are classified as grade I if the horizontal mobility is less than 1 mm, grade II if it is greater than 1 mm in the horizontal direction and grade III if the mobility is both horizontal and vertical.[10]

- Occasionally the use of supplementary diagnostic tests such as GCF evaluation can be used for the detection of periodontal disease; however, they are not commonly used. These approach detects the presence of associated substances, pathogens, enzyme detection, tissue breakdown and inflammatory biomarkers, present in periodontal patients.[8]

The diagnostic possibilities of periodontitis are based on knowledge of their etiology and pathogenesis. As mentioned above, current diagnosis methods to date have focused primarily on the clinical examination of the oral cavity, oral radiographs an occasionally supplementary test. Advances in research into the diagnosis of oral and periodontal diseases are moving towards techniques to help identify and quantify periodontal risk using molecular biology. These techniques allow to analyze and

quantify biomarker in different biological fluids of interest in dentistry, as saliva and crevicular fluids. As mentioned, these approaches are used on an occasional basis and only as a supplementary method to traditional diagnostic methods for the detection of periodontal disease.

Fig 2. Periodontal Diagnostic Methods. Reference: Own elaboration.

1.2 Periodontitis is an Inflammatory Disease

Periodontitis causes inflammation of the immune system, both local and systemic, through a rise of white blood cells, C-reactive protein, fibrinogen, proi-nflammatory cytokines and cell adhesion molecules. [5]The inflammatory response of periodontitis to the immune system at a systemic level enhances the risk of cardiovascular disease. Alternatively, there is the potential for various pathogens present in the mouth to infiltrate the blood stream and be incorporated into atherosclerotic plaques, promoting inflammation of these plaques. [5]

Although there is a strong pathophysiological relationship between the two diseases, it is possible that the association between periodontitis and cardiovascular disease is not a causal one. In many observational studies, the association of both diseases is explained by risk factors. Smoking, diabetes mellitus, increasing age and low socioeconomic status are shown to be risk conditions for periodontal diseases as well as for cardiovascular diseases (Fig. 3). These common risk factors between both diseases are relevant to the understanding of the relationship between them. Controlling them leads to a reduction in both diseases.[5]

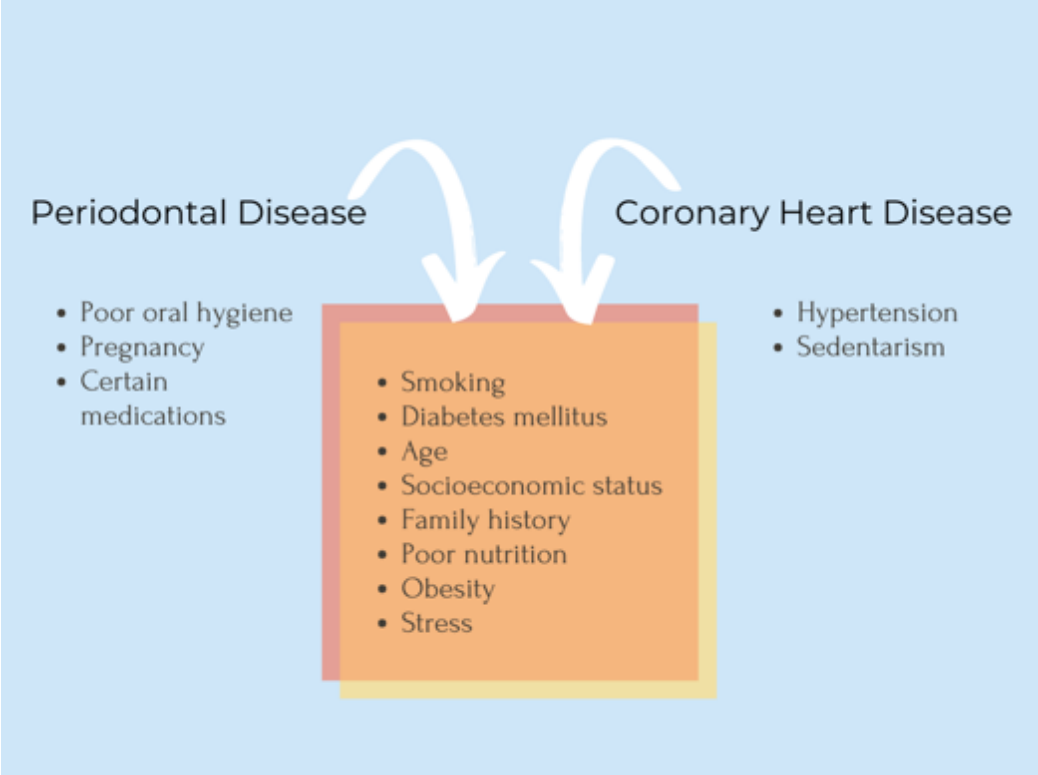

Fig 3. Risk factors for Periodontal Disease and Coronary Heart Disease. Reference: Stewart R, West M. Own elaboration

In 2012, the European Federation of Periodontology (EFP) together with the American Academy of Periodontology concluded that there is high evidence that indicates that periodontitis imposes an increased risk for future arteriosclerosis or cardiovascular disease. [1]The American Heart Association, also in 2012, stated that

there is no clear evidence that periodontal disease causes cardiovascular disease. Many studies show a strong evidence of an association between the two diseases, but this does not prove a causative relationship between periodontitis and coronary artery disease, [5] [11] but deservers further research as is shown in this work.

1.3 Coronary Artery Disease

Coronary artery disease is a cardiovascular disease that affects the arteries of the heart, causing a deficiency of oxygenated blood pumping to the heart. This disease is mainly caused by a buildup of plaque in the arteries or what is known as arteriosclerosis.[12] These plaques cause a blockage of the coronary arteries on the surface of the heart, decreasing the oxygen reaching the heart and causing myocardial ischemia. Coronary artery disease, including acute myocardial infarction (AMI), is responsible for 50% of deaths from cardiovascular disease.[13]

As mentioned above, most cardiovascular diseases, including coronary heart disease, are the result of an accumulation of risk factors such as age, environment, genetics, lifestyle, medical conditions, race and gender.[12]

The majority of patients with coronary heart disease suffer from severe symptoms.[13] However there is a percentage that is referred to as "silent' coronary disease, that don't show any symptoms or signs.[12] Angina pectoris is the most obvious symptom of coronary heart disease (CHD), where a pressure in the chest that may radiate to the shoulder causes pain for a few minutes.[13]

For the diagnosis of coronary heart disease, blood tests along with electrocardiograms are of great importance. However, there are other diagnostic tests such as coronary calcium scan, stress test, magnetic resonance imaging (MRI) for the detection of damaged tissue, coronary angiography, etc.[12]

Even though that both periodontitis and coronary artery disease have each an individual diagnostic method, there are some biochemical tests that can be used for the diagnosis of both diseases. These techniques are promising techniques for the future that are under development, which could include saving time and saving costs for the diagnosis of both periodontitis and coronary artery disease. Nonetheless, there are different types of saliva biomarkers and serum biomarkers involved in the immune system's response that demonstrate the early diagnosis of these diseases.

1.4 Molecular Biomarkers for the diagnosis of Periodontitis and early detection or risk of Coronary Artery Disease

According to the International Program on Chemical Safety, led by WHO (World Health Organization) and in cooperation with the United Nations (UN), the definition of a biomarkers is stated as "*any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease*".[14] A more extensive definition, takes into account not only the occurrence and outcome of a particular disease but also the effects of interventions and treatments. WHO cites that the real concept of a biomarker includes "*almost any measurement reflecting and interaction between a biological system and a potential hazard, which may be chemical, physical or biological". The measured response may be functional*

and physiological, biochemical at the cellular level, or molecular interaction".[14] By definition biomarkers are quantifiable objectives, which are features of any biological process. Biomarkers may be considered of great value in the diagnosis of diseases, as well as in their treatment and follow-up.[15]

The detection of biomarkers in biological fluids, such as saliva and blood, can be considered an important medical tool for the early diagnosis of periodontal diseases as well as cardiovascular diseases, and of special interest in dentistry. Early diagnosis of different diseases favor a greater probability of recovery and success. This is why the detection of biomarkers in body fluids, is of great significance in cardiovascular diseases and other pathologies, as periodontitis.[15]

Both disease have different biomarkers that can show a sign of the presence of these diseases. In periodontal diseases, when examining the destruction of periodontal structures such as alveolar bone, different biochemical markers, such as metalloproteases (MMPs), bone collagen fragments, and osteocalcin, can predict periodontal loss. [16] The cytokine IL1β together with tumor necrosis factor (TNFα) and prostaglandin E2 (PGE2) are responsible for neutrophil migration and alveolar bone resorption in periodontitis. A high concentration of these cytokines can be used as diagnostic indicators of the presence and progression of a periodontal disease. However, these biomarkers correspond only to the detection of periodontitis, not coronary artery disease, therefore they are not going to be discussed in this work. [17]In the case of cardiovascular diseases, there are several circulating markers that are associated with atherosclerosis such as cyclooxygenase-2 (COX-2), hepatocyte

growth factor (HGF), interleukin (IL), MMPs, etc.[18] Despite of the presence of several biomarkers, metalloproteinases (MMPs) are powerful biomarkers for the diagnosis of both periodontal and cardiovascular diseases, in saliva and in serum, and therefore this literature review will be based on them.

As mentioned above, the increase of the MMPs is also associated with periodontal disease. Of the most important, MMP-8 (metalloprotease-8), MMP-9 (metalloprotease-9) and TIMP-1 (tissue inhibitor metalloproteinase-1), are described as major saliva biomarkers for the detection of periodontal disease.[17] Alterations in MMP expression, although they are related to biological processes, they also appear during pathological processes, such as cardiovascular diseases and periodontal disease. [19] MMPs are created in a latent and non-active form, but can be activated depending on their molecular structure, either extracellular or intracellular. The main inhibitors of these enzymes are the TIMPs or tissue inhibitors, which restrict the decomposition of their extracellular matrix components.[20]

1.4.1 MMPs and TIMPs are Molecular Biomarkers for the diagnosis of Periodontitis and Coronary Artery Disease

MMPs are a group zinc-dependent enzymes responsible for the degradation of most of the extracellular matrix proteins during the organogenesis, the growth and the replacement of tissues, and in pathological processes. [21] Around 23 MMPs have been genetically identified in humans[20]. These 23 members of the MMPs family are arranged as a pro-peptide sequence of more than 80 amino acids (aa), a catalytic metalloproteinase domain of 170 aa, a linker peptide or hinge region and the

hemopexin domain of 200aa. Depending on their structural domain organization, MMPs are classified into collagenases, gelatinases, stromelysins, matrilysins, membrane type (MT-MMPs) and others. [19]

In dentistry, MMPs are biomarkers of interest for diagnosis of periodontitis and coronary artery disease. Thus, MMP8 also called collagenase 2 or neutrophil collagenase is main type of interstitial collagenase present in gingival crevicular fluid and saliva, oral rinse samples and the human gingival tissue affected by periodontitis. [22] MMP-8 in its active form, originating from neutrophils is known to be the main host cell-derived collagenase that produces periodontal connective tissue destruction as a result of gingival collagen and periodontal ligament breakdown. [23]

MMP9 or also known as gelatinase B, is an enzyme that breaks down type IV collagen and elastin. [24] They are produced by different cell types, including epithelial cells, fibroblasts, keratinocytes and osteoblasts. [19] An increased concentration of MMP-9 is widely associated with atherosclerosis and cardiovascular disease. This enzyme is known to be linked to the rupture of atherosclerotic plaque and to the destruction of myocardial tissue.[25] It has also been reported that serum MMP-9 levels are significantly elevated in people who have suffered a myocardial infarction, compared to healthy cardiovascular patients, showing that MMP 9 is a clear marker of cardiovascular disease.[26]

The activity of MMP enzymes is regulated by different inhibitors, where tissue inhibitors of metalloproteinases (TIMPs) plays the most important role. The balance of

MMPs and TIMPs is responsible for the control of extracellular matrix protein degradation, inflammation and downregulate cell growth and migration that can cause different diseases. [27] Each TIMPs or metalloproteinase inhibitor is composed of at least 190 amino acids (aa), organized into two domains, each stabilized by disulfide bonds. The N-terminus can function independently for the inhibition of MMPs through its catalytic domain. On the other hand, the function of its second domain, the C-terminus, is not fully understood, but it binds to the hemopexin domain of latent MMPs. [27]

Tissue inhibitor matrix metalloproteinase 1 or TIMP-1, is a secretory protein that belongs to the 4-member family of TIMPs (TIMp1, TIMP2, TIMP3 and TIMP4).[28] [29] Its interaction with specific metalloproteinases, such as MMP8 and MMP9, determines the function of the metalloproteinases. [30]

The structure of TIMP1 encodes to 931 base pair mRNA and a total of 207 amino acids.[28] This protein, according to studies, has been shown to have an inhibitory effect against most MMPs, except MMP14, MMP16, and MMP19. [31] The inhibition process is through the 1:1 formation of a non-covalent bond with MMPs, which regulates the balance of matrix remodeling during extracellular degradation.[28]

Although the main function of TIMPs is the inhibition of MMPs, they are also part of their transport and stabilization. Several studies have proposed that an imbalance of MMPs and their inhibitors results in the activation of periodontal disease. This takes place because an increment of MMPs and a reduction of TIMPs cause the breakdown

of connective tissue collagen and alveolar bone, fundamental pillars for a healthy periodontium. [29]

1.4.2 Techniques to Quantify MMPs and TIMPs in Biological Fluids

In order to study MMPs and TIMPs it is important to know about reliable methods to detect and quantify these molecules. The analysis of biomarkers in biological fluids, such as saliva and blood, can be considered an important medical tool for the early diagnosis of periodontal diseases as well as cardiovascular diseases, of especial interest in dentistry. As an example, an early diagnosis of both diseases have a greater probability of recovery and success. This is why the detection of biomarkers in body fluids, such as saliva, serum and gingival crevicular fluid (GCF) is of great significance in these pathologies.[15] Studies have shown that there are different techniques for detecting biomarkers on the market, such as gel electrophoresis, surface plasmon resonance or electrochemical assay. However, the most used are time-resolved immunofluorescence assay, also known as immunofluorometric assay (IFMA) and Enzyme-Linked ImmunoSorbent Assay commonly known as ELISA. [20]

ELISA is one of the most widely used biomarker detection methods for clinical diagnosis of different diseases. ELISA usually works with the use of antibodies raised in animals, targeted to specific biomarkers. This method is a useful method in the detection of biomarkers in biological fluids, so its use in studies in both saliva and serum biomarkers is very commonly used.[15]This is why ELISA is the method implemented in all the studies reviewed for the detection of MMPs.

On the other hand, IFMA is an immunofluorometric assay, also used in different studies for the detection of biomarkers (in saliva and serum) in both coronary and periodontal diseases, specifically active MMP8. [29] Together with ELISA, they are the two most commonly used methods for the detection of MMPs.[32] IFMA is an analytical method based on the reaction between an antigen and a specific antibody.[32]

As mentioned above, periodontal disease (PD) and coronary artery disease (CAD) are both common illnesses in people around the world. Although they are completely independent diseases, it has been scientifically proven that they have a relationship between them, mainly the inflammatory process of their pathophysiology (Fig 4). It has also been proven that periodontal diseases potentiate coronary diseases [11] The destruction of tissues, both in periodontitis and in coronary diseases, is reflected in an imbalance of MMPs and TIMPs [33]

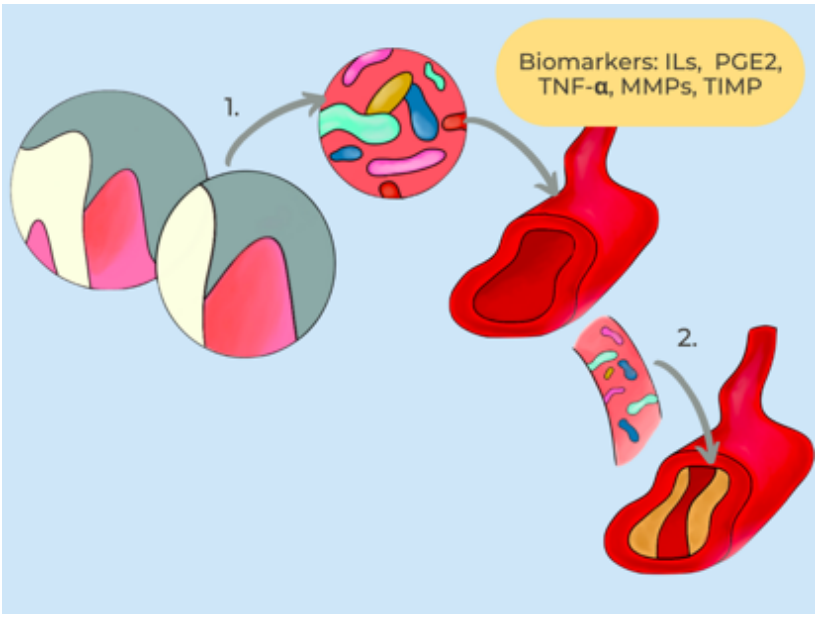

Fig 4. Schematic representation showing the relationship between Periodontal Disease and Coronary Artery Disease. Reference: (1) The presence of several pathogens of the biofilm in the oral cavity could lead to gingival epithelium inflammation and the release of biomolecules crucial for inflammation, immune response, and tissue destruction into saliva and blood stream. These molecules are interleukins (ILs), prostaglandin E2 (PGE2), tumor necrosis factor alpha (TNF-α). Furthermore, the continued inflammatory process induces alveolar bone resorption and degradation of ligament tissue by metalloproteases (MMPs). (2) At a chronic stage, oral pathogenic dissemination into the bloodstream could lead to the onset of

Given the role of MMPs and TIMPs in the breakdown of proteins in the extracellular matrix, both in coronary diseases and in periodontitis, it is prudent to study these molecular enzymes. Therefore, this work aims to find a relationship between

these biomarkers present in patients with periodontitis, both in saliva and blood, to assess if could be used also as a diagnostic method of coronary artery diseases in the dental clinic.

