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Serum Immunoglobulin Levels in Type 2 Diabetes Patients with Chronic Periodontitis

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Abstract

Aim: The association between diabetes and periodontal disease has been well documented. Periodontitis is associated with alterations in immune responses in both diabetic and nondiabetic subjects. While diabetes is considered to be a risk factor for periodontal disease progression, few studies have demonstrated an association between the level of glycemic control and periodontal disease. Although poor glycemic control is significantly associated with poor periodontal health, few studies have been performed in Saudi Arabia to evaluate the immune responses in poor and better glycemic control and its effect on periodontal tissue. The aim of this study is to assess serum immunoglobulin levels (IgA, IgG, IgM) in type 2 diabetic (poor control and better control) and nondiabetic subjects with chronic periodontitis.

Methods and Materials: A total of 105 female patients were included in the study and they were divided into three groups, with 35 patients in each group. Group 1 was comprised of cases of diabetes exhibiting better control (HbA1c≤9%) and Group 2 was comprised of cases of diabetes exhibiting poorer control (HbA1c>9%). The third group was comprised of nondiabetic subjects with chronic periodontitis. In this study, clinical examination included plaque index, bleeding on probing, probing pocket depth, and attachment level (measured in all three groups). Serum immunoglobulin (IgA, IgG, IgM) levels were estimated and compared to the levels estimated for diabetic controls.

Results: Mean plaque index, bleeding index, and probing pocket depth showed no significant differences among the three groups. However, mean clinical attachment loss was significantly higher for Group 2 as compared to Groups 1 and 3. IgA and IgG levels were found to be significantly higher in Group 2 (poorly controlled diabetes) as compared to Group 1 (better control) and Group 3 (control group).

There is a positive correlation between CAL and IgA and IgG, whereas there is a negative correlation between CAL and IgM.

Conclusion: The present study indicates that poor glycemic control may be associated with the increase in IgA and IgG serum antibodies. Elevated antibody levels may explain why poorly controlled diabetes exacerbates periodontal disease.

Clinical Significance: These findings demonstrate the importance of the immune system as well as good glycemic control, especially in patients diagnosed with periodontitis. The changes observed in immune response may be the cause or the effect of periodontal disease in diabetic patients. The increased incidence of periodontitis in diabetic patients suggests that the alteration in immune response may contribute to the pathogenesis of periodontitis in patients with poorly controlled diabetes.

Keywords: Immunoglobulins, diabetes mellitus, periodontitis

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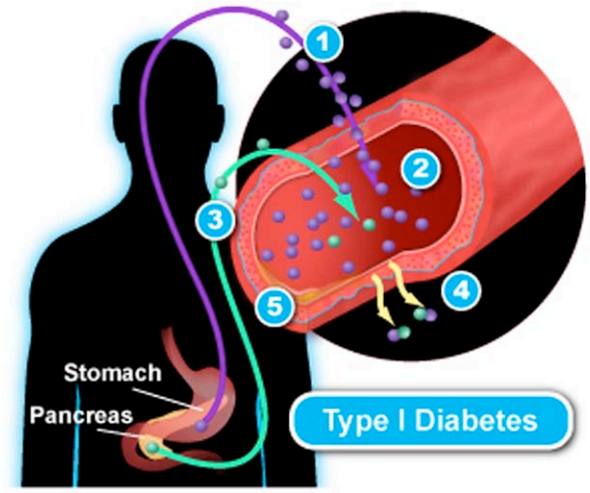
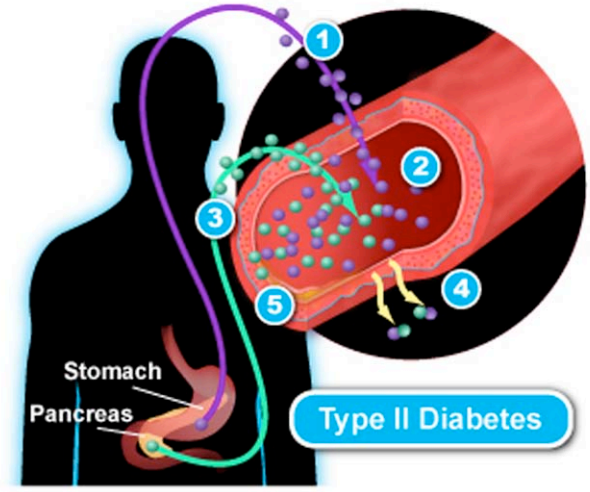


1) Stomach turns food into glucose
2) Glucose enters bloodstream
3) Pancreas produces little or no insulin
4) Glucose unable to enter bloodstream effectively
5) Glucose levels build in bloodstream



