glucosa en sangre disminuye la capacidad de activación de los granulocitos. Sugieren que el control glucémico deficiente en pacientes con DMT2 disminuye la capacidad de defensa y remodelación en el tejido periodontal.

CONCLUSIÓN

El incremento de los niveles de HbA1c esta correlacionado con la severidad de la periodontitis y los cambios clínicos periodontales, aunado con problemas microvasculares que se presentan durante el desarrollo de la enfermedad.

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Original research

Lack of glycemic control in type 2 diabetes mellitus increases the severity of periodontitis

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ABSTRACT

Introduction: Periodontitis is one of the main complications of Type 2 Diabetes Mellitus (T2DM), both diseases present a bidirectional relationship in which lack of glycemic control is a determining factor for the development of periodontitis. However, the degree of severity of the lack of glycemic control and periodontitis has not been thoroughly evaluated, for this reason the following raised. **Aim:** To assess the relationship between the lack of glycemic control in T2DM and the severity of periodontitis. **Material and methods:** Female and male patients with T2DM with and without chronic generalized periodontitis from «Dr. Donato G Alarcón» Hospital were included in the study, who gave their signed informed consent. A periodontal examination was performed, recording gingival redness, bleeding, suppuration, probing depth and clinical attachment loss level. Likewise, peripheral venous blood samples were obtained to determine glycated hemoglobin (HbA1c) levels, cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine, and granulocyte count. **Results:** 158 patients with T2DM were included. 42 patients (26%) with periodontal health, 36 (22%) with mild periodontitis, 26 (16%) with moderate periodontitis and 54 (34%) with severe periodontitis. Regarding HbA1c, 26 patients (16%) had good control, 56 (35%) had poor control, and 46 (48%) had a high risk of complications. A significant decrease in gingival redness and an increase in clinical attachment loss levels were observed in patients at high risk of complications. The latter also presented a significant increase in granulocytes. **Discussion:** The uncontrolled and prolonged rise in blood glucose levels has been correlated with several complications, including the development of periodontitis. However, the relationship between its degree of severity and lack of glycemic control has not been evaluated.

Keywords: Periodontis, type 2 diabetes mellitus.

INTRODUCTION

T2DM is considered one of the main causes of death worldwide,[1] the Secretaría de Salud in Mexico establishes it as one of the priority lines of medical care. Some epidemiological reports show that a lack of control of T2DM blood glucose levels increases the risk of presenting comorbidities, increases the number of hospitalizations and disabilities, which affect the life of the individual suffering from this disease.[2-4]

T2DM is a chronic inflammatory disease characterized by endocrine and metabolic alterations, represented by a variable degree of insulin resistance and alterations in the secretion of this hormone, whichprovokes problems in the metabolism of carbohydrates, lipids and proteins necessary for all biological functions.[5,6] The diminished action of insulin triggers an increase in blood glucose levels, activation of alternative pathways for obtaining energy and a biochemical imbalance with important consequences on metabolism. These events drive to the formation of advanced glycation end products (AGEs) and increase the levels of free fatty acids (cholesterol, triglycerides, HDL and LDL), which increases the risk of developing macrovascular complications (heart attacks and embolisms) and microvascular complications (retinopathies, kidney disease and periodontitis).[7] Furthermore, the persistent increase in glucose levels affects the collagen synthesis by fibroblasts and decreases the phagocytic activity of monocytes, leading to a loss of tissue regeneration capacity and increasing recurrent lesions.[8]

Periodontitis is a chronic, infectious and inflammatory disease associated with disbiosis in dental biofilm, causing loss of tooth support tissue. This disease increases the risk of developing

chronic degenerative diseases, such as heart disease and T2DM. It has been shown that there is a bidirectional relationship between periodontitis and T2DM,[9] finding some immunological, microbiological and physiological processes correlated in the feedback of these diseases.[10] According to this, the recurrent lack of glycemic control could increase the risk of developing and increasing the severity of periodontitis in patients with T2DM.[11-13] Therefore, this study aimed to assess the severity of periodontitis of patients with T2DM related to lack of glycemic control.

MATERIAL AND METHODS

Study population

This study was approved by the Committee of Ethics of the Ministry of Health of the State of Guerrero, Mexico, with number 03301117.

A total of 256 cases originating in the State of Guerrero, Mexico, were analyzed during the period of January to May 2018 at the General Hospital «Dr. Donato G Alarcón», Acapulco de Juárez, Guerrero, Mexico.

Criteria inclusion:

- Subjects aged 45-65 years, with chronic generalized periodontitis and without this disease.
- Subjects presenting nutritional control, weekly physical activation and medication by the diabetes clinic.