1. Objectives

2.1 General Objective

Review scientific data supporting the use of molecular oral biomarkers, in saliva and serum, as a diagnostic tool of coronary artery disease in patients with periodontitis.

2.2 Specific Objectives

- Review scientific data that support the value of MMP-8, MMP-9 and TIMP1 as diagnostic biomarkers in both coronary disease and periodontitis.
- Review the utility of MMP-8, MMP-9 and TIMP1 in saliva as a diagnostic marker of coronary disease in patients with periodontitis.

2. Methodology

PubMed, in advanced search and Wiley Online Library were used as databases for the compilation of articles for this study. The keywords included on the advanced search were the following: "biomarkers", "periodontitis" and "coronary artery disease".

The selected keywords were placed in the search as follows: "saliva and serum biomarkers" (anywhere), AND "periodontal disease" (anywhere) AND "coronary artery disease" (anywhere).

The advanced search revealed a total of 341 articles exposed in both platforms. Different inclusion criteria were used, such as the range of years of publication, and the language of publication. A total of 19 articles were exhibited on the PubMed platform and a total of 129 articles were exhibited in the Wiley Online Library.

Exclusion and inclusion criteria applied for the studies were the follow:

1. English and Spanish language
2. Last 10 years of publication

The category "Dentistry" was included in the advanced search of the 129 articles in the Wiley Online Library, in order to exclude all those other documents where there was no relevance in dentistry. A total of 36 of the 129 articles presented were displayed after the filter was applied.

The use of information from other sources like Google scholar and Government websites were used for specific data.

A total of 34 articles, were read and analyzed, to provide data and information for this study bibliographic research. Additional manually selected articles were included following the eligibility criteria. The use of information from other sources like Google scholar and Government websites were used for specific data. However, only 8 studies were examined in the result section of the study.

4. Results

Since periodontitis and coronary artery disease are related and most frequent diagnosed at advanced stage, finding biomarkers for early diagnosis of these pathologies is of tremendous importance to increase the probability of recovery and success and reduce mortality and improve quality of life of patients affected for both diseases. Research studies have been developed to identify different types of biomarkers. In this study, we discuss and describe general characteristics of known biomarkers, such as MMP-8, MMP-9 and TIMP-1 in periodontal disease and coronary artery disease, or in patients suffering both diseases; with the idea of discussing the utility of these biomarkers in the diagnosis of these pathologies. In Table 1, all the investigated diagnostic biomarkers with brief additional information are presented. More details about techniques and its detection of biomarkers are provided Table 2.

4.1 Type and number of studies reviewed

Most of the studies used for obtaining the results are of experimental type, specifically case control and cohort studies. In contrast, 2 studies followed a bibliographic and systemic review of the different MMPs. In Table 1, the different studies with specific details are stated.

Name of the study	Type of Study	Disease / Stage of disease	Biomarkers analyzed	Sample Type	Number of Patients	Population	Age	References
Salivary Matrix Metalloproteinase 8 and 9 and Myeloperoxidase in Relation to Coronary Heart and Periodontal disease	Case control	Coronary Artery Disease and Periodontitis	MMP8 MMP9 MPO TIMP-1	Stimulated Saliva samples	200 patients with MI admitted to coronary care units and 200 control without MI	No data	Under 75y	Nilminie et al.2015 [20]
Oral-fluid MMP analysis in the complementary diagnosis of periodontal disease	Bibliographic revision	Periodontal Disease	MMP-8 MMP-9 MMP-13	GCF and saliva	No data	No data	No data	Hernández et al. 2012 [22]
Acute Myocardial Infarction is Reflected in Salivary Matrix Metalloproteinase-8 Activation Level	No data	Acute Myocardial Infarction and systemically healthy with similar periodontal condition	MMP-8 (saliva and serum) MMP-7 (saliva) TIMP-1 (saliva and serum) MMP-9 (serum) MMP-13 (serum) TIMP-2 (serum)	Stimulated saliva and serum samples	92 patients 47: AMI + periodontal condition 28: non AMI+ periodontal condition 17: systemically and periodontally healthy (control group)	Izmir, Turkey	• AMI+ PD: 34-75y • Non AMI+ PD: 25-68y • Control: 26-44y	Buduneli et al. 2011 [26]
Effects of scaling and root planning and sub-microbial dose doxyclycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and	Cohort Study	Chronic Periodontitis and Coronary Artery Disease	MMP-1 MMP-8 MMP-13	GCF and serum	36 patients randomly selected	No data	Over 70y	Tüter et al. 2007 [34]
Full mouth profile of active MMP-8 in periodontitis patients	No data	Chronic Generalized Periodontitis	MMP-8	GCF	9 female	Saxon, Germany	35-66y	Kraft-Neumärker et al. 2011 [23]
Accuracy of single molecular biomarkers in saliva for diagnosis of periodontitis: A systematic review and meta-analysis	Systemic Review	Periodontitis	IL1beta IL6 MMP-8 MMP-9	Saliva	No data	No data	No data	Arias-Bujanda et al. 2019 [36]
Serum MMP-9 Diagnostics, Prognostics and Activation in Acute Coronary Syndrome and Its Recurrence	Case-control study	Acute Coronary Syndrome	MMP-9	Serum	345 patients included 108 unstable angina pectoris and 235 acute myocardial infarction	Patients admitted in the heart intensive care unit at Lund University Hospital	Under 80y	Lahdentausta et al. 2018 [30]
Saliva and serum biomarkers in periodontitis and coronary artery disease	Cohort study or Case control study	Periodontitis and Coronary Artery Disease	MMP-8 MMp-9 MPO TIMP-1	Saliva and serum samples	481 subjects • Periodontitis vs non periodontitis • ACS versus non-ACS	University of Helsinki	No data	Lahdentausta et al. 2018 [25]

Table 1. Global Review of articles reviewed in this work. Reference: Own Elaboration

Few studies describe the levels of MMPs in both periodontal and cardiovascular disease, for this reason we expand the analysis, including studies that quantify MMPs in periodontal disease (3 studies) and separately for MMPs in coronary artery disease (1 study), and both diseases together (4 studies).

Finally, few studies that focused on groups of all categories, patients with and without periodontal disease and patients with and without cardiovascular disease, were analyzed. The total number of participants exceeds 550 participants, which results in a large group of total participants, demonstrating that although the number of studies is small, the sample of participating individuals is significant. The number of participants and their characteristics in these studies are shown in Table 1.

Relevant information from each study is shown in Table 1, including population, stage of the diseases and other information that can be considered important of each study.

4.2 Biomarkers analyzed

The biomarkers analyzed on this bibliographic study where MMP8, MMP9 and TIMP-1, specifically. Different studies used different techniques for the detection of these biomarkers in different body fluids; saliva, serum and GCF (see Table 2).

- MMP8: stands for metalloproteinase-8. In all studies, the detection technique used was IFMA for the capture of this MMPs in both serum and saliva. However,

for the detection in GCF, some studies preferred the used of ELISA. The detection limit was between 0.05-0.08ng/ml

- MMP9: stands for metalloproteinase-9. In the studies reviewed, the use of ELISA was essential for the detection of MMP9 in both blood and saliva. No studies were analyzed for the detection of MMP9 in GCF. The detection limit was set to 0.05ng/ml
- TIMP-1: stands for tissue inhibitor metalloproteinase 1. As for MMP9, the analysis for this biomarker was in charge of ELISA technique, for blood and saliva. No studies were analyzed for the detection of TIMP-1 in GCF. The detection limit for both serum and saliva was 0.08ng/ml

	MMP-8	MMP-9	TIMP-1
Saliva	**IFMA & ELISA** Detection limit: 0.08ng/ml 0.05ng/ml	**ELISA** detection limit: 0.05ng/ml	**ELISA** detection limit: 0.08g/ml
Serum	**IFMA** Detection limit: 0.08ng/ml	**ELISA** detection limit: 0.05ng/ml	**ELISA** detection limit: 0.08ng/ml
GCF	**ELISA & IFMA** Detection limit: 0.05ng/ml	No data collected	No data collected

Table 2. Biomarkers analyzed in different biological fluids and limit detection for each. Reference: Own elaboration

4.3 Biomarkers under study: expression levels in periodontitis and coronary artery disease.

As indicated above, various methods were used to analyze the levels of MMP8, MMP9 and TIMP-1 in different body fluids from patients suffering either periodontitis and/or coronary artery disease, showing that technically it is possible to quantify and detect the presence of these biomarkers in saliva and serum in patients with periodontitis and coronary artery disease (Table 3).

However, there are some problems associated with its use the dental clinic. These mainly is due to the high complexity of these diseases under study and therefore the interpretation of data is difficult. Furthermore, factors such as age of the patient, diet, sex, if take medication, drugs, environment and lifestyle might interfere with the quantity of these biomarkers in biological fluids. In this study, we indicate the levels of biomarkers under study in different patients and in different pathological conditions to confirm the value of these biomarkers in the early diagnosis of periodontitis and coronary artery disease. To arrive at the results, all studies agreed on the same criteria considering a significant difference in expression levels when the p-value is less than 0.005 ($p = <0.005$).

Study biomarker	Disease/stage or severity	N° of patients	Sample type	expression levels (p value)	References
MMP-8 MMP-9 TIMP-1	Periodontitis and coronary artery disease	481 subjects	Saliva and Serum	Saliva (PD) •MMP-8: elevated (p=<0.001) •MMP-9: elevated (p=<0.001) •TIMP-1: reduced (p= 0.001) Serum (CAD) •MMP-8: elevated (p=<0.001) •MMP-9: elevated (p=<0.04) •TIMP-1: No data	Lahdentausta et al. 2018 [25]
MMP-9	Acute Coronary Syndrome: acute myocardial infarction (AMI) and unstable angina pectoris (UAP)	345 subjects: • 108 (UAP). • 235 (AMI)	Serum	Serum MMP-9 in ACS: elevated (p=<0.001) Serum MMP-9 in AMI: elevated (p=<0.001) Serum MMP-9 in UAP: elevated (p=<0.001)	Lahdentausta et al. 2018 [30]
MMP-8	Chronic Generalized Periodontitis	9 subjects	GCF	GCF MMP-8: elevated (p=<0.001)	Kraft-Neumärker et al. 2011 [23]
MMP-8	Chronic Periodontitis and Coronary Artery Disease	36 subjects with chronic periodontitis Group1: SRP + placebo Group 2: SRP +SDD therapy (doxycline)	GCF and serum	GCF after SRP and placebo (Group 1): reduced (p=<0.008) GCF after SRP and doxycycline (Group 2): reduced (p<0.003)	Tüter et al. 2007 [34]
MMP-8 (saliva and serum) TIMP-1 (saliva and serum) MMP-9 (serum)	Acute Myocardial infarction and systemically healthy subjects with similar periodontal condition	92 patients • 47: AMI + periodontal condition • 28: non AMI+ periodontal condition • 17: systemically and periodontally healthy (control group)	Saliva and serum	Saliva MMP8 Higher in **non AMI** than in AMI in all comparasion:p=<0.001 •Non AMI vs AMI: elevated (p=<0.001) •Gingivitis (non AMI vs AMI): elevated (p=<0.001) •Control vs non AMI vs AMI: elevated (p=<0.003) Saliva TMP-1: elevated in AMI than in non-AMI (p=<0.30) Serum MMP-8, MMP-9 and TIMP-1 higher in AMI than in non AMI •AMI vs non AMI: elevated (p=<0.001) •Periodontitis AMI vs Non AMI: elevated (p=<0.001) •Gingivitis AMI vs non AMI: MMP-8: elevated (p=0.003) MMP-9: elevated (p=0.013) TIMP-1: elevated (p=<0.001)	Buduneli et al. 2011 [26]
MMP-8 MMP-9 TIMP-1	Coronary Artery Disease and Periodontitis	400 subjects: • 200 with MI • 200 control	Saliva	Saliva MMP-8 MI vs AMI: elevated (p=0.008) Saliva MMP-9 MI vs AMI: no significan difference (p=0.88) Saliva TIMP-1 MI vs AMI: no significant difference(p=0.06)	Nilminie et al.2015 [20]

Table 3. Biomarkers results. Reference: Own elaboration

4.3.1 MMP-8 levels in periodontitis and coronary artery disease.

MMP8 is the metalloproteinase with the highest level in periodontal diseases. MMP-8 in saliva is higher in patients with PD than in those without (p=<0.001)[25] . MMP-8 is also shown in GCF, where the levels are high in the site affected by periodontitis (p=<0.001)[23]. On the other hand, results show that the level of MMP-8 is reduced after a proper periodontal treatment, such as scaling and root planning (SRP). Tüter and al., show that SRP treatment with and without additional SDD therapy as doxycycline, shows a reduction of MMP-8 (p=<0.003 and p=<0.008 respectively)[34]. On the other hand, salivary MMP-8, in Nilminie Rathnayake and al study shows a significant difference between myocardial infarction (MI) and AMI patients (p=0.008) (Table 3). However, in most of the study it is reflected that MMP8 in saliva is not useful for the diagnosis of coronary heart disease.

MMP8 in blood also shows an elevated level in patients with acute coronary syndrome (ACS) compared to those without the disease (p=<0.001)[25 26]. Nevertheless, it does not show significant results for the diagnosis of periodontitis.

4.3.2 MMP-9 levels in periodontitis and coronary artery disease.

MMP9, like MMP8, shows a significant difference in saliva in periodontal patients compared to non-periodontal patients (p=<0.001)[25]. However, for the diagnosis of coronary artery disease, there was not a significant difference between AMI and non AMI through saliva[20], as stated in Table 3. This is why, MMP9 in saliva is not useful for the diagnosis of coronary heart disease.

The authors when analyzing the biomarker MMP-9 in blood in patients with periodontitis, the results show no major difference between patients with and without heart disease. Serum MMP9 is shown to be insignificant for the diagnosis of ACS in patients with periodontitis. However the association of blood MMP-9 with ACS is considered significant (p=0.033). [25] Lahdentausta L et al, reflected results that show a significant difference between patients with non ACS and ACS, both, acute myocardial infarction (AMI) and unstable angina pectoris (UAP)(p=<0.001 and p=<0.001 respectively).[30] Buduneli et al, came to the same finding, noting that MMP9 in serum is significantly higher in patients with AMI compared to the non-AMI group.[26] (Table 3)

4.3.3 TIMP-1 levels in periodontitis and coronary artery disease

TIMP-1 is the only biomarker that is not able to differentiate in saliva between patients with periodontitis and patients without periodontal disease and patients without coronary heart disease. However, TIMP-1 shows a negative correlation with the inflammatory signs of periodontitis.[35] Even though, saliva TIMP-1 is higher in patients with AMI with periodontitis than in non-AMI with periodontitis, it does not reach a significant difference (p=0.30).[26] On the other hand, TIMP-1 in blood also does not distinguish patients with ACS from those with non-ACS[25]. (Table 3).

5. Discussion.

After an advanced search of different articles, for the purpose of this bibliographic research, different results were shown in a variety scientific. A number of studies have been conducted with the aim of finding a relationship between periodontal and cardiovascular diseases through saliva and serum biomarkers. Although there are

few studies that correlate both diseases, individual research of MMP8 and MM9 are found.

