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Review

Diabetes and periodontitis: A bidirectional relationship☆

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ABSTRACT

Diabetes mellitus is a group of metabolic diseases characterised by hyperglycemia resulting from defects in insulin secretion, a defect in insulin action or a combination of both. Periodontitis is now considered a chronic localised infection of the oral cavity that can trigger inflammatory host immune responses at local and systemic levels, and can also be a source of bacteremia. It is now known that periodontitis has an influence on the pathogenesis of certain systemic diseases. The biological relationship between diabetes and periodontal disease is well documented. In the mid-90s sufficient scientific support for the association between diabetes and periodontitis was published, and periodontitis was designated as the sixth complication of diabetes. There have been studies that show an improvement in both clinical and immunological parameters of periodontitis and glycemic control in long-term diabetes after treatment of periodontal disease. In addition, scientific evidence confirms that poorer glycemic control contributes to a worse periodontal condition.

The interplay between the two conditions highlights the importance of the need for a good communication between the internist and dentist about diabetic patients, considering always the possibility that the two diseases may be occurring simultaneously in order to ensure an early diagnosis of both.

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RESUMEN

La diabetes mellitus es un grupo de enfermedades metabólicas caracterizadas por una hiperglucemia resultante de un defecto en la secreción de insulina, un defecto en la acción de esta, o bien una combinación de ambos. La periodontitis se considera actualmente una infección crónica localizada en la cavidad oral, que puede activar la respuesta inmunitaria inflamatoria del hospedador a nivel local y sistémico, y que además puede ser una fuente de bacteriemia. Hoy en día se sabe que la periodontitis tiene una influencia sobre la patogénesis de ciertas enfermedades sistémicas. La relación biológica entre la diabetes y la enfermedad periodontal está bien documentada. A mediados de la década de 1990 se encontró soporte científico suficiente para la asociación entre la diabetes y la periodontitis, que se comenzó a designar como la sexta complicación de la diabetes. Se han realizado estudios que muestran una mejora tanto en los parámetros clínicos e inmunológicos de la periodontitis como en el control glucémico a largo plazo de la diabetes tras el tratamiento de la enfermedad periodontal. Además, la evidencia científica confirma que un peor control glucémico contribuye a un peor estado periodontal.

La interrelación entre ambas afecciones deja constancia de la importancia de la necesidad de una buena comunicación entre el médico internista y el odontólogo de los pacientes diabéticos, teniendo siempre en cuenta la posibilidad de que ambas enfermedades puedan estar ocurriendo simultáneamente, para garantizar el diagnóstico precoz de ambas.

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Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterised by hyperglycaemia resulting from a defect in insulin secretion, a defect in its action, or a combination of both.[1,2] The current prevalence of DM in Spain is around 8% in women and 12% in men, although a growing tendency has also been observed in recent years, both in Spain and on a global level.[3,4]

Periodontitis was traditionally considered to be a localised oral infection that only affected the periodontium, but is now regarded as a chronic localised infection of the oral cavity that can trigger the host inflammatory immune response at both local and systemic level, and can also be a source of bacteraemia. It is difficult to determine the prevalence of periodontitis. Some authors have estimated that gingivitis affects 50% of the US population, with the prevalence of periodontitis being 14%, although probably higher. It should be taken into account, however, that these estimations depend to a large extent on the diagnostic criteria established by each study.[5] Nowadays, it is known that periodontitis affects the pathogenesis of certain systemic diseases, and that it can increase their risk of presentation, which has led to the emergence and development of "Periodontal Medicine".[6]

Interrelationship between the two entities

The biological relationship between DM and periodontal disease is well documented. In the mid-1990s, after 30 years of exhaustive research and almost 90 published epidemiological studies, enough scientific evidence had been found to associate DM with periodontitis, which has become known as the sixth complication of DM.[7] DM was first shown to be a risk factor for periodontitis, and then an inverse influence was proposed, i.e., that periodontitis could be a risk factor for diabetic decompensation, a relationship backed up by various studies. This would therefore suggest a complex, two-way relationship between DM and periodontitis, creating a vicious circle that would exacerbate both diseases when both occur in the same individual.

The association between DM and periodontal disease has been extensively studied. Shlossman et al.[8] evaluated the periodontal status of 3219 individuals from the Pima Indian population (a population with a high prevalence of type 2 DM), and found a significantly higher prevalence of periodontitis in diabetics than in non-diabetics, with age being an independent factor. Following on from this study, Emrich et al.,[9] Nelson et al.[10] and Taylor et al.[11] found similar results in this same population. Taylor et al.[12] showed that advanced periodontitis is significantly associated with a risk of worsening glycaemic control.