Criteria exclusion:

- Subjects who did not attend more than 20% of appointments in a period of six months.
- Lactating or pregnant women.
- Subjects who currently smoke and/or who had stopped smoking the last 10 years.
- Subjects using any class of systemic antimicrobial in the three months prior to the evaluation.
- Subjects with any systemic disease in addition to T2DM, which could influence the course or severity of periodontal disease such as: human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), hemophilia, autoimmune diseases.
- Subjects with more than 8 teeth missing.
- Subjects who did not sign the informed consent.
- Subjects who wanted to leave the study at any time.
- Fulfilling the criteria described, the final number of patients included in the study was 158.

Clinical laboratory analysis

Subjects included in the study were analyzed in the state laboratory of public health «Dr. Galo Soberón y Parra» of the Secretaría de Salud del Estado de Guerrero. Every 3 months, studies were performed to determine Glycosylated hemoglobin (HbA1c) levels and every 6 months their levels of cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were measured. The HbA1c value is represented by the average of the intakes corresponding to 3 years and were grouped according to the American Diabetes Association (AAD) criteriain 3 groups: good control (HbA1c $\leq$5.9%), poor control (HBA1c 6.0-7.9%) and risk of complications (HBA1c > 8%).

Periodontal assessment

The clinical evaluation was carried out by means of two calibrated clinicians from the Unidad de Innovación Clínica y Epidemiológica del Estado de Guerrero (UICyEEG), with a Kappa coefficient equal to or greater than 0.85. Six areas in each tooth (mesiobuccal, buccal, distobuccal, distolingual, lingual, mesiolingual) of all teeth were evaluated, excluding third molars.[14] The following variables were recorded: dentobacterial plaque (1/0; detected/not detected); gingival redness (1/0); bleeding on probing (1/0); suppuration (1/0), probing depth, as well as clinical attachment loss levels. Measurements were taken by the same examiner at the same appointment. It was recorded to the nearest millimeter using a North Carolina periodontal probe (Hu-Friedy, Chicago, IL).

Classification of periodontitis

After periodontal examination, each subject was classified with chronic generalized periodontitis according to the AAP criteria, into 3 groups:

- Mild: two or more sites with a pocket depth of > 3 and < 5 mm and with a measurement of 1 to 2 mm clinical attachment loss.
- Moderate: two or more sites with a pocket depth of > 5 and < 4 mm pocket depth and with a measurement of 3 to 4 mm clinical attachment loss.
- Severe: two or more interproximal sites with a pocket depth of > 7 mm and a measurement of > 5 mm clinical attachment loss.

All of the above with a minimum of 30% of affected sites to determine the generalization of the disease.

Periodontal health is determined with less than 3mm pocket depth and attachment loss < 2 mm.

Peripheral blood cell count

A capillary blood sample was obtained, which was spread on a slide and fixed with heat. Then a Wright stain was performed, placing 5 ml of Wright's reagent for 10 min and then 5 ml of distilled water were added for 5 min; then the frotis were washed with bidistilled water until excess dye was removed. The frotis were observed under a light microscope at 100x with immersion oil and the first 100 nucleated cells were counted classifying them into eosinophils, lymphocytes, basophils, monocytes and segmented neutrophils; they were recorded in a cell counter.

Statistical analysis

Data on HbA1c, cholesterol, triglycerides, HDL, LDL, creatinine, granulocyte count, percentage of plaque, gingival redness, bleeding on probing, suppuration depth of probing, and attachment loss levels were analyzed by repeated measures of analysis of variance (ANOVA) followed by Bonferroni test (Prism 5 program, GraphPad Inc., San Diego, USA) values with $p < 0.05$ were considered with statistical significance. Data are presented as the mean ± standard deviation.

RESULTS

One hundred and fifty eight patients diagnosed with and without T2DM, chronic generalized periodontitis were included in the study. After performing a periodontal exploration the data were grouped according to the AAP criteria in 4 groups:

- Periodontal health. 42 individuals representing 26%.
- Mild periodontitis. 36 subjects representing 22%.
- Moderate periodontitis. 26 subjects representing 16%.
- Severe periodontitis. 54 subjects that represented 34%.

The following variables were considered: age, sex, years with T2DM and tooth loss, without finding significant differences between the evaluated groups *(Table 1)*.

HbA1c levels were also evaluated in proportion to periodontal status (periodontal health, mild periodontitis, moderate periodontitis and severe periodontitis) and a significant increase in the percentage of HbA1c was observed in the group of patients with severe periodontitis compared to the health periodontal group *(Figure 1)*.