The objective of many research studies for the detection of biomarkers of systemic diseases through saliva, are more and more frequent and of great interest in dentistry. The use of saliva as a diagnostic fluid is of great value in research given that the saliva collection method is non-invasive and rapid technique. [36]

Salivary biomarkers MMP8, MMP9 and TIMP-1 change significantly between patients with periodontal disease and those without. MMP8, MMP9 show increased levels in patients with periodontitis, unlike TIMP-1, which shows a reduction.[25]

A study conducted in Turkey, compared patients with and without periodontal diseases and patients who had suffered a myocardial infarction. For this purpose, both saliva and blood samples were recorded from a total of 92 patients. Of the total number of candidates 47 had suffered an MI (25 = gingivitis and 22 = periodontitis), 28 without a cardiac history (13 = gingivitis and 15 = periodontitis) and 17 individuals lacking both cardiac and periodontal diseases. The researchers' results were obtained after the detection and evaluation of the individual metalloproteinases with distinct laboratory techniques (ELISA and IFMA). MMP8 was clearly higher in patients without a cardiac history in all groups (gingivitis and periodontitis). This may demonstrate that salivary MMP8 is strongly present in periodontal diseases. [26]

Controversial data have been showed in terms of expression levels of TIMP-1 in saliva. Thus elevated saliva levels have been shown in both patients with periodontal diseases, with no difference between AMI and non-AMI. [26] These defers from previous studies, where levels of TIMP-1 decreases in the presence of a periodontal disease, giving a negative correlation with PD. [20] [25]

Metalloproteinases 8, 9 and TIMP-1 are also found to be elevated in the serum, in patients with acute myocardial infarction (AMI) compared to non-AMI, in both periodontitis and gingivitis. Demonstrating that serum MMP8, MMP9 and TIMP-1 are associated with AMI independently of the oral condition.[26] However some studies refer that blood MMP8, MMP9 do not differ between patients with and without periodontal disease. These values are shown to be insignificant for the diagnosis of periodontal disease through blood, but they do demonstrate a clear relationship with acute coronary syndrome (ACS), except TIMP-1.[25]

On the other hand, there are independent studies that demonstrate the importance of MMP9 and MMP8 in acute coronary syndrome (ACS). The levels of both biomarkers are significantly elevated in ACS groups compared to control groups. However, these levels are shown in patients in the acute phase of the disease. The levels decrease once the patient enters the recovery phase. Indicating that MMP9 can be used as an early stage diagnostic measure in blood of atherosclerosis plaque rupture.[30]

Investigators stated than in previous studies, authors such as Furuholm have shown that MMP8 levels increase the risk of periodontitis in patients with CHD compared to those without.[26] MMP8 in blood is the metalloproteinase with the strongest association with ACS. [25]

MMP8 in active form may have a negative impact on oral health, specifically in the loss of attachment in periodontal disease.[26] [36] There are many studies about the risk of periodontitis for heart disease, but Furuhorm highlights the importance of investigating whether coronary heart disease is a risk factor for the development of periodontal disease. [26]

In the detection of periodontitis, both MMP8, MMP9 have the same diagnostic value. [25] Saliva MMP8 and MMP9 have a great diagnostic value in periodontal disease, due to its specificity and sensitivity. Both, MMP8 and MMP9 have a good sensitivity of 76-90% and 70% respectively and a great specificity of 96 and 82%, respectively. However, MMP9 is hard to detect in salivary samples of control groups.[37] This is referenced and justified by studies showing that MMP8 values are elevated in other oral fluids such as GCF.[25]

Periodontal diseases can be reflected in oral fluids through biomarkers, mainly MMP8. Through IFMA and DentoAnalyzer, it has been shown that the detection of MMP8 at unstable sites with periodontal attachment loss is quite elevated. [22]

This demonstrates that MMP8 is involved in the pathogenesis of PD. This metalloproteinase is considered to be the most promising biomarker to use as a complementary diagnostic tool alongside with traditional methods such as BOP, periodontal pocket, x-rays, etc.[22] One important aspect to highlight is the fact that the concentration of biomarkers analyzed could be impacted by specific treatments. Thus elevated values of MMP8 decrease after non-surgical treatments such as scaling and root planning (SRP).[25] In a study of 36 individuals with periodontal disease, the efficacy of a treatment and the reduction of MMP8 levels in saliva were evaluated. The total participants were divided into two completely randomized groups, both of which underwent SRP treatment. The first group, however, underwent placebo and the second group underwent into an SDD treatment. Both groups were evaluated after therapy, and a reduction of MMP8 was shown in both of the groups, but the individuals on SDD therapy showed a much better result.[34]

Although MMP8 in saliva shows great value in the diagnosis of periodontal diseases, this metalloproteinase shows no difference in groups with and without AMI. This is refuted by several studies and justified by the time between saliva collection and AMI. There are also several factors, such as the medications that people with AMI are exposed to, which may also have an effect on MMP8, MMP9, which can be reflected as a limitation for results.[20] Therefore, the effects of medications should be considered as a factor that influence the levels of biomarkers under study. Studies have shown an interaction between angiotensin converting enzyme inhibitor (ACEI) and statins that can interfere with the expression of MMP8 and MMP9 in saliva.[20] Statins have been shown to decrease both metalloproteinase levels in patients who

take statins compared to patients who do not.[25] ACE inhibitors, on the other hand, decrease MMP9 levels in patients with acute or chronic coronary artery disease. [20]

6. Conclusions

- The metalloproteinases, MMP8, MMP9 and the inhibitor TIMP-1 are biomarkers of great value in diagnostic methods for periodontitis and coronary heart disease individually. Biological sample selection is crucial, since biomarkers reviewed in this study and present in saliva can be used to diagnose periodontal diseases, and these biomarkers in blood are susceptible for the diagnosis of coronary heart disease.

- Different techniques are available and easy to use for the detection of such biomarkers. However, the most common are ELISA and IFMA, given their high levels of sensitivity and specificity. Not differences in the limit of detection was observed for the biomarkers investigated in saliva and serum.

- After the analysis of the literature, it can be concluded that periodontal diseases can be diagnosed by measuring the biomarker MMP-8 in saliva. In relation to the diagnosis of coronary artery disease, the biomarker of choice would be MMP-9 in serum. Nevertheless, after analyzing the results of the articles, it cannot be concluded that TIMP-1 can be used for the diagnosis of both diseases, more research on this biomarker is required. It is important to note that the levels of these biomarkers can be blurred by certain treatments and medications. This should be

taken into consideration when using these biomarkers as a diagnostic method for periodontal and coronary heart disease.

- The use of biomarkers can assist health professionals, both dentists and cardiologists in the screening of both diseases. Although it is a topic of interest in the scientific community, much more research is needed to confirm and validate the diagnostic power of these biomarkers.

7. Responsibility

Coronary artery disease is a cardiovascular disease that affects the arteries of the heart, causing a deficiency of oxygenated blood pumping to the heart. Every year Coronary artery disease, represent the leading cause of cardiovascular mortality worldwide, claiming more than 4.5 million lives annually worldwide. On the other hand, periodontitis is also considered a highly prevalent disease, claiming around 40-50% of the world' s population, and up to 11.2% of them experience severe periodontitis.

This project contributes to the identification of biomarkers that can be used in clinical dental practice in periodontal patients at high risk of coronary heart disease. With this strategy we are promoting a personalized preventive medicine that always tries to offer the best diagnostic alternative, associated with the clinical profile and the patient's own risk factors. This strategy favours an early detection of coronary heart disease in patients with periodontitis and reduces the economic cost of treatment by offering an early diagnosis in many cases, alleviating the patient's suffering and reducing the number of deaths.

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Annexes

Academy Report

Position Paper

Diagnosis of Periodontal Diseases*

This position paper on the diagnosis of periodontal diseases was prepared by the Research, Science and Therapy Committee of the American Academy of Periodontology. It is intended for the information of the dental profession and other interested parties. The purpose of the paper is to provide the reader with a general overview of the important issues related to the diagnosis of periodontal diseases. It is not intended as a comprehensive review of the subject. *J Periodontol 2003;74:1237-1247.*

Plaque-induced periodontal diseases are mixed infections associated with relatively specific groups of indigenous oral bacteria.[1-6] Susceptibility to these diseases is highly variable and depends on host responses to periodontal pathogens.[7-11] Although bacteria cause plaque-induced inflammatory periodontal diseases, progression and clinical characteristics of these diseases are influenced by both acquired and genetic factors that can modify susceptibility to infection.[12-15]

TRADITIONAL APPROACH TO DIAGNOSIS

Despite our increased understanding of the etiology and pathogenesis of periodontal infections, the diagnosis and classification of these diseases is still based almost entirely on traditional clinical assessments.[16,17] To arrive at a periodontal diagnosis, the dentist must rely upon such factors as: 1) presence or absence of clinical signs of inflammation (e.g., bleeding upon probing); 2) probing depths; 3) extent and pattern of loss of clinical attachment and bone; 4) patient's medical and dental histories; and 5) presence or absence of miscellaneous signs and symptoms, including pain, ulceration, and amount of observable plaque and calculus.[18-20]

Plaque-induced periodontal diseases have traditionally been divided into two general categories based on whether attachment loss has occurred: gingivitis and periodontitis. Gingivitis is the presence of gingival inflammation without loss of connective tissue attachment.[16] Periodontitis can be defined as the presence of gingival inflammation at sites where there has been a pathological detachment of collagen fibers from cementum and the junctional epithelium has migrated apically. In addition, inflammatory events associated with connective tissue attachment loss also lead to the resorption of coronal portions of tooth-supporting alveolar bone.[16]

This simple separation of plaque-induced periodontal diseases into two categories is not as clear-cut as it first appears. For example, if sites that have been successfully treated for periodontitis develop some gingival inflammation at a later date, do those sites have recurrent periodontitis or gingivitis superimposed on a reduced but stable periodontium? There are currently no data to definitively answer this question. However, since not all sites with gingivitis necessarily develop loss of attachment and bone,[17] it is reasonable to assume that gingivitis can occur on a reduced periodontium in which ongoing attachment loss is not occurring. A similar problem exists when the term "periodontitis" is assigned to sites with attachment loss and periodontal pockets in which ongoing periodontal destruction is not occurring.

Demonstration of the progression of periodontitis requires documentation of additional attachment loss occurring between at least two time points. Since this is not always possible, especially when a patient is examined for the first time, most clinicians assign the diagnosis of "periodontitis" to inflamed sites that also have loss of attachment and bone. This is a prudent practice since such sites may be either currently progressing or are at an increased risk for further periodontal destruction. Therefore, demonstration of progressive attachment loss is not generally considered to be a requirement for using "periodontitis" as a diagnostic label.

At the 1999 International Workshop for Classification of Periodontal Diseases and Conditions, a reclassification of the different forms of plaque-induced periodontal diseases was developed.[21] This revised classification includes seven general types of plaque-induced periodontal diseases: 1) gingivitis, 2) chronic

* This paper was developed under the direction of the Research, Science and Therapy Committee and approved by the Board of Trustees of the American Academy of Periodontology in May 2003.

GLOBAL HEART

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EXPERT CONSENSUS DOCUMENT

Periodontitis and Cardiovascular Diseases. Consensus Report

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Background: In Europe cardiovascular disease (CVD) is responsible for 3.9 million deaths (45% of deaths), being ischaemic heart disease, stroke, hypertension (leading to heart failure) the major cause of these CVD related deaths. Periodontitis is also a chronic non-communicable disease (NCD) with a high prevalence, being severe periodontitis, affecting 11.2% of the world's population, the sixth most common human disease.

Material and Methods: There is now a significant body of evidence to support independent associations between severe periodontitis and several NCDs, in particular CVD. In 2012 a joint workshop was held between the European Federation of Periodontology (EFP) and the American Academy of Periodontology to review the literature relating periodontitis and systemic diseases, including CVD. In the last five years important new scientific information has emerged providing important emerging evidence to support these associations.

Results and Conclusions: The present review reports the proceedings of the workshop jointly organised by the EFP and the World Heart Federation (WHF), which has updated the existing epidemiological evidence for significant associations between periodontitis and CVD, the mechanistic links and the impact of periodontal therapy on cardiovascular and surrogate

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STATE-OF-THE-ART PAPER

Cardiovascular Disease in the Developing World

Prevalences, Patterns, and the Potential of Early Disease Detection

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Over the past decade or more, the prevalence of traditional risk factors for atherosclerotic cardiovascular diseases has been increasing in the major populous countries of the developing world, including China and India, with consequent increases in the rates of coronary and cerebrovascular events. Indeed, by 2020, cardiovascular diseases are predicted to be the major causes of morbidity and mortality in most developing nations around the world. Techniques for the early detection of arterial damage have provided important insights into disease patterns and pathogenesis and especially the effects of progressive urbanization on cardiovascular risk in these populations. Furthermore, certain other diseases affecting the cardiovascular system remain prevalent and important causes of cardiovascular morbidity and mortality in developing countries, including the cardiac effects of rheumatic heart disease and the vascular effects of malaria. Imaging and functional studies of early cardiovascular changes in those disease processes have also recently been published by various groups, allowing consideration of screening and early treatment opportunities. In this report, the authors review the prevalences and patterns of major cardiovascular diseases in the developing world, as well as potential opportunities provided by early disease detection. (J Am Coll Cardiol 2012;60:1207–16) © 2012 by the American College of Cardiology Foundation

Globally, cardiovascular diseases (CVDs), which include coronary heart disease (CHD), strokes, rheumatic heart disease (RHD), cardiomyopathy, and other heart diseases, represent the leading cause of death (1). In 2001, it was estimated that there were 16 million deaths from CVD, but somewhat surprisingly (given that the vast majority of studies concerning CVD are carried out in "developed" regions such as the United States and Western Europe), 13 million of these CVD deaths occurred in low-income and middle-income countries, compared with 3 million in high-income countries (1). Although CVDs have previously been characterized as affecting "rich" countries, age-specific rates of CVD have declined in these areas, while they are increasing rapidly in many middle-income and low-income countries. In low-income and middle-income countries, the proportion of all deaths due to CVD in 2001 was 28%, compared with 23% in 1990; the corresponding proportions in developed countries were 39% and 48% (1,2).

Although most CVDs in the world are due to atherosclerosis (CHD and ischemic strokes), other CVDs due to infection (e.g., RHD, Chagas' heart disease, cardiomyopathy from human immunodeficiency virus (HIV) infection, cerebrovascular complications of malaria) remain common in many regions of the developing world (Fig. 1). Early functional and structural changes of the vessels and/or heart (before the onset of symptoms and/or advanced disease) are now detectable in some of these diseases (particularly but not exclusively by ultrasound) (3,4), and recent studies of early detection using these modalities have been published and have provided insights into the early stages of these disease processes.

Particular challenges in addressing the increasing burden of CVD in developing countries include low budgets for health (including for screening, prevention, and treatment), as well as the education and skill mix of the health workforce.

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Coronary artery disease in the developing world

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Background Coronary artery disease (CAD) is the leading cause of cardiovascular mortality worldwide, with >4.5 million deaths occurring in the developing world. Despite a recent decline in developed countries, both CAD mortality and the prevalence of CAD risk factors continue to rise rapidly in developing countries. The objectives of the current article are to review (1) the literature regarding CAD mortality and the prevalence of CAD risk factors in the developing world, and (2) prevention and control measures.

Methods We conducted a MEDLINE search of the English language literature for the years 1990 to 2002 to identify articles pertaining to the prevalence of CAD in developing countries. The search was performed using the following key terms: coronary artery disease, developing countries, ischemic heart disease, incidence, prevalence, prevention and risk factors. We also obtained relevant statistical information from The World Health Organization's Internet database.

Results There is a paucity of data regarding CAD and its prevalence in the developing world. However, it is projected that CAD mortality rates will double from 1990 to 2020, with approximately 82% of the increase attributable to the developing world. Existing data suggest that rapid socioeconomic growth in developing countries is increasing exposure to risk factors for CAD, such as diabetes, genetic factors, hypercholesterolemia, hypertension, and smoking. There is a relative lack of prevention and control measures to decrease exposure to these risk factors in developing countries.

Conclusion Documented information on the prevalence of CAD in developing countries is sparse, but there is sufficient data to suggest an impending epidemic. Prevention and targeted control of risk factors for CAD could potentially reduce the impact of CAD in the developing world as it has in industrialized nations. (Am Heart J 2004;148:7–15.)

See related Editorial on page 1.

