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Association of periodontal disease and diabetic retinopathy

Asociación de la enfermedad periodontal y la Retinopatía Diabética

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Abstract:

The main problem of type II diabetes is that excessive levels of glucose in the blood damage the vascular endothelium causing complications, such as periodontal disease (PD) that, in people with diabetes, can compromise the patient's ability to maintain a normal metabolic control. Therefore, it is important to analyse the effect of PD status on complications in patients with type II diabetes; Previous studies have reported that there is a bidirectional relationship between PD and diabetic complications, but it has not been clarified whether PD affects the presence of complications such as diabetic retinopathy (DR). DR is a microvascular complication and is considered the main cause of visual loss worldwide, similarly, periodontitis is a microvascular chronic inflammatory condition that compromises the dental support tissues. This article was prepared as an update for health professionals and also to analyse PE and how it is related to the presence of DR. Based on the literature, it can be concluded that the number of teeth is an independent risk factor for DR, greater bleeding on probing could affect the presence of DR, and that patients with DR seem to show greater susceptibility to PD. The bibliography also mentions that more studies should be carried out with large samples, adequate models that adjust confounding variables such as obesity, hypertension, other chronic-degenerative diseases, use of substances such as alcohol or cigarettes, also carrying out prospective analyses of the conditions of periodontitis and DR.

Keywords:

Periodontal disease, diabetes, diabetic retinopathy, periodontitis

Resumen:

El principal problema de la diabetes tipo II, se debe a que los niveles excesivos de glucosa en sangre dañan al endotelio vascular causando complicaciones, como la enfermedad periodontal (EP) que, en personas con diabetes, puede comprometer la capacidad del paciente para mantener un control metabólico adecuado. Por ello es importante analizar el efecto del estado de la EP sobre las complicaciones en pacientes con diabetes tipo II; estudios previos han informado que existe una relación bidireccional entre la EP y las complicaciones diabéticas, pero no se ha aclarado si la EP afecta la presencia de complicaciones como la retinopatía diabética (RD). La RD es una complicación microvascular y es considerada la principal causa de pérdida visual a nivel mundial, de igual modo, la periodontitis es una condición inflamatoria crónica microvascular que compromete los tejidos de soporte dental. Este artículo fue elaborado como actualización para los profesionales de la salud y también para analizar la EP y como ésta se relaciona con la presencia de RD. Con base en la bibliografía podemos concluir que el número de dientes es un factor de riesgo independiente para padecer RD, un mayor sangrado al sondeo podría afectar la presencia de RD y que los pacientes con RD parecen mostrar una mayor susceptibilidad a la EP. También la bibliografía menciona que se deben realizar más estudios con muestra grandes, modelos adecuados que ajusten variables confusoras como la obesidad, la hipertensión, otras enfermedades crónico-degenerativas, uso de sustancias como el alcohol o el cigarro, realizando también análisis prospectivos de las condiciones de periodontitis y RD.

Palabras Clave:

Enfermedad periodontal, diabetes, retinopatía diabética, periodontitis

INTRODUCTION

Type II diabetes is a chronic metabolic disorder caused by a deficiency in the production and action of insulin affecting blood glucose homeostasis, those unregulated blood glucose levels damage the vascular endothelium causing complications in the body, these complications include cardiovascular diseases, diabetic nephropathy, neuropathy, diabetic foot, and DR.[1] In its initial stage, diabetes does not manifest itself with serious symptoms, in the last decade diabetes affected more than 217 million people, it is estimated that for in 2030 its prevalence is 4.4% for all age groups worldwide. According to the World Health Organization (WHO), millions of people around the world have diabetes. Vascular complications of diabetes are recognized as the most serious manifestations of diabetes, of which diabetic retinopathy and nephropathy are two of the main

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contributors to end-stage blindness and kidney disease, respectively.[2]