1) Stomach turns food into glucose
2) Glucose enters bloodstream
3) Pancreas produces sufficient insulin but body does not process properly
4) Glucose unable to enter bloodstream effectively
5) Glucose levels build in bloodstream

Introduction

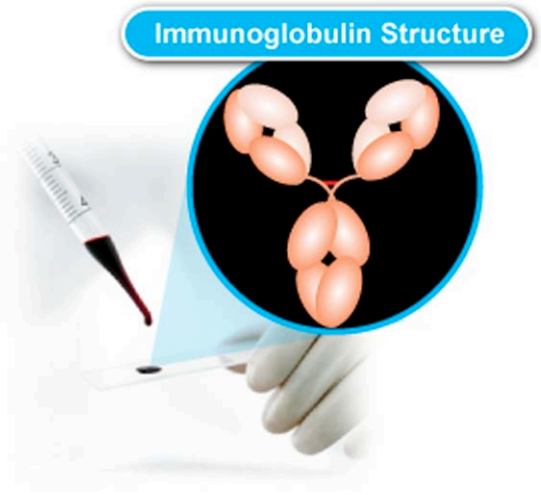
Periodontitis, one of the most common diseases of humans, is an infectious condition that can result in the inflammatory destruction of periodontal ligaments and alveolar bone.[1,2] A number of epidemiological studies have reported that the prevalence, severity, and extent of periodontal disease are greater in patients with diabetes mellitus (DM) than in nondiabetic controls.[3,4]

Diabetes mellitus is a multifactorial group of disorders characterized by abnormalities in glucose metabolism.[5] The two most common forms are type I diabetes, formerly called insulin-dependent diabetes (IDDM), and type 2 diabetes, previously known as non-insulin-dependent diabetes (NIDDM).[6]

The association between diabetes and periodontal diseases has been well documented.[1,2] It has been assumed that this association is due to the fact that diabetic patients have a compromised ability to respond to infectious challenges that predisposes them to bacterial infections such as periodontal disease.[7]

Epidemiological studies have found periodontal attachment loss to be more prevalent in subjects with either type 1 or type 2 diabetics, as compared to nondiabetic subjects.[8] Diabetes mellitus incurs an increased risk of periodontitis.[9] Rees[10] concluded that there is a direct relationship between diabetes and periodontal disease.

Although diabetes is not involved in the pathogenesis of periodontal disease, vascular and cellular changes associated with it provide an environment susceptible to attachment loss and compromised cellular immunity. Studies of the immunologic response in diabetics have elucidated



the etiology of severe periodontal disease observed in these patients. These studies propose that the increased sensitivity of diabetics to periodontal disease may be due to abnormalities in polymorph nuclear neutrophil (PMN) function,[11] changes in neutrophil activation and adherence, and defects in neutrophil chemotaxis. The alteration in neutrophil chemotaxis seems to affect probing depth measurements.[12] Therefore, diabetic patients are abnormally susceptible to infection and frequently present with severe periodontal disease.[13,14]

Immune mechanisms play an important role in the initiation and progression of periodontal disease. Previous studies have shown alterations to immune cell function and modified serum and gingival crevicular fluid inflammatory cytokine profiles in diabetic patients with periodontitis.[15,16] A recent study showed significantly elevated immunoglobulin levels in the gingival tissue of controlled type 2 diabetic patients with periodontitis.[17]

Findings from one longitudinal study indicated that poorly controlled diabetes results in more severe disease than does well-controlled diabetes.[18] Furthermore, there is a relationship between the severity of periodontitis at baseline examination and poor glycemic control at follow-up visits.[18]

Periodontal status and healing also are associated with the patient's level of control of his or her diabetes.[19] Metabolic control is assessed by plasma level and glycated hemoglobulin levels (HbA1c). The HbA1c score is a method used to indicate the level of metabolic control over the previous three months. Considering long-term rather than short-term control facilitates a more accurate assessment of periodontal disease among diabetic patients.

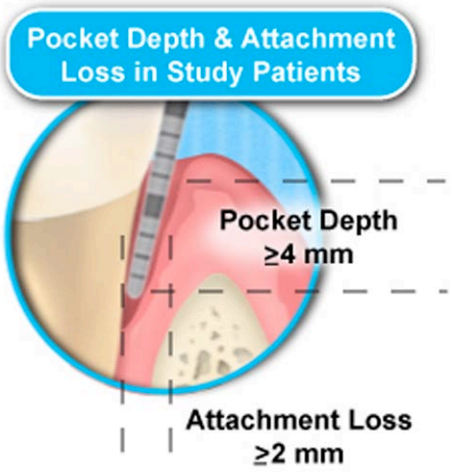
In Saudi Arabia, the prevalence of diabetes mellitus is about 2.55 percent among males and 5.32 percent among females.[20] El-Hazmi et al.[21] reported the prevalence of type I and type 2 diabetes in the male population to be 0.23 percent and 5.63% percent, respectively, and 0.30 percent and 4.53 percent, respectively, in the female population.