Coronary artery disease (CAD) is among the cardiovascular disease (CVD) entities, which also include hypertension, stroke, and valvular, muscular, and congenital heart disease. In 1996, 29% of worldwide mortality was attributable to CVD, making it the leading cause of death globally.[1] CAD was estimated to have caused almost half of these deaths.[1] By 2020, it is expected that CAD will be the largest cause of disease burden worldwide.[2] In the developing world, demographic and lifestyle changes are resulting in an "epidemiological transition" from perinatal and infectious diseases to noncommunicable diseases such as CAD.[3]

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It is projected that CAD will be the leading cause of death in developing countries by the year 2020.[2–4] Identification of risk factors for CAD, namely diabetes, genetics, hypercholesterolemia, hypertension, and smoking, has led to successful preventive efforts in industrialized nations. In contrast, exposure to these risk factors in developing nations appears to be increasing via a "globalization" of dietary habits,[5] and urbanization.[6–8] Unfortunately, systematically documented data on both CAD prevalence and incidence in developing countries are scarce.[1] Thus, the first objective of this paper is to review the data regarding mortality from CAD and the prevalence of risk factors associated with CAD in the developing world. The second objective is to discuss prevention and control measures.

Methods

We conducted a review of the MEDLINE database to identify English language articles for the years 1990 to 2002 pertaining to CAD prevalence in developing countries. The search was performed using the following key terms: coronary artery disease, developing countries, ischemic heart disease, incidence, prevalence, prevention and risk factors. References from selected articles were also reviewed as was the Internet database of the World Health Organization (WHO). The Internet was also used to identify information on past

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Research Article

Global Prevalence of Periodontal Disease and Lack of Its Surveillance

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Background. Periodontal disease is a public health problem and is strongly associated with systemic diseases; however, its worldwide distribution is not fully understood. *Objective.* To evaluate global data of periodontal disease: (1) among adolescents, adults, and older population and (2) in low-, middle-, and high-income countries. *Methods.* This ecological study included data of periodontal disease from the World Health Organization's data bank which are based on the Community Periodontal Index of Treatment Needs (CPITN code: 0 = no disease; 1 = bleeding on probing; 2 = calculus; 3 = periodontal pocket (PD) 4-5 mm; 4 = PD (6+ mm). Age- and income-related periodontal disease inequalities were evaluated across the globe. *Results.* Compared with 9.3% of adults and 9.7% of older persons, 21.2% of adolescents had no periodontal disease ($P = 0.005$). Nearly 18.8% of adolescents compared with 8.9% of adults and 5% of older persons had bleeding on probing ($P \leq 0.001$). Similarly, 50.3% of adolescents, 44.6% of adults, and 31.9% older persons demonstrated the occurrence of calculus ($P = 0.01$). On the other hand, older persons had the highest prevalence of PD 4-5 mm and PD 6+ mm than adults and adolescents ($P \leq 0.001$). The distribution of periodontitis (CPITN code 3 + 4) in adults differed significantly in low- (28.7%), lower-middle- (10%), upper-middle- (42.5%), and high-income countries (43.7%) ($P = 0.04$). However, no significant differences in periodontitis (CPITN code 3 + 4) were observed in adolescents and older persons in low- to high-income countries. *Conclusions.* Within the limitations of data, this study found that the distribution of periodontal disease increases with age. Periodontitis was the most common in older persons and in population from high-income countries.

1. Introduction

Periodontal disease which comprises gingivitis and periodontitis is a common oral infection that affects the tissues that surround and support teeth [1]. The condition often presents as gingivitis which is characterized by bleeding, swollen gums, and pain, and if left untreated, it progresses to periodontitis which involves the loss of periodontal attachment and supporting bone [2]. According to the Global Burden of Disease Study (2016), severe periodontal disease was the 11th most prevalent condition in the world [3]. The prevalence of periodontal disease was reported to range from 20% to 50% around the world [4]. It is one of the major causes of tooth loss which can compromise mastication, esthetics, self-confidence, and quality of life [5, 6]. Globally, periodontal diseases accounted for 3.5 million years lived with disability (YLD) in 2016 [3]. During the period from 1990 to 2010, there was a 57.3% increase in the global burden of periodontal disease [7]. In 2010, worldwide loss of productivity due to severe periodontitis was estimated to be US$54 billion per year [8]. The global prevalence of periodontal disease is expected to increase in coming years due to growth in the aging population and increased retention of natural teeth due to a significant reduction in tooth loss in the older population [9].

Increasing Evidence for an Association Between Periodontitis and Cardiovascular Disease

Ralph Stewart, MD; Malcolm West, MD

Periodontitis is a chronic inflammatory disease caused by bacterial colonization, which results in destruction of the tissues between the tooth surface and gingiva, loss of connective tissue attachment, erosion of alveolar bone, and tooth loss.[1] Periodontitis is common and increases with age. In a US survey, about half of adults aged >30 years have some periodontitis and almost 10% have severe disease.[2] Evidence for an association between periodontitis and atherosclerotic vascular disease, including stroke, myocardial infarction, peripheral vascular disease, abdominal aortic aneurysm, coronary heart disease, and cardiovascular death, comes from >50 prospective cohort and case control studies undertaken during the past 25 years.[3–6] More recent analyses from large-cohort studies suggest new onset, and prevalent periodontitis, as well, is associated with increased coronary heart disease risk,[7] and there is a graded association between tooth loss and stroke, cardiovascular death, and all-cause mortality in patients with stable coronary artery disease.[8] If causal, these associations would be of great importance because of the potential that preventing or treating periodontal disease could reduce the risk of major adverse cardiovascular events.

Article see p 576

Individual studies have limitations, which include the use of imprecise measures of periodontal disease, inadequate accounting for potential confounders, and low statistical power for clinically important events. The Periodontal Disease and the Relation to Myocardial Infarction (PAROKRANK) study,[9] published in this issue of *Circulation*, strengthens the evidence for a link between periodontal disease and first myocardial infarction. This Swedish study compared periodontal disease in 805 patients who had presented with a first myocardial infarction with 805 controls. Panoramic x-ray films were used to measure resorption of alveolar bone adjacent to the tooth root and apex. This objective measure of periodontal disease was evaluated blind to clinical information and study group in a core laboratory. At least mild periodontitis was observed in about one-third of subjects. The odds ratio for first myocardial infarction for persons with any periodontitis in comparison with no periodontitis was 1.49 (95% confidence interval, 1.21–1.83), and, after multivariable adjustment, it was 1.28 (1.03–1.60).

Several mechanisms have been proposed to explain the association between periodontal and cardiovascular disease. Periodontitis causes both a local and systemic inflammatory and immune response, with increases in white blood cell count, C-reactive protein, fibrinogen, cell adhesion molecules, and proinflammatory cytokines.[10] Treatment of periodontal disease temporarily increases the blood levels of inflammatory markers, and worsens endothelial function, probably from the release of bacteria or inflammatory cytokines into the blood stream.[11] However, after several weeks, inflammatory markers are lower[11,12] and endothelial dysfunction is better than before treatment.[11] In the Oral Infections and Vascular Disease Epidemiology Study (INVEST) study, carotid intimal-medial thickness was associated with the volume of pathogenic bacteria on periodontal examination.[13] Small studies have reported reduction in carotid intimal-medial thickness 6 months after treatment of severe periodontal disease.[14]

The systemic inflammatory or immune response to periodontal infection may increase cardiovascular risk. Also, pathogens from the mouth can enter atherosclerotic plaques via the blood stream, and this could promote an inflammatory or immune response within the atherosclerotic plaque. A diverse range of oral bacterial pathogens and bacterial DNA have been detected in atherosclerotic plaque.[15,16] In animal models, infection with *Porphyromonas gingivalis* increases atherosclerotic plaque volume with the accumulation of cholesterol esters and inflammatory mediators.[17] In humans, serum IgA antibodies to *P gingivalis* are higher in patients with myocardial infarction than in controls.[18]

Although there is a strong pathophysiological rationale to support the importance of these mechanisms, it is possible the association between periodontitis and atherosclerotic vascular disease is not causal. In almost all observational studies, at least part of the association is explained by adjustment for cardiovascular risk factors. Smoking, diabetes mellitus, increasing age, and poor socioeconomic conditions are risk factors for periodontitis, and for cardiovascular disease, as well.[3] In the PAROKRANK study[9] controls were matched to cases for age, sex, and area of residence, a surrogate indicator of socioeconomic status. However, there were modest differences in smoking, diabetes mellitus, hemoglobin A1c, and divorce or living alone between cases and controls. Adjustment for these variables about halved the strength of the association. In most previous cohort and case control studies, adjustment for known cardiovascular risk factors also only partly explained associations between periodontal disease and cardiovascular disease.[3,5] This has been interpreted as evidence that the

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JOURNAL OF Periodontology

2017 WORLD WORKSHOP

Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions

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Las enfermedades periodontales como infecciones bacterianas

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Bascones Martínez A, Figuero Ruiz E. *Las enfermedades periodontales como infecciones bacterianas.* Av Periodon Implantol. 2003; 17, 3: 147-156.

RESUMEN

Las infecciones periodontales son un conjunto de enfermedades localizadas en las encías y estructuras de soporte del diente. Están producidas por ciertas bacterias provenientes de la placa bacteriana. Estas bacterias son esenciales para el inicio de la enfermedad, pero existen factores predisponentes del hospedador y microbianos que influyen en la patogénesis de la enfermedad. La microbiota bacteriana periodontopatógena es necesaria pero no suficiente para que exista enfermedad, siendo necesaria la presencia de un hospedador susceptible. Estas enfermedades se han clasificado en gingivitis, limitadas a las encías y periodontitis, extendidas a tejidos más profundos. La clasificación de las enfermedades periodontales ha ido variando a lo largo de los años y es en el International Workshop for a Clasification of Periodontal Diseases and Conditions, en 1999, cuando se aprueba la clasificación que se expone en este trabajo. En él, se hace una revisión global de los diferentes cuadros de las enfermedades periodontales. Posteriormente, se propone el empleo de antibioterapia de utilización sistémica como la amoxicilina, amoxicilina-clavulánico y metronidazol como primera opción de tratamiento coadyuvante de estas enfermedades.

PALABRAS CLAVE

Clasificación, enfermedades periodontales, biofilm

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INTRODUCCIÓN

El término infección se emplea para referirse a la presencia y multiplicación de microorganismos en el cuerpo (1). Las infecciones periodontales son un conjunto de enfermedades que, localizadas en la encía y las estructuras de soporte del diente (ligamento y hueso alveolar), están producidas por ciertas bacterias provenientes de la placa subgingival (Fig.1). Las bacterias anaerobias gramnegativas más importantes y prevalentes en el área subgingival son el *Actinobacillus actinomycetemcomitans (Aa), Porphyro-monas gingivalis (Pg), Prevotella intermedia (Pi) y Tannerella forsythensis (Tf)*. Estas bacterias tienen un importante papel en el comienzo y posterior desarrollo de la periodontitis participando en la formación de la bolsa periodontal, destrucción del tejido conectivo y reabsorción del

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JOURNAL OF Periodontology

2017 WORLD WORKSHOP

Periodontal health

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The proceedings of the workshop were jointly and simultaneously published in the *Journal of Periodontology* and *Journal of Clinical Periodontology*.

Abstract

Objectives: To date there is a paucity of documentation regarding definitions of periodontal health. This review considers the histological and clinical determinants of periodontal health for both intact and reduced periodontium and seeks to propose appropriate definitions according to treatment outcomes.

Importance: Defining periodontal health is can serve as a vital common reference point for assessing disease and determining meaningful treatment outcomes.

Findings: The multifactorial nature of periodontitis is accepted, and it is recognized that restoration of periodontal health will be defined by an individual's response to treatment, taking into account allostatic conditions.

Conclusions: It is proposed that there are 4 levels of periodontal health, depending on the state of the periodontium (structurally and clinically sound or reduced) and the relative treatment outcomes: (1) pristine periodontal health, with a structurally sound and uninflamed periodontium; (2) well-maintained clinical periodontal health, with a structurally and clinically sound (intact) periodontium; (3) periodontal disease stability, with a reduced periodontium, and (4) periodontal disease remission/control, with a reduced periodontium.

KEYWORDS

Clinical health, gingiva, periodontal remission, periodontal stability, pristine health

INTRODUCTION

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[1] In accordance with this definition by the World Health Organization, periodontal health should be defined as a state free from inflammatory periodontal disease that allows an individual to function normally and not suffer any consequences (mental or physical) as a result of past disease. However, while this definition is holistic and patient-outcome based, it seems an impractical and limiting definition for the purposes of clinical management of periodontal diseases. Therefore, a more practical definition of periodontal health would be a state free from inflammatory periodontal disease. This, in turn, means that absence of inflammation associated with gingivitis or periodontitis, as assessed clinically, is a prerequisite for defining periodontal health.

It is a matter of debate if altered morphological conditions resulting from previous exposure to disease processes (eg, gingival recession, loss of attachment, and bone loss) may be redefined as novel healthy conditions in the absence of clinical signs and symptoms of inflammation.

Interestingly, there are almost no studies or reports attempting to define periodontal health.[2] Defining periodontal health is very important if we are to have a common reference point for assessing periodontal disease and determining meaningful treatment outcomes. Health can be evaluated at both the histological and clinical levels and should be considered in the context of a preventive starting point and a therapeutic end point. Thus, periodontal health can exist before disease commences

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BMC Oral Health

PROCEEDINGS Open Access

Detection and diagnosis of periodontal conditions amenable to prevention

Philip M Preshaw

From Prevention in practice - making it happen
Cape Town, South Africa. 29 June 2014

Abstract

Gingivitis and chronic periodontitis are highly prevalent chronic inflammatory diseases. Gingivitis affects the majority of people, and advanced periodontitis is estimated to affect 5-15% of adults. The detection and diagnosis of these common diseases is a fundamentally important component of oral health care. All patients should undergo periodontal assessment as part of routine oral examination. Periodontal screening using methods such as the Basic Periodontal Examination/Community Periodontal Index or Periodontal Screening Record should be performed for all new patients, and also on a regular basis as part of ongoing oral health care. If periodontitis is identified, full periodontal assessment is required, involving recording of full mouth probing and bleeding data, together with assessment of other relevant parameters such as plaque levels, furcation involvement, recession and tooth mobility. Radiographic assessment of alveolar bone levels is driven by the clinical situation, and is required to assess bone destruction in patients with periodontitis. Risk assessment (such as assessing diabetes status and smoking) and risk management (such as promoting smoking cessation) should form a central component of periodontal therapy. This article provides guidance to the oral health care team regarding methods and frequencies of appropriate clinical and radiographic examinations to assess periodontal status, to enable appropriate detection and diagnosis of periodontal conditions.

Introduction

Periodontal diseases are highly prevalent chronic inflammatory conditions that affect the supporting tissues of the teeth. In broad terms, and of most relevance to the global community, these include gingivitis (i.e. plaque-induced gingivitis) and chronic periodontitis. This paper will review the methods for detection and diagnosis of gingivitis and chronic periodontitis, these being periodontal lesions that are amenable to prevention, and will take the form of a narrative review.

Pathogenesis of periodontal conditions

Gingivitis and chronic periodontitis are highly prevalent, chronic inflammatory conditions. The last 40-50 years have witnessed a transformation in our understanding of the pathogenesis of these common conditions. The role of bacterial plaque in initiating gingival inflammation is unquestioned, and was first demonstrated in experimental gingivitis studies in the 1960s [1]. Much of the 1960s and 1970s were dominated by treatment concepts that focussed exclusively on removal of calculus and "necrotic" root cementum that was believed to be infected by bacterial toxins such as lipopolysaccharide (LPS). However, ongoing research in the 1980s and 1990s resulted in increasing awareness of the importance of the inflammatory host response as an important determinant of risk for disease [2,3]. As technological advances have been made in the fields of microbiology, immunology and inflammation, we now recognise that inflammation is at the heart of the destructive responses that lead to the tissue breakdown that we recognise clinically as gingivitis and periodontitis. Accumulation of plaque bacteria in the subgingival environment results in diffusion of bacterial products and toxins across the junctional epithelium into the host tissues. As a result, the host mounts an immune-inflammatory response that is characterised by a complex network of cellular and molecular interactions

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CORONARY HEART DISEASE (S. VIRANI AND S. NADERI, SECTION EDITOR)

Periodontal Inflammation and the Risk of Cardiovascular Disease

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Abstract

Purpose of Review The role of oral bacteremia and periodontal inflammation driving atherosclerosis is still under investigation. This review article highlights the role of periodontal inflammation and oral microorganisms in the development and progression of atherosclerosis and cardiovascular diseases.

Recent Findings Association between periodontal and cardiovascular diseases has been well characterized, but causal correlation is yet to be established. For instance, untreated gingivitis can progress to periodontitis. Periodontal disease has been associated with several systemic diseases one of which is atherosclerosis. One possible association that was documented in literature is that poor oral hygiene leads to bacteremia, which in turn can cause bacterial growth over atherosclerotic coronary artery plaques and possibly worsen coronary artery disease.