DR is one of the most common complications in patients with diabetes, as it progresses, it can cause blindness affecting quality of life, because this disease progresses gradually and the patient barely notices its progression, in most patients it passes completely unnoticed until an intraocular effusion occurs due to the rupture of a blood vessel, in these circumstances the patient presents a sudden loss of vision. DR is a disorder that affects the retinal microvasculature, estimating that DR is the most frequent cause of new cases of blindness among adults aged 20 to 74 years. It is estimated that around 2% of the world population with diabetes has some degree of DR at some point in life, although DR is one of the main causes of blindness in the active population, only between 35 and 55%. of patients with diabetes undergo regular ophthalmologic evaluations.[1,3]

PD is defined as an inflammatory condition with potential destruction of the supporting tissues and structures of the dental organ; including the periodontal ligament, bone, cementum, and soft tissues. There is increasing evidence indicating that periodontitis is a risk factor for various systemic diseases, PD is one of the most commonly known chronic disorders in humans, with a prevalence that varies between 10 and 60% in adults.[3]

Periodontitis manifests with high prevalence in patients with diabetes. According to the US National Health and Nutrition Examination Survey, patients with glycated hemoglobin (HbA1c) levels >9% have a higher prevalence of severe periodontitis compared to non-diabetic patients. The bacterial level resulting from periodontitis is a persistent source of inflammatory mediators that can promote negative effects in diabetes such as insulin resistance, which can increase the appearance of complications.[4] It has recently been shown that there is a correlation between the severity of PD and DR and that many patients with DR suffer from PD. However, when considering the studies on the relationship between DR and PD, the information remains limited. Most studies include a small number of subjects and do not consider possible confounding factors such as obesity, hypertension, other chronic-degenerative diseases, use of substances such as alcohol or smoking.[1, 5] Therefore, this article aims at gathering studies that evaluate the presence of DR in patients with diabetes with and without periodontitis, analyzing the evidence to find out if there is a significant association between both diseases.

DIABETES

The American Diabetes Association and the International Diabetes Federation define diabetes as a set of heterogeneous metabolic disorders whose main finding is chronic hyperglycemia; the cause of this hyperglycemia is impaired insulin secretion or impaired insulin effect, or usually both.[6, 7]

The American Diabetes Association made a classification based on the etiology of diabetes (Table 1) in order to understand the various causes of diabetes.

Table 1. Classification by etiology established by the American Diabetes Association.[6]

Etiological of diabetes.

• Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
  o Autoimmune
  o Idiopathic
• Type 2 diabetes (can range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
• Other specific types
  o Genetic defects of β-cell function
  o Genetic defects in insulin action
  o Diseases of the exocrine pancreas
  o Endocrinopathies
  o Drug or chemical induced
  o Infections
  o Other genetic syndromes sometimes associated with diabetes
  o Gestational diabetes

In patients suffering from diabetes, various complications can manifest and among the most feared complications is DR, in addition to diabetic macular edema and the consequences that damage the organ of vision. It is currently known that DR and glaucoma are the main causes of blindness in the working-age population, with a devastating impact at an economic and social level and on the quality of life of the individual who suffers from it.[7] In the beginning of type II diabetes, hyperglycemia is the result of the inability of the body's cells to fully respond to insulin, which is known as "insulin resistance", during this stage, the hormone is not effective, which leads to an increase in insulin production. After some time, inadequate insulin production can occur as the pancreatic beta cells do not keep up with the demand. This type of diabetes is seen most often in older adults, but is increasingly being seen in children and young adults due to rising levels of obesity, physical inactivity, and poor diet.[7]