Few studies have been carried out in Saudi Arabia to estimate the serum levels of immunoglobulin in poorly controlled as compared to better-controlled type 2 diabetic patients and in nondiabetic subjects with periodontitis.

The aim of the study was to compare the serum immunoglobulin levels (IgA, IgG, and IgM) of diabetic patients with nondiabetic subjects, all of whom were diagnosed with chronic periodontitis.

Methods and Materials

Female diabetic patients were recruited from the Diabetic Centre attached to King Abdulaziz Hospital, Riyadh, Saudi Arabia. Nondiabetic patients were selected from among patients attending the periodontal clinic at the dental college. Seventy diabetic and 35 nondiabetic patients (aged 35–70) with chronic periodontitis were included in the study. The diabetic patients (70) were divided in two groups (n=35 each). Group 1 consisted of better-controlled diabetics with HbA1c≤9%, while patients in Group 2 were



poorly controlled diabetics with HbA1c>9%. The 35 nondiabetic patients (Group 3) served as a control group.

The periodontal status of the test patients (Groups 1 and 2) and control subjects was assessed according to the American Academy of Periodontology. To be accepted for participation in the study, patients had to be diagnosed as having clinical attachment loss of ≥2 mm and pocket depth ≥4 mm in each quadrant of the their mouth. The study was approved by the College of Dentistry Research Center and Ethics Committee. Informed consent was obtained from every patient enrolled in the study. Participants were screened clinically, biochemically, and biophysically to exclude individuals with systemic illness. Those patients selected for participation (1) had at least 20 permanent teeth; (2) were not pregnant; (3) lacked dental caries; (4) had no history of salivary gland infection, rheumatoid arthritis, allergy, or autoimmune disorders; and (5) had not received periodontal treatment and/or antibiotic therapy within the preceding three months.

Diabetes status and degree of glycemic control were assessed by laboratory assays for fasting plasma glucose and HbA1c, respectively. Subjects with fasting plasma glucose >126 mg/dL were classified as having diabetes.

Clinical Periodontal Examination

A medical history was obtained via written questionnaire and interview. Each patient received a complete examination of extraoral and intraoral full-mouth clinical parameters, and the number of teeth present (excluding the third molars) was documented.

The examination sets and clinical measurements were taken by a single calibrated examiner. However, calibration exercises for probing measurements were first performed on five patients before the actual study began.

The following periodontal variables were recorded in a randomized half-mouth examination (third molars excluded) at four sites on each tooth (mesio-buccal, mid-buccal, disto-buccal, and mid-lingual).

For each tooth, the following parameters were recorded: plaque index (PI), as described by

O'Leary et al.[22] bleeding on probing (BOP);[23] periodontal probing depth (PPD); and clinical attachment level (CAL). These parameters were measured at the mesial, distal, buccal, and lingual aspects for each tooth.

Serum Collection and Estimation of Immunoglobulin

Ten milliliters of venous blood sample were collected from each patient by venipuncture in the antecubital fossa without excessive venous stasis. The blood samples were collected using EDTA-containing vacuum tubes. The samples were centrifuged at 3000 rpm for 10 min to separate the plasma. The plasma samples obtained were transferred to plastic vials and stored at -20°C for the immunoglobulin estimations. Estimations of total serum immunoglobulin (IgA, IgG, and IgM) were quantitatively determined with the help of immunoturbidimetry. This method is based on assessing the immunoprecipitation reaction by measuring the intensity of transmitted light with the help of immunoturbidimetric methods.

REFERENCE RANGE:
IgM: 40–230 mg/dl
IgA: 70–400 mg/dl
IgG: 700–1600 mg/dl

Data Analysis and Statistical Methods

The data were analyzed using SPSS software, version 10 (SPSS Inc., Chicago, Illinois, USA), to calculate the means and standard deviations for age, duration of disease, number of teeth, PI, BOP, PPD, CAL, and serum antibody levels (IgA, IgG, and IgM) for patients in each of the three groups.

Differences among the three groups for all variables were determined with one-way analysis

of variance (ANOVA). When the overall ANOVA showed statistical significance, Tukey-Kramer multiple comparison tests were performed to identify any differences between the groups. An unpaired Student's t-test was used to test the significance of the differences between group means for PPD and CAL. A forward, stepwise multiple regression analysis was used to assess the relationship between periodontitis and diabetic status (glycemic control).

Pearson coefficient correlation (r) was used to assess the strength of association between the clinical variables and the serum antibody levels, with a two-tailed p-value of 0.05 used as a threshold for significance.