Summary It is crucial that clinicians understand the association between periodontal and cardiovascular disease. A comprehensive treatment for periodontitis and re-establishment of a healthy periodontium can help in reduction of overall inflammation in the body. This may play an important role in prevention of cardiovascular disease, though future research is needed to establish this.

Keywords Periodontitis · Inflammation · Atherosclerosis

Introduction

Periodontal disease (PD) and cardiovascular disease (CVD) are both highly prevalent globally with a high healthcare burden worldwide [1]. Multiple epidemiologic and observational studies have consistently demonstrated that PD is independently associated subclinical and clinical CVD across diverse populations [1]. Both conditions are multifactorial and share many risk factors—with inflammation playing an important role in their pathogenesis (Fig. 1). Recent evidence from large cohort studies have shown that periodontitis is associated with increased coronary artery disease (CAD) and all-cause mortality risk; moreover, this association also extended to subclinical CVD as well as stable CAD [2•]. In addition, genetic studies have also suggested a shared susceptibility gene that is involved in the pathogenesis of both PD and CVD [3].

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This article is part of the Topical Collection on *Coronary Heart Disease*

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Coronary Heart Disease

Also known as Coronary Artery Disease, Coronary Microvascular Disease, Coronary Syndrome X, Ischemic Heart Disease, Nonobstructive Coronary Artery Disease, Obstructive Coronary Artery Disease

Leer en español

Heart disease is a catch-all phrase for a variety of conditions that affect the heart's structure and function. Coronary heart disease is a type of heart disease that develops when the arteries of the heart cannot deliver enough oxygen-rich blood to the heart. It is the leading cause of death in the United States.

Coronary heart disease is often caused by the buildup of plaque, a waxy substance, inside the lining of larger coronary arteries. This buildup can partially or totally block blood flow in the large arteries of the heart. Some types of this condition may be caused by disease or injury affecting how the arteries work in the heart. Coronary microvascular disease is another type of coronary heart disease. It occurs when the heart's tiny blood vessels do not work normally.

Symptoms of coronary heart disease may be different from person to person even if they have the same type of coronary heart disease. However, because many people have no symptoms, they do not know they have coronary heart disease until they have chest pain, a heart attack, or sudden cardiac arrest.

If you have coronary heart disease, your doctor will recommend heart-healthy lifestyle changes, medicines, surgery, or a combination of these approaches to treat your condition and prevent complications.

Explore this Health Topic to learn more about coronary heart disease, our role in research and clinical trials to improve health, and where to find more information.

Causes

Chronic Coronary Artery Disease: Diagnosis and Management

ANDREW CASSAR, MD, MRCP; DAVID R. HOLMES JR, MD; CHARANJIT S. RIHAL, MD; AND BERNARD J. GERSH, MBChB, DPHIL, FRCP

On completion of this article, you should be able to: (1) integrate the information obtained from a history, physical examination, and a stress test to diagnose and stratify the risk of patients with chronic coronary artery disease; (2) apply evidence-based management strategies to improve survival in patients with chronic coronary artery disease; and (3) determine when revascularization is indicated in a patient with chronic coronary artery disease, and, if indicated, choose the preferred method for each patient.

Coronary artery disease (CAD) is the single most common cause of death in the developed world, responsible for about 1 in every 5 deaths. The morbidity, mortality, and socioeconomic importance of this disease make timely accurate diagnosis and cost-effective management of CAD of the utmost importance. This comprehensive review of the literature highlights key elements in the diagnosis, risk stratification, and management strategies of patients with chronic CAD. Relevant articles were identified by searching the PubMed database for the following terms: *chronic coronary artery disease* or *stable angina*. Novel imaging modalities, pharmacological treatment, and invasive (percutaneous and surgical) interventions have revolutionized the current treatment of patients with chronic CAD. Medical treatment remains the cornerstone of management, but revascularization continues to play an important role. In the current economic climate and with health care reform very much on the horizon, the issue of appropriate use of revascularization is important, and the indications for revascularization, in addition to the relative benefits and risks of a percutaneous vs a surgical approach, are discussed.

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BMS = bare metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CT = computed tomography; DES = drug-eluting stent; FFR = fractional flow reserve; LAD = left anterior descending artery; LBBB = left bundle branch block; LV = left ventricular; MI = myocardial infarction; MRI = magnetic resonance imaging; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With TAXUS and Cardiac Surgery

Chronic coronary artery disease (CAD) is estimated to affect 16.8 million people in the United States; of these, 9.8 million have angina pectoris, and nearly 8 million have had a myocardial infarction (MI).[1] In 2005, CAD was the single most frequent cause of death in American men and women, causing 607,000 deaths (about 1 in every 5 deaths).[1] In 2006, 1.76 million patients were discharged from US hospitals with a diagnosis of CAD. The estimated direct and indirect economic cost of CAD in the United States for 2009 is $165.4 billion.[1] Worldwide, cardiovascular disease is becoming pandemic as developing countries experience the epidemiologic transition described by Omran from pestilence and famine to receding pandemics and degenerative diseases.[2] In 2002, out of 57 million deaths worldwide, approximately 16.7 million were due to cardiovascular disease (as compared with approximately 5 million due to tuberculosis, human immunodeficiency virus, and malaria combined), and 80% of these cardiovascular deaths were in the developing world.[3] Coronary artery disease (including acute MI) is responsible for about half of these cardiovascular deaths.[4] Mortality from cardiovascular disease is predicted to reach 23.4 million in 2030. Moreover, in the developing world, cardiovascular disease tends to affect people at a younger age and thus could negatively affect the workforce and economic productivity.[5] The morbidity, mortality, and socioeconomic importance of CAD make its diagnosis and management fundamental for all practicing physicians.

The article provides a state-of-the-art review of the literature on chronic CAD for interested physicians; appropriate articles were identified by searching the PubMed database for the following terms: *chronic coronary artery disease* or *stable angina*. This article highlights key points in diagnosis and risk stratification and delineates evidence-based management strategies for patients with chronic CAD, with particular emphasis on the indications for revascularization and the preferred method for each patient.

DIAGNOSIS OF CHRONIC CAD

Chronic stable angina, the initial manifestation of CAD in approximately 50% of all patients,[6] is usually caused by the obstruction of at least 1 large epicardial coronary artery by atheromatous plaque. Angina is due to the mismatch be-

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Determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes

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Abstract

Mutations in genes encoding ion channel pore-forming α-subunits and accessory β-subunits as well as intracellular calcium-handling proteins that collectively maintain the electromechanical function of the human heart serve as the underlying pathogenic substrate for a spectrum of sudden cardiac death (SCD)-predisposing heritable cardiac arrhythmia syndromes, including long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT). Similar to many Mendelian disorders, the cardiac "channelopathies" exhibit incomplete penetrance, variable expressivity, and phenotypic overlap, whereby genotype-positive individuals within the same genetic lineage assume vastly different clinical courses as objectively assessed by phenotypic features such electrocardiographic abnormalities and number/type of cardiac events. In this Review, we summarize the current understanding of the global architecture of complex electrocardiographic traits such as the QT interval, focusing on the role of common genetic variants in the modulation of ECG parameters in health and the environmental and genetic determinants of incomplete penetrance and variable expressivity in the heritable cardiac arrhythmia syndromes most likely to be encountered in clinical practice.

INTRODUCTION

Over the past decade, the discovery that mutations in genes encoding cardiac ion channel α- and β-subunits serve as the primary genetic substrate for a spectrum of sudden cardiac death (SCD)-predisposing inherited cardiac "channelopathies"[1, 2], including long QT sydrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT), has impacted profoundly how these genetic disorders are diagnosed, risk stratified, and managed clinically. While the availability of genetic testing provides an important opportunity to identify and deliver prophylactic

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Analyst

CRITICAL REVIEW

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Biomarker detection technologies and future directions

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Biomarkers play a vital role in disease detection and treatment follow-up. It is important to note that diseases in the early stage are typically treated with the greatest probability of success. However, due to various technical difficulties in current technologies for the detection of biomarkers, the potential of biomarkers is not explored completely. Therefore, the developments of technologies, which can enable the accurate detection of prostate cancer at an early stage with simple, experimental protocols are highly inevitable. This critical review evaluates the current methods and technologies used in the detection of biomarkers. The aim of this article is to provide a comprehensive review covering the advantages and disadvantages of the biomarker detection methods. Future directions for the development of technologies to achieve highly selective and sensitive detection of biomarkers for point-of-care applications are also commented on.

1. Introduction

Biomarkers play a vital role in disease detection and treatment follow-up. The detection of the biomarkers in body fluids such as blood and urine is a powerful medical tool for early diagnosis and treatment of diseases.[1] However, due to various technical difficulties in current technologies for the detection of biomarkers, the potential of biomarkers is not explored completely.[2] The biomarkers are often present at very low concentrations mixed with various other proteins which makes it more difficult to identify them. In many cases detection of biomarkers at a very low concentration is difficult and time-consuming. It is important to note that the diseases in the early stage are typically treated with the greatest probability of success. Therefore, the early detection of biomarkers is very important in the case of cancer, cardiovascular disorders, and other pathological conditions.[3,4]

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Diagnostic Biomarkers for Oral and Periodontal Diseases

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Periodontitis is a group of inflammatory diseases that affect the connective tissue attachment and supporting bone around the teeth. It is widely accepted that the initiation and the progression of periodontitis are dependent on the presence of virulent microorganisms capable of causing disease. Although the bacteria are initiating agents in periodontitis, the host response to the pathogenic infection is critical to disease progression [1–3]. After its initiation, the disease progresses with the loss of collagen fibers and attachment to the cemental surface, apical migration of the junctional epithelium, formation of deepened periodontal pockets, and resorption of alveolar bone [4]. If left untreated, the disease continues with progressive bone destruction, leading to tooth mobility and subsequent tooth loss. Periodontal disease afflicts over 50% of the adult population in the United States, with approximately 10% displaying severe disease concomitant with early tooth loss [5].

A goal of periodontal diagnostic procedures is to provide useful information to the clinician regarding the present periodontal disease type, location, and severity. These findings serve as a basis for treatment planning and provide essential data during periodontal maintenance and disease-monitoring phases of treatment.

Traditional periodontal diagnostic parameters used clinically include probing depths, bleeding on probing, clinical attachment levels, plaque index, and radiographs assessing alveolar bone level [6]. The strengths of these traditional tools are their ease of use, their cost-effectiveness, and that they are relatively noninvasive. Traditional diagnostic procedures are inherently limited, in that only disease history, not current disease status, can be assessed. Clinical attachment loss readings by the periodontal probe and radiographic evaluations of alveolar bone loss measure damage from past episodes of destruction and require a 2- to 3-mm threshold change before a site can be identified as having experienced a significant anatomic event [7]. Advances in oral and periodontal disease diagnostic research are moving toward methods whereby periodontal risk can be identified and quantified by objective measures such as biomarkers (Table 1).

There are several key questions regarding current clinical decision making: How can clinicians assess risk for periodontal disease? What are the useful laboratory and clinical methods for periodontal risk assessment? and What can be achieved by controlling periodontal disease using a risk profile?[8–11]. Risk factors are considered modifiers of disease activity. In

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Review

Salivary Biomarkers and Their Application in the Diagnosis and Monitoring of the Most Common Oral Pathologies

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Abstract: Saliva is a highly versatile biological fluid that is easy to gather in a non-invasive manner—and the results of its analysis complement clinical and histopathological findings in the diagnosis of multiple diseases. The objective of this review was to offer an update on the contribution of salivary biomarkers to the diagnosis and prognosis of diseases of the oral cavity, including oral lichen planus, periodontitis, Sjögren's syndrome, oral leukoplakia, peri-implantitis, and medication-related osteonecrosis of the jaw. Salivary biomarkers such as interleukins, growth factors, enzymes, and other biomolecules have proven useful in the diagnosis and follow-up of these diseases, facilitating the early evaluation of malignization risk and the monitoring of disease progression and response to treatment. However, further studies are required to identify new biomarkers and verify their reported role in the diagnosis and/or prognosis of oral diseases.

Keywords: salivary biomarker; cytokines; oral pathology; diagnosis

1. Introduction

The gold standard for the identification and diagnosis of oral mucosal diseases is the clinical examination by dental health professionals, followed by histopathological examination of suspicious areas [1,2]. Many diseases of the oral cavity can undergo malignant transformation. Oral squamous cell carcinoma (OSCC) is one of the most frequent oral cancers and still has a five-year survival rate of only 50–65% despite diagnostic and therapeutic advances, in part attributable to diagnostic delay [3]. In most cases of OSCC, the diagnosis is based on the histopathological study of a biopsy. The analysis of saliva, which does not require an invasive procedure, is an attractive alternative option for the diagnosis and prognosis of this oral disease [4,5]. Samples can be readily obtained in a pain-free manner, their processing is relatively simple, their composition is less complex, and they are more stable in comparison to other sources [6,7]. Saliva also offers real-time results, being produced by exocrine glands, and therefore, yielding information on patients at the time the sample is taken [8]. Besides the components secreted by these glands, saliva contains other molecules that can potentially be associated with the disease phenotype and facilitate diagnosis and prognosis, including metabolites, proteins,

UPDATE

Biomarkers in Cardiovascular Medicine

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Cardiovascular disease is the principal cause of death in developed countries. The underlying pathological process is arterial wall thickening due to the formation of atherosclerotic plaque, which is frequently complicated by thrombus, thereby giving rise to the possibility of acute coronary syndrome or stroke. One of the major challenges in cardiovascular medicine is to find a way of predicting the risk that an individual will suffer an acute thrombotic event.

During the last few decades, there has been considerable interest in finding diagnostic and prognostic biomarkers that can be detected in blood. Of these, C-reactive protein is the best known. Others, such as the soluble CD40 ligand, can be used to predict cardiovascular events. However, to date, no biomarker has been generally accepted for use in clinical practice. At present, there are a number of high-performance techniques, such as proteomics, that have the ability to detect multiple potential biomarkers. In the near future, these approaches may lead to the discovery of new biomarkers that, when used with imaging techniques, could help improve our ability to predict the occurrence of acute vascular events.

Key words: *Biomarkers. Atherothrombosis. Proteomics.*

Biomarcadores en la medicina cardiovascular

Las enfermedades cardiovasculares son la primera causa de muerte en el mundo occidental. El proceso patológico que subyace a ellas es un engrosamiento de la pared arterial debido a la formación de placas ateroscleróticas, las cuales se complican frecuentemente con un trombo y pueden dar lugar a síndrome coronario agudo o accidente cerebrovascular. Uno de los mayores retos de la medicina cardiovascular es encontrar la manera de predecir el riesgo de un sujeto de sufrir un evento trombótico agudo.

En las últimas décadas, hay un gran interés en la búsqueda de biomarcadores diagnósticos y pronósticos que puedan ser identificados en sangre. Entre ellos, la proteína C reactiva es la más conocida. Otros, como el ligando de CD40 soluble, pueden predecir eventos cardiovasculares. En cambio, hasta el momento no hay un biomarcador aceptado en la práctica clínica. Actualmente, existen diversas técnicas de alto rendimiento como la proteómica, que permite la detección de múltiples biomarcadores potenciales. Estas aproximaciones pueden identificar en un futuro próximo nuevos biomarcadores que, junto con las técnicas de imagen, pueden ayudar a mejorar la predicción de eventos vasculares agudos.

Palabras clave: *Biomarcadores. Aterotrombosis. Proteómica.*

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INTRODUCTION

Cardiovascular disease is the leading cause of death in the western world.[1] Among these diseases, atherosclerosis is the main cause of the enormous rates of morbidity and mortality. The pathological process that underlies this disease is arterial wall thickening due to the formation of atherosclerotic plaques.[2] Although these normally evolve gradually, atherosclerotic plaques may become complicated due to a thrombus and lead to a sudden obstruction of the vascular lumen. Depending on its location, this obstruction may lead to acute coronary syndrome (ACS) or stroke, and can cause sudden death or severe sequelae among the patients who develop

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Biochemical and Biological Attributes of Matrix Metalloproteinases

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Abstract

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are involved in the degradation of various proteins in the extracellular matrix (ECM). Typically, MMPs have a propeptide sequence, a catalytic metalloproteinase domain with catalytic zinc, a hinge region or linker peptide, and a hemopexin domain. MMPs are commonly classified on the basis of their substrates and the organization of their structural domains into collagenases, gelatinases, stromelysins, matrilysins, membrane-type (MT)-MMPs, and other MMPs. MMPs are secreted by many cells including fibroblasts, vascular smooth muscle (VSM) and leukocytes. MMPs are regulated at the level of mRNA expression and by activation of their latent zymogen form. MMPs are often secreted as inactive proMMP form which is cleaved to the active form by various proteinases including other MMPs. MMPs cause degradation of ECM proteins such as collagen and elastin, but could influence endothelial cell function as well as VSM cell migration, proliferation, Ca^{2+} signaling and contraction. MMPs play a role in tissue remodeling during various physiological processes such as angiogenesis, embryogenesis, morphogenesis and wound repair, as well as in pathological conditions such as myocardial infarction, fibrotic disorders, osteoarthritis, and cancer. Increases in specific MMPs could play a role in arterial remodeling, aneurysm formation, venous dilation and lower extremity venous disorders. MMPs also play a major role in leukocyte infiltration and tissue inflammation. MMPs have been detected in cancer, and elevated MMP levels have been associated with tumor progression and invasiveness. MMPs can be regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs), and the MMP/TIMP ratio often determines the extent of ECM protein degradation and tissue remodeling. MMPs have been proposed as biomarkers for numerous pathological conditions and are being examined as potential therapeutic targets in various cardiovascular and musculoskeletal disorders as well as cancer.