DIABETIC RETINOPATHY

The human retina consists of three layers of nerve cells interspersed by two plexiform layers that have exceptionally high metabolic demands, and neural function depends on the constant availability of oxygen and nutrients. Due to this demand, two vascular beds nourish the retina, each with different anatomy and function. Lying beneath Bruch's membrane is a dense network of highly fenestrated capillaries derived from the posterior ciliary artery that oxygenates the outer retina. The intraretinal vasculature is a terminal artery multilayer capillary network that perfuses the inner retina.[8] One of the most striking complications of diabetes, together with diabetic maculopathy, and which are the main cause of blindness in patients with diabetes, is DR, which is the result of a disorder affecting the retinal microvasculature after prolonged

exposure to high blood glucose levels due to poor long-term control of diabetes.[9-11]

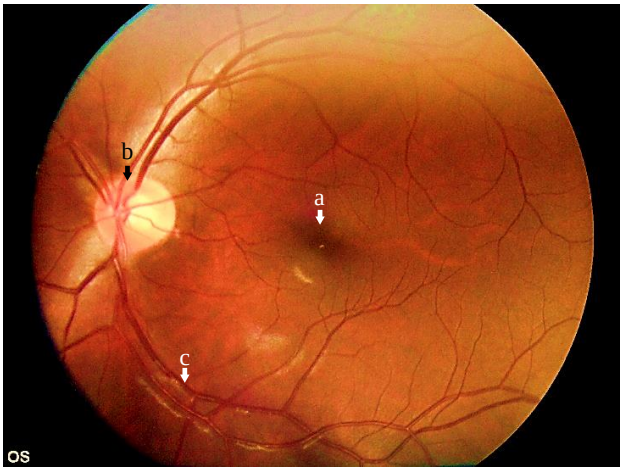

Figure 1. The fundus study shows the anatomy of the retina, a) macula, b) optic nerve, c) blood vessels.[8]

DR is defined as the presence of one or more retinal microaneurysms or hemorrhages with or without serious lesions such as hard or soft exudates, microvascular abnormalities in the retina, venous counts, neovessels, preretinal and/or vitreous hemorrhage, using the standards of Early Treatment DR Study classification.[12-14]

DR is clinically classified into two stages:

- Non-proliferative Diabetic Retinopathy: represents the initial stage, mainly observing an increase in vascular permeability (exudates) and capillary-vascular occlusion of the retina. Various retinal conditions such as microaneurysms, hemorrhages, and hard exudates are seen at this stage and can be detected by fundus examination, although patients may be asymptomatic.
- Proliferative Diabetic Retinopathy: it is the most advanced stage and is characterized by neovascularization. At this stage, patients may experience severe vision impairment when abnormal new vessels burst causing vitreous hemorrhage or when traction causes retinal detachment.[11-13]

As the severity of DR progresses, the lack of capillary perfusion leads to retinal ischemia which, in turn, causes an upregulation of proangiogenic cytokines causing pathological intraretinal and intravitreal neovascularization. Neovascularization occurs at the interface between the perfused and nonperfused retina and is associated with a poor prognosis for visual outcome. These new vessels often grow on the surface of the retina and penetrate the internal limiting membrane into the vitreous humor. These vessels are often fenestrated, brittle, and leaky, which can lead to vitreous hemorrhage. Repeated vitreous hemorrhage is associated with gliosis and fibrovascular scarring.[8]

The most common pathology of vision loss in patients with DR is diabetic macular edema and is characterized by macular thickening, due to the amount of fluid infiltrated and accumulated in the subretinal and intraretinal areas of the macula, caused by the rupture of the blood-retinal barrier.[13, 15]