According to published articles, several authors agree that DM acts as a risk factor in periodontal disease. Mealey[13] states that, after adjusting for other confounding factors such as age or sex, DM appears to increase the probability of presenting periodontitis 3-fold.

A systematic review by Borgnakke et al.[14] included 17 articles; based on these, they determined that there is little evidence to support a negative effect of periodontal disease on glycaemic control, DM complications and development of type 2 DM, and possibly gestational diabetes.

However, other reviews carried out in recent years have clearly established the effect of DM on periodontal diseases.[15,16] There is also evidence of a relationship between the severity of periodontitis and type 2 DM complications; moderate-to-severe periodontitis is associated with an increase in macroalbuminuria, end-stage renal disease, atheromatous plaque calcification, carotid intima-media thickening and cardiorenal mortality.[17]

Some biochemical markers of DM are altered by periodontal disease. Glycated haemoglobin (HbA1c) is used as a marker of glycaemia, and since the 2013 Workshop on DM[13], has been used as a standard response variable in the control of DM.

Pathogenesis

Periodontitis is a chronic inflammatory disease in which periodontal tissue inflammation is stimulated by the prolonged presence of subgingival biofilm. The inflammatory response is characterised by unregulated secretion of host-derived mediators of inflammation and tissue destruction. The most extensively studied are interleukin (IL)-1β, IL-6, prostaglandin E2 (PGE2), tumour necrosis factor (TNF)-α, RANKL and matrix metalloproteinases (MMPs, especially MMP-8, MMP-9 and MMP-13), as well as regulatory T cells that produce cytokines (e.g. IL-12 and IL-18) and chemokines. The cytokine network in the pathogenesis of periodontal disease is quite complex, and there is also considerable heterogeneity in the nature of the inflammatory response among individuals.[18,19]

Inflammation is the most central characteristic in the pathogenesis of both DM and periodontal disease. Both type 1 and type 2 DM are associated with high levels of systemic inflammatory markers. The elevated inflammatory state in DM contributes to both macrovascular and microvascular complications, and hyperglycaemia can result in the activation of pathways that increase inflammation, oxidative stress and apoptosis. High IL-6 and TNF-α levels have been found in DM and obesity. The onset of type 2 DM can be predicted through serum IL-6 and C-reactive protein (CRP) levels. High CRP levels are also associated with insulin resistance, type 2 DM and cardiovascular disease. Acute-phase proteins, including CRP, are mainly induced by TNF-α and IL-6, which also damage intracellular insulin signalling, potentially contributing to insulin resistance. Serum IL-6 and CRP levels are also high in patients with periodontitis, and there is a correlation between the IL-6 values and the extent of the periodontal disease. As such, the systemic inflammation associated with periodontal disease could encourage development of a diabetic state.[18,19]

DM increases inflammation in the periodontal tissues. PGE2 and IL-1β values in gingival crevicular fluid (GCF) are higher in patients with type 1 DM and gingivitis or periodontitis compared to non-diabetic individuals with the same degree of periodontal disease. In a study of patients with type 2 DM, those with HbA1c >8% had significantly higher IL-1β values in the GCF than patients with HbA1c <8%, and the HbA1c and glucose values were independent predictors of a high IL-1β value in the GCF.[18,19]

Following the damage caused by the lipopolysaccharide, the monocytes in patients with type 1 diabetes produce significantly higher concentrations of TNF-α, IL-1β and PGE2 than the monocytes of non-diabetic patients. Various studies have even shown defects in polymorphonuclear (PMN) leucocyte activity in diabetic patients, including impaired chemotaxis, phagocytosis and bactericidal functions. PMNs need energy to perform these functions, so these defects may be related to the metabolic changes that occur in DM. Diabetic patients with advanced periodontitis have been shown to have decreased chemotaxis compared to diabetic patients with mild periodontitis, as well as defective PMN apoptosis. This can cause an increase in PMN retention in the periodontal tissues, leading to increased tissue destruction due to the continuous secretion of MMP and reactive oxygen species (ROS). DM prolongs the inflammatory response to *Porphyromonas gingivalis*, with an increase in the production of TNF-α as an inflammatory mediator. However, periodontal treatment reduces the serum values of inflammatory mediators such as IL-6, TNF-α, CRP and MMP in patients with or without DM.[18,19]