Keywords

Cell Signaling; Collagen; Extracellular Matrix; Proteinases; Protein Degradation; Remodeling

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CONFLICT OF INTEREST
None

PLOS | ONE

RESEARCH ARTICLE

Salivary Matrix Metalloproteinase-8 and -9 and Myeloperoxidase in Relation to Coronary Heart and Periodontal Diseases: A Subgroup Report from the PAROKRANK Study (Periodontitis and Its Relation to Coronary Artery Disease)

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Abstract

Background and Objective

Matrix metalloproteinase (MMP) -8, -9 and myeloperoxidase (MPO) are inflammatory mediators. The potential associations between MMP-8, -9, MPO and their abilities to reflect cardiovascular risk remains to be evaluated in saliva. The objective of this study was to investigate the levels and associations of salivary MMP-8, -9, MPO and tissue inhibitors of metalloproteinase (TIMP)-1 in myocardial infarction (MI) patients and controls with or without periodontitis.

Materials and Methods

200 patients with a first MI admitted to coronary care units in Sweden from May 2010 to December 2011 and 200 controls matched for age, gender, residential area and without previous MI were included. Dental examination and saliva sample collection was performed 6-10 weeks after the MI in patients and at baseline in controls. The biomarkers MMP -8, -9, MPO and TIMP-1 were analyzed by time-resolved immunofluorescence assay (IFMA), Western blot and Enzyme-Linked ImmunoSorbent Assay (ELISA).

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REVIEW ARTICLE

Matrix metalloproteinases (MMPs) in oral diseases

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Matrix metalloproteinases (MMPs) are a group of enzymes that in concert are responsible for the degradation of most extracellular matrix proteins during organogenesis, growth and normal tissue turnover. The expression and activity of MMPs in adult tissues is normally quite low, but increases significantly in various pathological conditions that may lead into unwanted tissue destruction, such as inflammatory diseases, tumour growth and metastasis. MMPs have a marked role also in tissue destructive oral diseases. The role of collagenases, especially MMP-8, in periodontitis and peri-implantitis is the best-known example of the unwanted tissue destruction related to increased presence and activity of MMPs at the site of disease, but evidence has been brought forward to indicate that MMPs may be involved also in other oral diseases, such as dental caries and oral cancer. This brief review describes some of the history, the current status and the future aspects of the work mainly of our research groups looking at the presence and activity of various MMPs in different oral diseases, as well as some of the MMP-related aspects that may facilitate the development of new means of diagnosis and treatment of oral diseases.
Oral Diseases (2004) **10**, 311–318

Keywords: matrix metalloproteinases; oral; periodontitis; cancer; caries

Introduction

Since the microbial nature of many oral diseases has been recognized long ago, for decades research has aimed to fight the microbes behind the diseases. More recently it has been realized that the host-related factors may be the keys to the fundamental understanding of the disease processes in many oral diseases. One of these host factors is a family of enzymes called matrix metalloproteinases (MMPs). Our research groups have for years been working to evaluate the presence, activity, function and regulation of MMPs in healthy and diseased oral tissues. In collaboration with other groups around the world, the work has resulted into the development of pharmacological agents for MMP inhibition in the treatment of oral diseases, as well as utilizing MMP measurements as diagnostic tools.

MMPs are a family of structurally related but genetically distinct enzymes that degrade extracellular matrix (ECM) and basement membrane (BM) components. This group of 23 human enzymes is classified into collagenases, gelatinases, stromelysins, membrane-type MMPs and other MMPs, mainly based on the substrate specificity and molecular structure. MMPs are involved in physiological processes such as tissue development, remodelling and wound healing (Uitto *et al*, 2003), and play important roles in the regulation of cellular communication, molecular shedding and immune functions by processing bioactive molecules including cell surface receptors, cytokines, hormones, defensins, adhesion molecules and growth factors. MMP activity is controlled by changes in the delicate balance between the expression and synthesis of MMPs and their major endogenous inhibitors, tissue inhibitors of matrix metalloproteinases (TIMPs). The catalytic competence of MMPs is controlled through the activation of proenzymes, and the inhibition of the activation or activity by TIMPs (Uitto *et al*, 2003).

As the roles of MMPs in tissue degenerative diseases have became evident, attempts to control their activities by pharmacological means have gained much attention. Although the exact roles of individual MMPs in various diseases are not fully understood, it is clear that MMPs are often up-regulated in groups forming activation cascades both in the inflammatory and malignant diseases (Uitto *et al*, 2003).

MMP activation and inhibition

MMPs are mostly produced in latent, non-active form, and activation through a so-called cysteine switch is required for the enzyme function. In most cases, activation involves removal of the prodomain, resulting into lower molecular weight active forms (reviewed by

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Revisión Bibliográfica

Análisis de MMPs en fluidos orales en el diagnóstico complementario de las enfermedades periodontales

Oral-fluid MMP analysis in the complementary diagnosis of periodontal diseases

Hernández P[1], Mäntylä P[2], Tervahartiala T[3], Sorsa T[4], Hernández M[5]

RESUMEN

La periodontitis constituye la infección bacteriana más prevalente a nivel mundial y representa un factor de riesgo para diversas patologías sistémicas. El estado de inflamación y destrucción periodontal se manifiestan a través de la presencia de biomarcadores en el suero y fluidos orales, tales como el fluido gingival crevicular (FGC), saliva y enjuague oral. Enzimas como las metaloproteinasas de matriz (MMP) y mieloperoxidasa, constituyen biomarcadores potenciales para ensayos moleculares complementarios a la clínica de uso en el sillón dental. A continuación se presenta una revisión de la literatura respecto de la aplicación potencial del análisis de metaloproteinasas de matriz extracelular (MMPs) en el diagnóstico complementario de las enfermedades periodontales. Se ha demostrado que los niveles de MMP-9, -13 y particularmente de MMP-8, se asocian con el grado de inflamación periodontal, y pueden diferenciar entre sujetos sanos, con gingivitis, periodontitis y peri-implantitis, mientras que la mejoría de los parámetros clínicos en respuesta al tratamiento periodontal se asocia con la reducción de la activación y niveles de estas enzimas en FGC, como así también en el suero. Se concluye que la determinación, particularmente de MMP-8 en fluidos orales presenta un elevado potencial como complemento de los métodos clínicos tradicionales para identificar a los pacientes con periodontitis o en riesgo de desarrollar la enfermedad, monitorear fases del tratamiento y mejoría de signos periodontales e incluso evaluar el estado de inflamación sistémica.
Rev. Clín. Periodoncia Implantol. Rehabil. Oral Vol. 5(3); 150-153, 2012.

Palabras clave: MMPs, diagnóstico molecular, periodontitis, enfermedades cardiovasculares.

ABSTRACT

Periodontal disease is the most common bacterial infection worldwide and it can contribute to enhance the risk for the development of several systemic diseases. The status of periodontal inflammation and destruction can be reflected in biomarker measurement in serum and oral fluids, like gingival crevicular fluid (GCF), saliva and mouth-rinse. Some enzymes, such as matrix metalloproteinases (MMPs) and myeloperoxidase are potential candidates for chair-side point-of-care oral fluid assays. This review is focused on the utility of matrix metalloproteinase (MMP) analysis in oral fluid as a complementary diagnostic method to chronic periodontitis. Levels of MMP-9,-13 and specially of MMP-8, reflect oral inflammatory status and discriminate among healthy, gingivitis, periodontitis and perimplantitis individuals, whereas MMP levels and activation in GCF and serum are in line with the improvement of clinical parameters in response to periodontal treatment. As a conclusion, MMP-8 assessment in GCF could represent a helpful adjunctive method to traditional diagnostics to identify periodontitis or patients at risk to develop the disease, monitor treatment phases, improvement of periodontal signs and even screen the systemic inflammation status.
Rev. Clín. Periodoncia Implantol. Rehabil. Oral Vol. 5(3); 150-153, 2012.

Key words: MMPs, chair-side point-of-care diagnosis, periodontitis, cardiovascular diseases.

Los fluidos orales (fluido gingival crevicular (FGC), saliva, muestras de enjuagues orales y fluido sulcular peri-implantario (FSPI)) contienen mediadores moleculares llamados frecuentemente biomarcadores, los cuales son capaces de reflejar variadas condiciones fisiológicas y patológicas. Los cambios cualitativos y cuantitativos en estos biomarcadores a nivel de fluidos orales pueden reflejar el estad de salud periodontal y han demostrado ser de potencial utilidad para el diagnóstico y tratamiento de distintos desórdenes orales y sistémicos, tales como enfermedades periodontales y cardiovasculares, respectivamente[1]. Entre estos, las metaloproteinasas (MMPs) de matriz extracelular de la familia de las colagenasas, particularmente MMP-8 y MMP-13, son enzimas proteolíticas que degradan los colágenos fibrilares, componentes centrales de la matriz extracelular periodontal[2]. A continuación se presenta una revisión de la literatura de los últimos 10 años respecto de la aplicación potencial del análisis de metaloproteinasas de matriz extracelular (MMPs) en el diagnóstico complementario de las enfermedades periodontales.

La periodontitis resulta de la interacción entre bacterias periodontopatógenas organizadas en la biopelícula subgingival y la respuesta inmune e inflamatoria del hospedero, y constituye la infección bacteriana más prevalente a nivel mundial. Algunos estudios revelan que 10-15% de los adultos a nivel mundial tienen periodontitis avanzada. La enfermedad periodontal puede contribuir a una disfunción severa de la salud oral, así como a un aumento de la susceptibilidad frente a otras

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Full-mouth profile of active MMP-8 in periodontitis patients

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Kraft-Neumärker M, Lorenz K, Koch R, Hoffmann T, Mäntylä P, Sorsa T, Netuschil L. Full-mouth profile of active MMP-8 in periodontitis patients. J Periodont Res 2012; 47: 121–128. © 2011 John Wiley & Sons A/S

Background and Objective: MMP-8 in gingival crevicular fluid is considered as a protease with high destructive potential because of its ability to degrade collagen in periodontitis-affected patients. The aim of this study was to investigate whether there was a relationship between clinical diagnostic parameters and the concentration of active MMP-8 (aMMP-8) in gingival crevicular fluid in a site-level full-mouth analysis. Based on these data, the prognostic value of aMMP-8 levels in relation to pocket depth may be evaluated.

Material and Methods: Clinical measurements of pocket depth, bleeding on probing (BOP), plaque index (PII) and gingival index (GI), as well as samples of gingival crevicular fluid, were obtained from four sites of each tooth of nine healthy female patients with chronic generalized periodontitis. The aMMP-8 concentration in gingival crevicular fluid was quantified by ELISA using specific monoclonal antibodies. Multiple linear regression models for the single measures of aMMP-8 and pocket depth were calculated with GI and BOP as additional variables.

Results: Between 92 and 112 recordings were obtained for each parameter in each patient. Mean values of between 31.5 and 88.8% were calculated for pocket depths of ≥ 4 mm. Mean pocket depths ranged from 3.11 to 4.73 mm, the mean BOP values ranged from 34.0 to 96.7% and the mean full-mouth gingival crevicular fluid aMMP-8 concentration ranged from 3.2 to 23.7 ng/mL.

Conclusion: In this sample of female periodontitis patients, a broad range of intra-individual and interindividual aMMP-8 values was found. Although the explained variance was rather weak, a statistically significant relationship between aMMP-8 and pocket depth was proven.

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Key words: clinical indices; full-mouth analysis; matrix metalloproteinases; matrix metalloproteinase-8; periodontitis

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Periodontitis is a general inflammatory condition that has a systemic influence on health. It has been estimated that the area of inflamed periodontitis tissue represents a dimension of 20–70 cm (1,2). Without being the sole causative factor, the periodontitis-imposed inflammatory burden apparently plays a major role in interactions with various systemic diseases. Therefore, periodontitis can be regarded as a risk factor for diabetes and metabolic disease, rheumatoid arthritis, and cardiovascular disease and stroke (2–6).

The diagnosis of periodontal disease is traditionally based on clinical parameters and indices that reflect a history of periodontal diseases but cannot predict future disease activity. These conventional clinical approaches are often amended by microbial analysis. Early diagnosis of ongoing tissue destruction in progressive periodontitis is particularly important in

Review

Matrix metalloproteinase interactions with collagen and elastin

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Abstract

Most abundant in the extracellular matrix are collagens, joined by elastin that confers elastic recoil to the lung, aorta, and skin. These fibrils are highly resistant to proteolysis but can succumb to a minority of the matrix metalloproteinases (MMPs). Considerable inroads to understanding how such MMPs move to the susceptible sites in collagen and then unwind the triple helix of collagen monomers have been gained. The essential role in unwinding of the hemopexin-like domain of interstitial collagenases or the collagen binding domain of gelatinases is highlighted. Elastolysis is also facilitated by the collagen binding domain in the cases of MMP-2 and MMP-9, and remote exosites of the catalytic domain in the case of MMP-12.

Introduction

Collagens and elastin comprise highly abundant fibrils that are each repetitive in sequence, enriched in polyproline II conformation, cross-linked, insoluble when assembled, and resistant to most proteolytic enzymes. The "monomer" unit of type I collagen comprises two extended α1 chains and one α2 chain twisted together into a triple helix. The detailed structural features of collagen, the many types of collagen, and the supramolecular assembly of the fibrils have been reviewed [1]. Elastin provides the extraordinary, enduring elasticity of the aorta and lung and is integrated with other proteins from the extracellular matrix in elastic fibrils [2–5]. The tropoelastin monomer is boot-shaped and contains the elasticity in the elongated N-terminal coil region [5,6]. The foot-like C-terminal end can bind cells and was proposed to grasp the next monomer in a head-to-tail manner in the extended polymer [5]. Proteolytic fragments of elastin are highly chemotactic and stimulating of inflammation, proliferation, and angiogenesis [7].

Collagenolysis and elastolysis by matrix metalloproteinases (MMPs) occur in development, wound healing, and major inflammatory diseases [7,8]. The MMPs proposed to be elastolytic have been MMP-2, MMP-7, MMP-9, MMP-12, and MT1-MMP, but with MMP-3 and MMP-10 in doubt [4]. Experiments using highly elastolytic human monocyte-derived macrophages (MDMs) asserted MMP-7 to be the principal elastolytic MMP under the very elastolytic conditions when activated by a urokinase-type plasminogen activator pathway [9]. Parallel experiments using the MDMs suggested the unlikelihood of direct elastolysis by MMP-9, and rather that MMP-12 deposited on elastin fibrils is the MMP required for digesting elastin in the absence of plasminogen. The authors proposed that MMP-12 might influence elastolysis indirectly by digesting chemokines and other extracellular proteins [9]. (Chemokines and numerous non-matrix proteins have been identified as physiological substrates of MMP-12 [10–12]). Degradation of interstitial collagen fibrils, e.g., types I and III, to generate the classic 3/4 and 1/4 fragments is catalyzed by MMP-1, MMP-8, MMP-13, MT1-MMP, MT3-MMP, and presumably MT2-MMP [8]. MMP-2 digests *solubilized* monomers of collagens I, II, and III [13–15]. MMP-9 digests solubilized collagen I and III monomers [16]. Mechanistic insights into MMP binding and hydrolysis of fibrillar collagens and elastin are surveyed below. The specific questions considered regard how do MMPs (i) move across collagens to sites for attack, (ii) interact with and

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Saliva and serum biomarkers in periodontitis and coronary artery disease

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Abstract

Aim: Matrix metalloproteinase (MMP)-8, MMP-9, tissue inhibitor of matrix metalloproteinase (TIMP)-1 and myeloperoxidase (MPO) participate in extracellular matrix breakdown both in periodontium and atherosclerotic plaques. We investigated the diagnostic value of serum and saliva biomarkers in periodontitis and acute coronary syndrome (ACS).