On the other hand, DR is a major cause of blindness and occurs as a result of long-term cumulative damage to the small blood vessels of the retina. 2.6% of global blindness can be attributed to diabetes.[16] Some authors identified 288 studies of 3,983,541 participants contributing data from 98 countries; mentioning that the number of people affected by blindness due to DR increased between 1990 and 2015 from 0.2 million to 0.4 million and by visual impairment due to DR increased from 1.4 million to 2.6 million. Blindness and vision impairment at all ages in 2015 was due to DR more common in women than in men.[17, 18] Information obtained from the International Agency for the Prevention of Blindness (IAPB) mentions that DR contributes minimally to vision loss in 2020. However, it is the only cause of blindness that showed a global increase in age-standardized prevalence among 1990 and 2020. DR has long been recognized as a microvascular disease. Hyperglycemia is considered to play an important role in the pathogenesis of retinal microvascular damage. Multiple metabolic pathways have been implicated in hyperglycemia-induced vascular damage, including the polyol pathway, accumulation of advanced glycation end products, the protein kinase C pathway, and the hexosamine pathway.[19, 20] The early responses of retinal blood vessels to hyperglycemia are dilation and changes in blood flow, changes that are considered metabolic autoregulation to increase retinal metabolism in subjects with diabetes. Loss of cells from blood vessels is another hallmark of early DR events. Evidence of apoptosis of the cells that form the walls of blood vessels triggered by high glucose levels has been shown in in vitro and in vivo studies. Since blood vessel cells are responsible for providing structural support to capillaries, their loss leads to the formation of localized pockets of capillary walls. This process is associated with the formation of microaneurysms, which is the first clinical sign of DR. In addition to loss of pericytes, endothelial cell apoptosis and basement membrane thickening are also detected during the pathogenesis of DR, which collectively contribute to the impairment of the blood-retinal barrier.[21, 22] The role of inflammation and leukocytosis in DR is well documented and is a key driver of capillary occlusion and hypoxia that ultimately drives vascular endothelial growth factor expression and the attendant distinctive vascular abnormalities that characterize DR. In patients with DR, a significant increase in the expression of systemic proinflammatory cytokines (TNF-α and IL-6) is observed and elevation of retinal chymosin synthesis is also present. Several studies have also reported that the relative expression of these factors correlates with the rate of DR progression, and recent evidence has also implicated the activation of various immune cells with disease onset. The central role of inflammation is the driving of vascular endothelial growth factor secretion.[10] There is growing evidence that retinal neurodegeneration may be an independent pathophysiology of DR. In diabetic patients, thinning of the

inner retina with no or minimal DR (microaneurysms) was detected.[23] The presence of DR means that the microcirculation has already been damaged by diabetes and can therefore be considered a reliable biomarker of the fatal effects of diabetes in a given individual.[24] The diagnosis of DR is made by clinical manifestations of vascular abnormalities in the retina, clinically it is divided into two stages: non-proliferative DR and proliferative DR. Non-proliferative DR represents the early stage of DR, in which increased vascular permeability and capillary occlusion are two main observations in the retinal vasculature. During this stage, retinal pathologies, including microaneurysms, hemorrhages, and hard exudates, can be detected by fundus photography, although patients may be asymptomatic.[25] In addition, there is new evidence suggesting that retinal imaging could be useful in identifying people at risk of cardiovascular disease or cognitive decline, potentially expanding the role of screening for DR beyond prevention of diseases that threaten sight.[26] As health professionals it is our duty to prevent the natural progression and identify retinopathy from early stages, it must be the main objective to fight against this pathology in patients suffering from diabetes. Modern therapies target the later stages of retinopathy and can slow vision loss by temporarily preventing the formation of abnormal retinal vessels. However, they cannot restore damaged neural tissue or restore 100% visual acuity. Retinal damage and the neovascularization process in retinopathy are closely related to the oxidative environment induced by hyperglycemia.[27]