To determine the relationship between the lack of glycemic control and alterations in levels of free fatty acids in the blood, the data were grouped based on the percentage of HbA1c in three groups: good control (≤ 5.9% HbA1c) with 26 patients representing 16%; poor control (6.0-7.9% HbA1c) with 56 patients representing 35% and high risk of complications (> 8% HbA1c) with 46 patients representing 48% of the study population. A significant increase was found in patients in cholesterol and LDL levels in the high risk of complications group compared to the good control group *(Table 2)*.

In addition, the clinical characteristics of the periodontium were evaluated related to the percentage of glycosylated hemoglobin: good control ≤ 5.9%, poor control 6.0-7.9% and high risk of complications > 8%. A significant decrease in gingival redness ($p < 0.04$) and a significant increase in clinical attachment loss ($p < 0.02$) were observed in patients of high risk of complications group compared with the participants in good control group *(Table 3)*.

High blood glucose levels trigger deteriorating effects on the immune response, it has been revealed that the activity of granulocyte cells decreases in patients with T2DM,exacerbating the inflammatory process and thusfeeding back the inflammatory process of periodontitis. Related to that a peripheral blood granulocyte and lymphocyte count was performed, finding a significant increase in granulocytes in the high risk of complications group (> 8% HbA1c) compared to the good glycemic control group (< 5.9% HbA1c). However, the lymphocytes showed no significant change between the groups *(Figure 2 A and B)*.

DISCUSSION

This study compared and analyzed a sample made up of 158 patients with 2TDM from the «Dr. Donato G Alarcon» Hospital, located in Guerrero, Mexico. Clinical parameters of study population showed an increase in the percentage of patients with severe periodontitis compared to those who had a healthy periodontal status. Similar studies have revealed a positive relationship between T2DM and periodontitis development.[15-17] Likewise, patients with T2DM and good control of blood glucose levels have been described to decrease the risk possibilities for developing periodontitis compared to subjects with poor glycemic control.[18,19] However, as periodontitis is a multifactorial disease, the presence of periodontal pathogenic bacteria and subject's immunological response play an extremely important role in the

development of this disease. Our results show a positive correlation between the increase in high levels of HbA1c and the severity of chronic generalized periodontal disease.

The persistent increase in blood glucose levels in patients with T2DM triggers immunological, biochemical, physiological and psychological complications.[20-23] These complications initially generated by a process of insulin resistance, activate alternate pathways to obtain energy such as beta-oxidation of fatty acids, among others. These alterations generate changes in the standard concentrations of some biomolecules such as cholesterol and LDL[24,25] whichare linked to cardiovascular problems, finding a positive relationship between these two molecules and HbA1c levels.[26-28] In the results obtained, a positive correlation was observed between lack of control and high cholesterol and LDL levels, suggesting that poor control of blood glucose levels increases the risk of developing microvascular complications in diabetic patients.

Among the microvascular complications of T2DM is periodontitis, which is a chronic and inflammatory disease that affects the supporting tissues of the tooth.[29,30] Periodontitis can be modified in its evolution and severity by factors such as diet, harmful habits and systemic disease.[31] Likewise, a lack of glycemic in T2DM can change the etiopathology of periodontitis.[11]

The data obtained show an increase in the HbA1c percentages related to the severity of periodontitis, suggesting a close relationship between both diseases. In this way, periodontal clinical parameters were evaluated in relation to glycemic control, finding a decrease in the percentage of gingival redness and an increase in attachment loss level in high risk of complications group, compared to those with good glycemic control. These data suggest that high blood glucose levels generate a microvascular problem in the periodontium, impairing the capacity for regeneration, which leads to the development of periodontal disease.

Uncontrolled blood glucose has shown impairment of host defenses, including decreased activity and mobilization of granulocyte leukocytes, chemotaxis, phagocytic activity, and increased oxidative stress, affecting the metabolic, genetic, and hemodynamic system, and increases advanced glycation end products.[28,32,33] Finding that the number of granulocytes in the blood in individuals at risk of developing complications. This suggests to us that the inflammatory process generated by high HbA1c levels is favoring the increase of these cells to exacerbate the immune response. However, studies have shown that increased blood glucose levels decrease the activation capacity of granulocytes and suggest that poor glycemic control in T2DM patients decreases defense and remodeling capacity in periodontal tissue.

CONCLUSION

The increase in HbA1c levels is correlated with the severity of periodontitis and periodontal clinical changes coupled with microvascular problems that occur during the development of the disease.

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