Materials and methods: The population was PAROGENE (*n* = 481), a random cohort of patients with an indication for coronary angiography. All patients underwent a clinical and radiographic oral examination. Groups consisting of periodontitis versus non-periodontitis, and ACS versus non-ACS patients were compared.

Results: Saliva MMP-8, MMP-9 and MPO provided significant area-under-curve (AUC) values for periodontitis, 0.69 (<0.001), 0.66 (<0.001) and 0.68 (<0.001), respectively. Serum MMP-8, MMP-9 and MPO levels distinguished ACS from non-ACS patients with AUCs of 0.73 (<0.001), 0.58 (0.03) and 0.68 (<0.001), respectively. Periodontitis confounded the use of serum MMP-9 in diagnostics of ACS. Cardiac status complicated the use of saliva TIMP-1 in periodontal diagnostics. Saliva biomarkers could not be used in ACS diagnosis, and serum biomarkers were not useful in diagnosis of periodontitis.

Conclusions: MMP-8, MMP-9, TIMP-1and MPO are valuable biomarkers for both ACS and periodontitis, but the selection of sample material is crucial; serum is suitable for ACS and saliva for periodontal diagnostic aid.

KEYWORDS
acute coronary syndrome, biomarker, MMP-8, MMP-9, myeloperoxidase, periodontitis, saliva, serum, TIMP-1

Acute Myocardial Infarction is Reflected in Salivary Matrix Metalloproteinase-8 Activation Level

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Background: The aim of this study is to compare salivary and serum biomarker levels and degrees of matrix metalloproteinase (MMP) activation between patients with acute myocardial infarction (AMI) and systemically healthy patients (non-AMI) with similar periodontal conditions.

Methods: A total of 92 patients (47 AMI and 28 non-AMI patients with gingivitis or periodontitis; and 17 systemically and periodontally healthy patients as a control group) were recruited. Clinical periodontal measurements were recorded; stimulated whole saliva and serum samples were collected. AMI patients were clinically examined within 3 to 4 days after admission to the coronary care unit. Saliva samples were analyzed for levels of MMP-8, MMP-7, and tissue inhibitor of matrix metalloproteinase (TIMP)-1. Serums were tested for MMP-8, MMP-9, TIMP-1, and TIMP-2 levels by immunofluorometric assay and enzyme-linked immunosorbent assay. Molecular forms and degree of activation of salivary MMP-8, MMP-9, and MMP-13 were analyzed by computer-scanned immunoblots.

Results: Total salivary MMP-8 assessed by immunofluorometric assay method and immunoblot densitometric units was higher in non-AMI than in AMI patients' saliva but a significantly higher percentage of AMI patients was activated polymorphonuclear leukocyte type (PMN) MMP-8 ($P<0.001$) regardless of periodontal diagnosis. Serum MMP-8, MMP-9, and TIMP-1 levels were significantly higher in AMI (for all markers and all comparisons, $P<0.05$). Characteristic for AMI was dominance of active PMN MMP-8 in saliva.

Conclusions: Enhanced MMP-8 activation in the saliva of AMI patients is evidently, in part, of systemic origin. Consequently, AMI is reflected in serum but also in saliva. *J Periodontol 2011;82:716-725.*

KEY WORDS

Matrix metalloproteinases; myocardial infarction; pathogenesis; periodontal disease; saliva; serum.

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Coronary artery disease is one of the leading causes of death worldwide, and acute myocardial infarction (AMI) is responsible for about 15% of all such deaths.[1] Several pathophysiologic mechanisms play an important role in the pathogenesis of AMI, such as inflammation; prothrombotic and thrombotic activity; shear stress, endothelial responsiveness to dilatation; and collagen degradation.[2] Periodontitis results from the interaction of periodontopathic plaque bacteria and host inflammatory and immune responses and is the most common persistent bacterial infection worldwide. The association of periodontitis with coronary heart disease has been investigated in several clinical studies.[3-6] However, the pathogenic mechanisms and potential links between both diseases are not completely clarified.

The host-derived matrix metalloproteinases (MMPs) are known to be the main endogenous proteinases of physiologic tissue remodeling and pathologic extracellular matrix degradation in periodontitis.[7,8] Increased gingival crevicular fluid (GCF) and salivary MMP-8 levels are associated with progressive loss of connective tissue attachment in periodontitis.[8-10] MMP-9 has been shown to be the major gelatinase present in periodontitis-affected inflamed human gingival tissue, dental plaque, saliva, and GCF samples.[8,11] Matrilysin-1 (MMP-7), the smallest of

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SERIES "MATRIX METALLOPROTEINASES IN LUNG HEALTH AND DISEASE"
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Biological role of matrix metalloproteinases: a critical balance

S. Löffek*, O. Schilling# and C-W. Franzke*

ABSTRACT: **Matrix metalloproteinases (MMPs) are members of the metzincin group of proteases which share the conserved zinc-binding motif in their catalytic active site. It was originally thought that their main function is to degrade the various components of the extracellular matrix (ECM), yet recent studies have led us to appreciate their significance as regulators of extracellular tissue signalling networks. Due to the broad spectrum of their substrate specificity, MMPs contribute to the homeostasis of many tissues and participate in several physiological processes, such as bone remodelling, angiogenesis, immunity and wound healing. MMP activity is tightly controlled at the level of transcription, pro-peptide activation and inhibition by tissue inhibitors of MMPs. Dysregulated MMP activity leads to pathological conditions such as arthritis, inflammation and cancer, thus highlighting MMPs as promising therapeutic targets. Analysis of MMP mutant mice has proved to be an essential tool for the identification of novel functions and interactions of single MMP members. Advancing our understanding of the MMP contribution to tissue homeostasis will lead us to identify causal relationships between their dysregulation and the development of disease pathologies, thus guiding us to successful MMP-directed therapies.**

KEYWORDS: **Collagen, degradation, extracellular matrix, immunity, substrate, tissue inhibitor of metalloproteinase**

The matrixins or matrix metalloproteinases (MMPs) are members of the large metzincin superfamily like the astacins, serralysins, reprolysins, and adamalysins or disintegrin metalloproteinases (ADAMs). In the classical view, MMPs are collectively capable of degrading all components of the extracellular matrix (ECM) and basement membrane, restricting their functions to tissue remodelling and maintenance. However recent substrate identification studies reveal that MMPs are regulating the release or activation of chemokines, cytokines, growth factors, antibiotic peptides, and other bioactive molecules thus participating in physiological processes such as innate and adaptive immunity, inflammation, angiogenesis, bone remodelling, and neurite growth.

High sequence similarity to MMP catalytic domains is found in almost all kingdoms of life. At least 25 different vertebrate MMPs have been characterised up to now and 24 different MMPs are found in humans, including the two identical forms for MMP-23, encoded by two distinct genes, *i.e. MMP23A* and *MMP23B*. The diversity of the current mammalian MMP gene families is derived particularly from an extensive gene tandem duplication and exon shuffling during evolution in the tetrapod lineages. Taking this into account, some of the actual MMP members are most likely derivatives from a single gene resulting in a MMP gene cluster, whose organisation is preserved from amphibians to mammals. The cluster in the human genome is located at chromosome 11q22 and contains MMP-1, -3, -7, -8, -10, -12, -13, -20 and -27. In contrast, most of the other human MMP genes are located on different chromosomes, resulting in a total of 10 distinct chromosomes for all 24 human MMP genes [1].

Although the activity of MMPs has been shown to be essential in cell biological processes and many fundamental physiological events involving tissue

For editorial comments see page 12.

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RESEARCH Open Access

TIMP1 is a prognostic marker for the progression and metastasis of colon cancer through FAK-PI3K/AKT and MAPK pathway

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Abstract

Background: Tissue inhibitor matrix metalloproteinase 1 (TIMP1) plays a vital role in carcinogenesis, yet its precise functional roles and regulation remain unclear. In this study, we aim to investigate its biological function and clinical significance in human colon cancer.

Methods: We analyzed the expression of TIMP1 in both public database (Oncomine and TCGA) and 94 cases of primary colon cancer and matched normal colon tissue specimens. The underlying mechanisms of altered TIMP1 expression on cell tumorigenesis, proliferation, and metastasis were explored in vitro and in vivo.

Results: TIMP1 was overexpressed in colon tumorous tissues and lymph node metastasis specimens than in normal tissues. The aberrant expression of TIMP1 was significantly associated with the regional lymph node metastasis ($p = 0.033$), distant metastasis ($p = 0.039$), vascular invasion ($p = 0.024$) and the American Joint Committee on Cancer (AJCC) stage ($p = 0.026$). Cox proportional hazards model showed that TIMP1 was an independent prognostic indicator of disease-free survival (HR = 2.603, 95 % CI: 1.115–6.077, $p = 0.027$) and overall survival (HR = 2.907, 95 % CI: 1.254–6.737, $p = 0.013$) for patients with colon cancer. Consistent with this, our findings highlight that suppression of TIMP1 expression decreased proliferation, and metastasis but increased apoptosis by inducing TIMP1 specific regulated FAK-PI3K/AKT and MAPK pathway.

Conclusion: TIMP1 might play an important role in promoting tumorigenesis and metastasis of human colon cancer and function as a potential prognostic indicator for colon cancer.

Keywords: TIMP1, Colon cancer, Prognosis, Tumorigenesis

Background

Colon cancer represents one of the most common malignancies worldwide and a common cause of morbidity and mortality [1]. Despite increased treatment advances in the past 20 years, early diagnosis can still improve the prognosis of this disease [2]. Molecular studies have revealed a large number of genetic alterations that occur during colon carcinogenesis, however, precise genetic changes responsible for the occurrence and progression of colon cancer is still poorly understood [3, 4]. Therefore, identification of molecular markers remains crucial for designing novel and efficient treatment strategy.

Tissue inhibitor matrix metalloproteinase 1 (TIMP1), located on chromosome Xp11.3-p11.23, belongs to the Tissue Inhibitor of Metalloproteinases family which included four identified members (TIMP1, TIMP2, TIMP3, and TIMP4). TIMP1 encodes a 931 base-pair mRNA and a 207 amino acid protein. Studies have shown that this protein may inhibit the proteolytic activity of matrix metalloproteinases (MMPs) by forming noncovalent 1:1 stoichiometric complexes and regulate the balance of matrix remodeling during degradation of extracellular matrix [5]. In addition to its inhibitory effect on most of the known MMPs, which are thought

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Journal of Clinical Periodontology

Salivary MMP-8, TIMP-1, and ICTP as markers of advanced periodontitis

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Abstract

Aim: Salivary matrix metalloproteinase (MMP)-8 and -14, tissue inhibitor of matrix metalloproteinase (TIMP)-1, and pyridinoline cross-linked carboxyterminal telopeptide of type I collagen (ICTP) were analysed aiming to detect potential markers of advanced periodontitis in saliva. In addition, we compared two MMP-8 detection methods, a time-resolved immunofluorometric assay (IFMA) and an enzyme-linked immunoassay (ELISA), to differentiate periodontitis subjects from controls.

Material and Methods: Concentrations of MMP-8, MMP-14, TIMP-1, and ICTP were analysed from salivary specimens of 165 subjects, including 84 subjects having at least 14 teeth with periodontal pocket (pocket depth ≥4 mm) and 81 subjects without pocket depth as their controls.

Results: Salivary MMP-8 detection by IFMA differentiated periodontitis subjects from controls more strongly than by ELISA. Salivary MMP-8, TIMP-1, and ICTP concentrations were higher in periodontitis subjects than those in controls. When only smokers were included in the analysis these differences were lost. The MMP-8/TIMP-1 ratio and the combination of MMP-8 and ICTP differentiated periodontitis and control groups even in smoker subjects.

Conclusion: Salivary MMP-8, TIMP-1, ICTP, and especially their ratios and combinations are potential candidates in the detection of advanced periodontitis. Differentiating periodontitis and control subjects with salivary MMP-8 detection is dependent on the selected techniques.

Key words: ICTP; MMP-14; MMP-8; saliva; TIMP-1

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Conflict of interest and sources of funding statement

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In periodontal tissue destruction, the degradation of connective tissue and alveolar bone is mainly induced by activated host cell enzymes (Tatakis & Kumar 2005). Among these enzymes, matrix metalloproteinases (MMPs) form the most important group of proteinases that take part not only in the degradation of matrix proteins during periodontitis but also during normal turnover in health and wound healing. The imbalance between MMPs and tissue inhibitors of matrix metalloproteinases (TIMPs) is considered to trigger the degradation of extracellular matrix, basement membrane, and alveolar bone, and thus to initiate periodontal disease (Sorsa et al. 2004).

MMP-8 in oral fluids, gingival crevicular fluid (GCF), and saliva associates with the initiation and progression of periodontitis and reflects its severity (Sorsa et al. 1988, Uitto et al. 1990, Sorsa et al. 2006). Activation of MMP-8 has been suggested to occur in a cascade of events, where reactive oxygen species and MMP-14 play an important role (Weiss 1989, Holopainen et al. 2003, Sorsa et al. 2006). TIMPs, on the other hand, regulate the activities of MMPs. Although the major function of TIMPs is the inhibition of MMPs, they can also

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ORIGINAL ARTICLE

Serum MMP-9 Diagnostics, Prognostics, and Activation in Acute Coronary Syndrome and Its Recurrence

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Abstract

Matrix metalloproteinase (MMP)-9 is crucial in atherosclerotic plaque rupture and tissue remodeling after a cardiac event. The balance between MMP-9 and endogenous inhibitor, tissue inhibitors of matrix metalloproteinase 1 (TIMP-1), is important in acute coronary syndrome (ACS). This is an age- and gender-matched case-control study of ACS ($N = 669$). Patients (45.7%) were resampled after recovery, and all were followed up for 6 years. The molecular forms of MMP-9 were investigated by gelatin zymography. Diagnostically, MMP-9 and the MMP-9/TIMP-1 molar ratio were associated with ACS (OR 5.81, 95% CI 2.65–12.76, and 4.96, 2.37–10.38). The MMP-9 concentrations decreased 49% during recovery ($p < 0.001$). The largest decrease of these biomarkers between acute and recovery phase (ΔMMP-9) protected the patients from major adverse cardiac events, especially the non-fatal events. The fatal events were associated with in vitro activatable MMP-9 levels ($p = 0.028$). Serum MMP-9 and the MMP-9/TIMP-1 molar ratio may be valuable in ACS diagnosis and prognosis. High serum MMP-9 activation potential is associated with poor cardiovascular outcome.

Keywords Atherosclerosis · Coronary artery disease · Serum biomarker · Cardiovascular diseases · Plaque rupture · Inflammation

Introduction

Atherosclerosis is a chronic inflammatory process of arteries [1, 2]. Matrix metalloproteinases (MMPs) destabilize atherosclerotic plaques by degrading extracellular matrix (ECM), especially in the shoulder regions. This may lead to plaque rupture and a fatal acute coronary syndrome (ACS) event. Inflammatory and oxidative mediators increase the amounts of MMPs [3]. MMPs enable leukocytes and inflammatory mediators to migrate across tissues [4], accelerating the development of pathogenic atherosclerotic plaques.

Matrix metalloproteinase-9 (MMP-9), also known as gelatinase B, is an enzyme that degrades mainly type IV collagen and elastin [5]. MMP-9 is secreted by various cell types, such as neutrophils, macrophages, endothelial cells, and smooth muscle cells. Interactions with specific tissue inhibitors of matrix metalloproteinases (TIMPs) determine the function of MMP-9 [6, 7] by binding to MMP at a molar equivalence [8]. Inactive, latent pro-form MMP-9 may be activated

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ARTICLE

Tissue inhibitor of matrix metalloproteinase 1 (TIMP1) controls adipogenesis in obesity in mice and in humans

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Abstract
Aims/hypothesis Extracellular matrix reorganisation is a crucial step of adipocyte differentiation and is controlled by the matrix metalloproteinase–tissue inhibitor of matrix metalloproteinase (TIMP) enzyme system. We therefore sought to define the role of TIMP1 in adipogenesis and to elucidate whether upregulation of TIMP1 in obesity has direct effects on adipocyte formation.
Methods TIMP1 protein levels and mRNA were measured in lean and obese mice with a focus on levels in adipose tissue. We also analysed the effect of recombinant murine TIMP1 on adipogenesis, adipocyte size and metabolic control in vitro and in vivo.
Results TIMP1 levels were increased in the serum and adipose tissue of obese mouse models. Recombinant murine TIMP1 inhibited adipocyte differentiation in 3T3-L1 as well as in subcutaneous primary pre-adipocytes. Conversely, neutralising TIMP1 with a specific antibody enhanced adipocyte differentiation. In vivo, injection of recombinant TIMP1 in mice challenged with a high-fat diet led to enlarged adipocytes. TIMP1-treated mice developed an impaired metabolic profile with increased circulating NEFA levels, hepatic triacylglycerol accumulation and accelerated insulin resistance. Altered glucose clearance in TIMP1-injected mice was due to changes in adipose tissue glucose uptake, whereas muscle glucose clearance remained unaffected.
Conclusions/interpretation TIMP1 is a negative regulator of adipogenesis. In vivo, TIMP1 leads to enlarged adipocytes in the state of overnutrition. This might contribute to the detrimental metabolic consequences seen in TIMP1-injected mice, such as systemic fatty acid overload, hepatic lipid accumulation and insulin resistance.