PERIODONTAL DISEASE

PD is a chronic inflammatory pathology of multifactorial origin, whose primary etiological factor is a highly organized bacterial biofilm in an ecological niche favorable for its growth and development; which, with the intervention of additional factors of local and systemic origin, can lead to irreversible damage to the supporting tissues (periodontal ligament, cement and alveolar bone) surrounding the teeth with consequent tooth loss; One of the main determinants of the development and progression of PD is represented by a higher concentration of pathogenic bacteria.[28-30] Its main clinical manifestations include bleeding, dental mobility, gingival recession, periodontal pocket formation, masticatory dysfunction, and loss of dental organs. There is also scientific evidence that links PD with other chronic diseases such as diabetes, chronic obstructive pulmonary disease, cardiovascular disease, cancer, among others. This pathology is considered by the World Health Organization as one of the two main oral health problems worldwide. In addition, the distribution of these chronic diseases shows a strong association with a certain level of vulnerability, since these diseases affect groups with social and economic disadvantages in greater proportion. In addition, several studies relate periodontitis to a negative impact on people's quality of life. This pathology produces different effects on patients including: deterioration, discomfort and inconvenience, limitation in the masticatory function; it also affects appearance, self-esteem and psychosocial well-being.[28, 31] Importantly, recent studies have clearly shown that the harmful effects of PD are not only limited to the oral cavity, but can affect the overall health of an individual.[29] Periodontitis has been associated with several systemic conditions, including adverse pregnancy outcomes, cardiovascular diseases, type II diabetes mellitus, respiratory diseases, mortality from pneumonia in hemodialysis patients, chronic kidney disease, and metabolic syndrome.[32] Non-surgical and surgical periodontal treatment are predictable procedures in terms of infection control, reduction of pocket depth on probing, and achievement of clinical attachment level. Good conventional periodontal treatment consisting of mechanical removal of subgingival biofilm by scaling and root scaling is considered the gold standard non-surgical treatment for periodontitis. Even teeth with extensive periodontal destruction can be preserved and treated.[33] Therefore, conventional periodontal treatment can reduce gingival bleeding on probing in approximately 45% of sites. After non-surgical periodontal treatment, pocket depth reduction on probing was 1-1.3 mm for pockets with an initial depth of 5-6 mm and 2-2.2 mm for pocket depth >7 mm; the clinical attachment level could improve between 0.5 and 2 mm. The type of tooth, the degree of periodontal destruction, local factors, medical history, and the age of the patients tend to be considered; can interfere with the effectiveness of scaling and root scaling. Other pharmacological therapies complementary to scaling and root scaling include amoxicillin and metronidazole that have demonstrated strong scientific evidence for their use in daily clinical practice. Intraosseous and furcation defects can be treated by conservative, resective, or regenerative surgery.[32, 33] Periodontitis is a widespread disease, with the most severe form affecting an estimated 743 million people worldwide in 2010.[34] According to the Epidemiological Surveillance System for Oral Pathologies (SIVEPAB) 2019 in Mexico, the information on the community periodontal index available for 131,903 incident patients of the first level health services from 20 to 99 years of age. It was reported that approximately 59.2% had some sign of PD, 22% had gingivitis, 3.3% had signs of mild PD, and 0.6% had signs of advanced PD.

PERIODONTAL DISEASE AND DIABETIC RETINOPATHY

Experts in the field have identified a relationship between PD and DR. They mention that patients suffering from various stages of PD suffer or are more likely to suffer from DR. Another important aspect is to consider DR as a marker of the patient's general condition, since the presence of proliferative DR indicates that the patient has a higher cardiovascular risk, with an increased rate of acute myocardial infarction, myocardium, amputation and death.[2, 6, 7, 14] In a study by Noma et al. (2004) investigated whether PD correlates with DR. The study was based on a prospective review of 73 eyes in 73 patients with diabetes. Where the severity of PD was significantly correlated with the severity of DR (P=0.0012), and the risk of proliferative DR was significantly higher in the