Keywords Adipocyte hypertrophy · Adipogenesis · Diet-induced obesity · Insulin resistance · TIMP1 · Tissue inhibitor of metalloproteinase 1

Abbreviations

MMP	Matrix metalloproteinase
SVF	Stromal–vascular fraction of adipose tissue
TIMP	Tissue inhibitor of matrix metalloproteinase

Introduction

Obesity is the main risk factor for type 2 diabetes and has become a growing health problem in the last decades [1–3]. Expansion of adipose tissue results from an imbalance between energy intake and energy expenditure. Secondary complications caused by obesity partly depend on how well adipose tissue can adapt to an extended nutrient supply [4, 5]. One way of buffering excess nutrients in adipose tissue is the generation of fat cells through de novo differentiation. This hyperplastic response is preferable to a hypertrophic reaction, where nutrients are stored in pre-existing adipocytes. Adipocyte hypertrophy commonly leads to enlarged, insulin-resistant fat cells with a high lipolytic rate, thus promoting ectopic

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A review of fluoroimmunoassay and immunofluorometric assay

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The immediate future of laboratory practice will continue to lie with immunoassay because of its specificity, potential sensitivity, practicality and, in particular, wide applicability. There has been considerable recent interest in the use of fluorescent molecules as a label for immunoassay purposes. This review attempts to explain simply the basis of immunoassay with particular reference to fluoroimmunoassay (FIA) and immunofluorometric analysis (IFMA); to compare the advantages and disadvantages of fluorescent labels as compared with radioisotopes and other non-isotopic alternatives; and to consider the many different analytical approaches made possible by use of a fluorescent tracer.

Basis and types of immunoassay

As its name implies, an immunoassay is an analytical procedure based on the reaction between an antigen and a specific antibody, which obeys the Law of Mass Action:

$$\underset{\text{(Free fraction)}}{Ag + Ab} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \underset{\text{(Bound fraction)}}{Ag : Ab}$$

where Ag represents the antigen, Ab the antibody, and Ag : Ab the bound complex. At equilibrium, some of the free reactants will be combining, with a rate constant k_1, to form more of the complex, while some of the complex will be dissociating, with a rate constant k_2, to give free antigen and antibody.

Immunoassays are most commonly employed to quantitate antigens in biological fluids, and it is with this role that the present review is primarily concerned. Nonetheless, it should be noted that immunoassays are also frequently used to detect the presence of circulating antibodies or immune complexes. Indeed, Berson and his colleagues' pioneer work in radioimmunoassay followed their use of ^{131}I-labelled insulin to demonstrate the presence of circulating antibodies in patients treated with insulin.[1]

Immunoassays for the detection or quantitation of an antigen can be categorised into those in which no labelled reactant is required, those employing labelled antigen, and others in which specific antibodies are labelled.

NON-LABELLED IMMUNOASSAYS

Several immunoassay techniques do not require the use of a labelled reactant.[2] Some depend on the precipitation line which forms in a gel support when a protein antigen comes into contact with its specific antibody while other manual and automated procedures depend, for end-point detection, on the increase in light scattering produced. Despite their extensive and rapidly increasing use, non-labelled techniques are limited to the assay of proteins and other large molecules present at relatively high concentrations, since only in such circumstances are the resultant antigen : antibody complexes sufficiently large to form a precipitin line or scatter light. Additional disadvantages include the need for relatively large amounts of monospecific antisera; problems with very turbid or haemolysed samples; and the possibility of erroneous results in the presence of antigen excess—due to the prozone phenomenon.

IMMUNOASSAYS EMPLOYING LABELLED ANTIGEN

The use of antigen labelled with a radioisotope, by Yalow and Berson in a radioimmunoassay (RIA) for insulin,[3] proved an important milestone. It made possible the assay of haptens (such as drugs and the thyroid and steroid hormones) as well as proteins; resulted in a million-fold increase in sensitivity; removed the need for monospecific antisera and markedly reduced the amounts of antisera required; avoided the problem of antigen excess; and enabled the assay of haemolysed and turbid samples. In the same year, Ekins had recognised the wider implication of this approach and developed techniques for both thyroxine (T_4)[4] and vitamin B_{12}[5] employing

Zymographic techniques for the analysis of matrix metalloproteinases and their inhibitors

Patricia A.M. Snoek-van Beurden and Johannes W. Von den Hoff

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The balance between matrix metalloproteinases (MMPs) and their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs), is largely responsible for the remodeling of tissues. Deregulation of this balance is a characteristic of extensive tissue degradation in certain degenerative diseases. To analyze the role of MMPs and TIMPs in tissue remodeling under normal and pathological conditions, it is important to have reliable detection methods. This review will focus on zymographical techniques for the analysis of MMPs and TIMPs. MMPs can be analyzed with several zymographical techniques, but substrate zymography is the most commonly used. This technique identifies MMPs by the degradation of their preferential substrate and by their molecular weight. Several substrates that can be used for zymography are described. Reverse zymography, which detects TIMPs by their ability to inhibit MMPs, is also discussed. Finally, in situ zymography is described, which is used to localize MMPs in tissue sections. Common problems encountered during sample preparation, zymography itself, and the data analysis are discussed. Hints are given to improve the sensitivity and accuracy of zymographical methods. In conclusion, zymography is a valuable tool for research purposes and for the development of new diagnostic techniques and therapies for pathological conditions such as rheumatoid and osteoarthritis, and tumor progression.

INTRODUCTION

Matrix metalloproteinases (MMPs) are a family of calcium-dependent, zinc-containing endopeptidases that are structurally and functionally related (1). They are secreted in an inactive (latent) form, which is called a zymogen or a pro-MMP. These latent MMPs require an activation step before they are able to cleave extracellular matrix (ECM) components (1). The activity of MMPs is regulated by several types of inhibitors, of which the tissue inhibitors of metalloproteinases (TIMPs) are the most important (2). The TIMPs are also secreted proteins, but they may be located at the cell surface in association with membrane-bound MMPs (3). The balance between MMPs and TIMPs is largely responsible for the control of degradation of ECM proteins (4). MMPs are involved in the remodeling of tissues during embryonic development, cell migration, wound healing, and tooth development (5–8). However, a deregulation of the balance between MMPs and TIMPs is a characteristic of diverse pathological conditions, such as rheumatoid and osteoarthritis, cancer progression, and acute and chronic cardiovascular diseases (3,9,10). To analyze the role of MMPs and TIMPs in tissue remodeling under normal and pathological conditions, it is important to have reliable detection methods. This review will briefly describe all known MMPs, their activation, and their role in tissue remodeling and pathology. It will focus on zymographical techniques for the analysis of MMPs and TIMPs.

THE MMP FAMILY

The family of human MMPs consists of 23 different forms that are divided into six groups (11–14). In order to classify the MMPs, knowledge of their characteristics is essential. It has been shown that each MMP consists of a specific domain sequence with several domain motifs. This sequence includes the signal peptide, the propeptide domain, the catalytic domain, and the C-terminal hemopexin-like domain, which are present in almost all MMPs (15). However, several MMPs have additional domains such as a transmembrane or a cytoplasmic domain (15,16). The organization of the MMP domains, together with their substrate specificity and sequence similarity, define the MMP classification. Six groups can be distinguished (Table 1; subgroups 1–6). (1.) The collagenase group includes MMP-1, MMP-8, and MMP-13. These are generally able to cleave the interstitial collagens I, II, and III. Collagenases are also able to digest certain other ECM and non-ECM proteins (8,12,17). (2.) The gelatinase group, which consists of MMP-2 and MMP-9, mainly digests gelatin, the denatured form of collagen (8,12). (3.) The stromelysins, MMP-3 and MMP-10, digest ECM components such as collagen IV and fibronectin. MMP-11 is also called stromelysin-3, but its sequence and substrate specificity are different from that of MMP-3 and MMP-10. Therefore, MMP-11 is usually placed in the heterogeneous subgroup (see subgroup 6) (8,12,17). (4.) The matrilysins, MMP-7 and MMP-26, which are categorized differently among the MMP subgroups by

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Effects of scaling and root planing and sub-antimicrobial dose doxycycline on oral and systemic biomarkers of disease in patients with both chronic periodontitis and coronary artery disease

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Abstract

Objectives: This study evaluated the effects of scaling and root planing (SRP) ± sub-antimicrobial dose doxycycline (SDD) on gingival crevicular fluid (GCF) levels of matrix metalloproteinase (MMP) -1, -8, -13 and on serum levels of high-sensitivity C-reactive protein (HsCRP) and lipid fractions in patients with *both* chronic periodontitis (CP) and coronary artery disease (CAD).

Material and Methods: Thirty-six patients were randomly distributed into two groups (Placebo or SDD; 6 weeks) and both received two regimens of SRP. At baseline and 6 weeks, GCF and blood were collected and clinical indices were recorded. MMPs, HsCRP and lipid fractions were assayed.

Results: There were statistically significant improvements for all clinical parameters, GCF volumes, GCF MMPs and serum levels of HsCRP, apolipoprotein-A (APO-A), high-density lipoprotein (HDL) and lipoprotein-a between pre- and post-treatment in both groups. Between groups, there were statistically significant greater improvements in pocket depth (PD), gingival index (GI), APO-A and HDL, favouring the group receiving SDD adjunctive to SRP ($p < 0.05$).

Conclusion: Greater improvement was detected for PD and GI, and for serum levels of APO-A and HDL cholesterol when using SRP+SDD compared with SRP+placebo in this study. An investigation with larger numbers of patients and a longer duration of drug treatment is needed to confirm these preliminary findings.

Key words: adjunctive treatment; cardiovascular disease; C-reactive protein; gingival crevicular fluid/analysis; host modulation therapy; matrix metalloproteinases; periodontitis/therapy; plasma lipids; subantimicrobial dose doxycycline

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RESEARCH ARTICLE

Salivary Matrix Metalloproteinase-8 and -9 and Myeloperoxidase in Relation to Coronary Heart and Periodontal Diseases: A Subgroup Report from the PAROKRANK Study (Periodontitis and Its Relation to Coronary Artery Disease)

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Abstract

Background and Objective

Matrix metalloproteinase (MMP) -8, -9 and myeloperoxidase (MPO) are inflammatory mediators. The potential associations between MMP-8, -9, MPO and their abilities to reflect cardiovascular risk remains to be evaluated in saliva. The objective of this study was to investigate the levels and associations of salivary MMP-8, -9, MPO and tissue inhibitors of metalloproteinase (TIMP)-1 in myocardial infarction (MI) patients and controls with or without periodontitis.

Materials and Methods

200 patients with a first MI admitted to coronary care units in Sweden from May 2010 to December 2011 and 200 controls matched for age, gender, residential area and without previous MI were included. Dental examination and saliva sample collection was performed 6-10 weeks after the MI in patients and at baseline in controls. The biomarkers MMP -8, -9, MPO and TIMP-1 were analyzed by time-resolved immunofluorescence assay (IFMA), Western blot and Enzyme-Linked ImmunoSorbent Assay (ELISA).

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VIEWPOINT

Salivary biomarkers in cardiovascular disease: An insight into the current evidence

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Keywords
cardiovascular disease; CK-MB; C-reactive protein; salivary biomarkers; troponin

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Cardiovascular diseases (CVDs) are the most common cause of mortality worldwide. In acute cardiovascular conditions, time is a crucial player in the outcomes of disease management. Given the ease and noninvasiveness of obtaining saliva, salivary biomarkers may provide a rapid and efficient diagnosis of CVD. Here, we reviewed the published data on the value of salivary molecules for diagnosis of CVD, especially in acute care settings. In this review, we show that some biomarkers such as salivary creatinine kinase myocardial band, C-reactive protein, troponin-1, and myoglobin exhibited promising diagnostic values that were comparable to their serum counterparts. Other molecules were also investigated and showed controversial results, including myeloperoxidase, brain natriuretic peptide, and some oxidative stress markers. Based on our review, we concluded that the clinical use of salivary biomarkers to diagnose CVD is promising; however, it is still in the early stage of development. Further studies are needed to validate these findings, determine cutoff values for diagnosis, and compare them to other established biomarkers currently in clinical use.

Introduction

Cardiovascular diseases (CVDs) are the most common cause of mortality; both globally and in the United States. Solely, they were responsible for 20% and 24% of the total age-matched worldwide liability of disease in 2016, respectively. Among CVDs, the most common is ischemic heart disease [174 million disability-adjusted life-years [DALYs; crude range 170–180 million]), then stroke [116 million DALYs (crude range 111–121 million)] [1]. In the USA, 116.4 million, or 46% of adults, are estimated to have hypertension, with ~ 2303 deaths owing to CVD daily and 389.4 daily deaths related to stroke alone. In Europe, 4 475 990 individuals were estimated to die from CVD in 2017 [2]. By 2030, the excepted direct medical costs for CVD will reach $818 billion in comparison with $273 billion in 2010 [3].

Acute myocardial infarction (AMI) is a common cardiovascular emergency with a high case-fatality ratio. The cornerstone for emergency diagnosis of AMI is electrocardiography (ECG) in addition to analysis of the classic cardiac biomarkers, including troponin I (TnI), serum creatine kinase myocardial band

Abbreviations
8-OHdG, hydroxydeoxyguanosine; AHSG, alpha-2-HS-glycoprotein; AMI, acute myocardial infarction; ASA, alcohol septal ablation; BNP, B-type natriuretic peptide; CAT, catalase; CHD, chronic heart disease; CK-MB, Creatinine kinase myocardial band; CPK, Creatine phosphokinase; CRP, C-reactive protein; CVD, cardiovascular disease; DCFH-DA, 2′7′ dichlorodihydrofluorescein diacetate; HDL, high-density lipoprotein; IMA, ischemic modified albumin; LDL, low-density lipoprotein; LR, logistic regression; MDA, malondialdehyde; MMP, matrix metalloproteinase; MPO, myeloperoxidase; MYO, myoglobin; NES, neuron-specific enolase; TG, triglyceride; TIMPs, tissue inhibitors of metalloproteinases; TnI, troponin I; VLDL, very-low-density lipoprotein.

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SYSTEMATIC REVIEW

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WILEY

Accuracy of single molecular biomarkers in saliva for the diagnosis of periodontitis: A systematic review and meta-analysis

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Abstract

Aim: To analyse, using a meta-analytical approach, the diagnostic accuracy of single molecular biomarkers in saliva for the detection of periodontitis in systemically healthy subjects.

Materials and Methods: Articles on molecular biomarkers in saliva providing a binary contingency table (or sensitivity and specificity values and group sample sizes) in individuals with clinically diagnosed periodontitis were considered eligible. Searches for candidate articles were conducted in six electronic databases. The methodological quality was assessed through the tool Quality Assessment of Diagnostic Studies. Meta-analyses were performed using the Hierarchical Summary Receiver Operating Characteristic model.

Results: Meta-analysis was possible for 5 of the 32 biomarkers studied. The highest values of sensitivity for the diagnosis of periodontitis were obtained for IL1beta (78.7%), followed by MMP8 (72.5%), IL6 and haemoglobin (72.0% for both molecules); the lowest sensitivity value was for MMP9 (70.3%). In terms of specificity estimates, MMP9 had the best result (81.5%), followed by IL1beta (78.0%) and haemoglobin (75.2%); MMP8 had the lowest specificity (70.5%).

Conclusions: MMP8, MMP9, IL1beta, IL6 and Hb were salivary biomarkers with good capability to detect periodontitis in systemically healthy subjects. MMP8 and IL1beta are the most researched biomarkers in the field, both showing clinically fair effectiveness for the diagnosis of periodontitis.

KEYWORDS
diagnostic accuracy, meta-analysis, molecular biomarkers, periodontitis, predictive values, prevalence, saliva, sensitivity, specificity, systematic review

1 | INTRODUCTION

An estimated 743 million people are affected by periodontitis, which is considered to be the sixth most prevalent disease globally (Kassebaum et al., 2014). In periodontics, the diagnosis of periodontitis is a crucial element in the success of treatment, as the progression of the disease causes an irreversible loss of periodontal structures (Kinane, Stathopoulou, & Papapanou, 2017). The traditional clinical and radiographic parameters are the best measures currently available for diagnosing the disease and monitoring