presence of PD (odds ratio=2.80, P=0.036). There was a significant relationship between the severity of DR and the duration of diabetes (P=0.002). The significant relationship between PD and DR severity was evidenced, but it was not clear if PD directly affects DR progression.[35] The mean duration of type II diabetes was directly correlated with the severity of DR in the study by Amiri et al., who reported a mean duration of diabetes of 10.5 years, the severity of PD was significantly correlated with the severity of DR ($P < 0.011$), and the risk of proliferative DR was significantly higher in the presence of PD ($OR = 2.80$, $P < 0.029$).[4] Another study by Song et al. (2017) in which a sample of 2078 Korean patients with type 2 diabetes was investigated, of whom 358 (17.2%) had DR. A significant difference was observed in the prevalence of DR, according to the number of remaining teeth. In comparison, diabetic patients with teeth ≥25 and patients with teeth ≤4 was more than twice as likely to have DR (12.3% vs 28.6%). In this study he also mentions that his results are in agreement with previous studies that show that there is an association between PD and DR, supporting the hypothesis that diabetes not only acts as a risk factor for PD, but also that conversely, periodontal health status is a risk factor for diabetes-related complications. Consequently, both periodontitis and DR are associated with increased levels of inflammatory markers, and the chronic inflammation associated with periodontitis can lead to systemic endothelial dysfunction, which can compromise the endothelium of the retinal vessels and subsequently lead to the development of DR.[11] A further study conducted by Veena in 2018, involved 200 adult diabetic patients (144 men and 56 women), of whom 151 had DR of varying severity. In the study, the mean duration of type II diabetes was directly correlated with the severity of DR. A statistically significant correlation was found between the severity of DR and the severity of PD ($p < 0.001$).[12] In another study, carried out by Horikawa et al (2020) in a Japanese population, it was shown that the prevalence of DR occurs more frequently in diabetic subjects with PD than in those without (15.1% vs. 7.8%, $P<0.001$). In particular, the difference in DR prevalence between subjects with and without PD was statistically significant even at HbA1c 6.0-6.9% (15.2% vs 7.3%, $P < 0.01$).31

Lindner et al. (2021) conducted a study on the association of periodontitis and diabetic macular edema in various stages of DR, concluding that patients with mild or moderate DR were more likely to have severe periodontal conditions than patients with severe or proliferative DR; 14 patients with mild DR (82.4%), 7 patients with moderate DR (87.5%), 4 patients with severe DR (100.0%) and 15 patients with proliferative DR (93.8%) had some degree of PD. Periodontal inflammation and the percentage of bleeding on probing were significantly higher in patients with early stages of DR than in those with late stages ($p < 0.05$). Therefore, patients with generalized PD required significantly more intravitreal injections in the last year than those with milder stages of periodontitis ($n = 6.9 \pm 3.1$ versus $n = 5.0 \pm 3.5$, $p = 0, 03$).[13]

In another study by Yamamoto et al. (2020), the patients who were recruited were 45 men and 59 women who suffered from diabetes, between October 2016 and August 2018. In this study, through Bayesian network analysis, it was shown that the presence of DR was directly affected by bleeding on probing; indicating the gingival inflammatory conditions caused by PD. Consequently, these results indicate that gingival inflammation in diabetic patients could have affected the development of DR. Based on this study, it can be concluded that the bleeding on probing of subjects with DR was greater than that of subjects without DR. In addition, the gingival inflammation exhibited by bleeding on probing influenced the presence of DR in type 2 diabetes. Therefore, the control of gingival inflammation by treating PD could reduce the development of DR.[1]

CONCLUSION

Based on the bibliography, it can be concluded that DR is a preventable disease if it is detected in early stages, for this reason it is significant to show the importance of detecting this pathology in a timely manner, a poorly controlled diabetes is considered a determining factor for the appearance of the disease. DR, on the other hand, some authors mention that there is a relationship between patients with diabetes who have PD and suffer from retinopathy, knowing risk situations, promoting a culture of prevention and achieving control of PD should be considered an integral part of the strategies of diabetes control, avoiding future complications. The main strategy that the dentist must apply to all patients suffering from periodontal disease and who could potentially suffer from retinopathy is timely referral to health services (ophthalmology and/or endocrinology).

DECLARATION OF INTERESTS

The author declares that the manuscript was written in the absence of commercial or financial relationships that could be interpreted as a potential conflict of interest.

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