The results were tabulated and analyzed statistically for significance: *p*-values of <0.05 were considered statistically significant. Graph Pad Instate version 3.00 software (Graph Pad Software, San Diego, California, USA, www.graphpad.com) was used for analysis of the results.

Results

The mean age of the patients and the duration of disease were similar in all diabetic patients. The number of remaining teeth in half of the mouth decreased from 13.4±1.2 in the control patients (Group 3) to 12.8±1.7 in the poorly controlled diabetic patients (Group 2), although the difference between group means was not statistically significant (Table 1).

Periodontal Observation

The plaque index mean and standard deviation for each group are reported in Table 2. The results showed that there was no significant difference among the three groups.

The mean bleeding indexes were 0.421 ± 0.44 for Group 1, 0.459 ± 0.42 for Group 2, and 0.443 ± 0.44 for the control group (Group 3). The *p*-value did not vary significantly among the three groups (Table 3). The mean periodontal pocket depth for

Table 1. Mean ± SD for age, duration, and number of teeth.

	Group 1 (better-controlled) Mean ± SD N=35	Group 2 (poor-controlled) Mean ± SD N=35	Group 3 (control) Mean ± SD N=35
Age (years)	46.32 ± 7.1	48.18 ± 7.9	45.66 ± 8.6
Duration (years)	6.7 ± 2.4	7.1 ± 1.9	
Number of teeth	13.2 ± 0.9	12.8 ± 1.7	13.4 ± 1.2

Table 2. The plaque index mean and standard deviation.

Periodontal Parameter	Group 1 (better-controlled) Mean ± SD	Group 2 (poor-controlled) Mean ± SD	Group 3 (control) Mean ± SD
Plaque Index	0.520 ± 0.379	0.534 ± 0.423	0.361 ± 0.401
Bleeding Index	0.421 ± 0.44	0.459 ± 0.42	0.443 ± 0.44

Table 3. Bleeding index, mean and standard deviation.

Group 1 (better-controlled) Mean ± SD	Group 2 (poor-controlled) Mean ± SD	Group 3 (control) Mean ± SD
0.421 ± 0.44	0.459 ± 0.42	0.443 ± 0.44

Table 4. Periodontal pocket depth.

Group 1 (better-controlled) Mean ± SD	Group 2 (poor-controlled) Mean ± SD	Group 3 (control) Mean ± SD
4.492 ± 1.81	4.53 ± 1.99	4.32 ± 1.71

Table 5. Attachment level.

Group 1 (better-controlled) Mean ± SD	Group 2 (poor-controlled) Mean ± SD	Group 3 (control) Mean ± SD
5.35 ± 1.82	7.27 ± 1.87*	4.80 ± 1.91
*Significantly different from Group 1 and Group 3 (p<0.05).		

Table 6. Significance (p-values) within groups.

Group 1 vs.	Group 2	0.47*
	Group 3	0.75
Group 2 vs.	Group 1	0.47*
	Group 3	0.005*
*Group 2 is significantly different from Group 1 and Group 3 (p<0.05).		

Table 7. Serum antibody levels of IgA, IgG, and IgM in Group 1 (better control), Group 2 (poor control), and Group 3 (nondiabetic patients with periodontitis).

Group (n=35) In each group	IgA	IgG	IgM
Group 1	384.68 ± 135.7	1352.978 ± 110.6	103.358 ± 42.1
Group 2	508.748 ± 130.3*	1745.198 ± 361.3*	59.96 ± 35.5†
Group 3	387.978 ± 87.8	1364.978 ± -100.7	104.778 ± -30.1
*Group 2 is significantly higher than Group 1 and Group 3 (p<0.001). †Group 2 is significantly lower than Group 1 and Group 3 (p<0.001).			

the various groups was 4.49 ± 1.81, 4.53 ± 1.99, and 4.32 ± 1.71 for Group 1, Group 2, and Group 3, respectively (Table 4). There was no significant difference among the three groups.

The mean CAL was significantly higher in Group 2 as compared to Groups 1 and 3 (Table 5). A statistically significant difference existed between Group 2 and Group 3, as well as a statistically significant difference between Group 1 and Group 2 (p-value<0.05), as seen in Table 6.

Immunoglobulin Levels (IgA, IgG, and IgM)

The mean concentrations of IgA, IgG, and IgM are presented in Table 7. The IgA and IgG levels were found to be significantly higher in Group 2 (poorly controlled diabetics) as compared to Group 1 (better-controlled diabetics) and Group 3 (control group).

The IgA levels were 384.68 mg/dl, 508.748 mg/dl, and 387.978 mg/dl in Groups 1, 2, and 3,

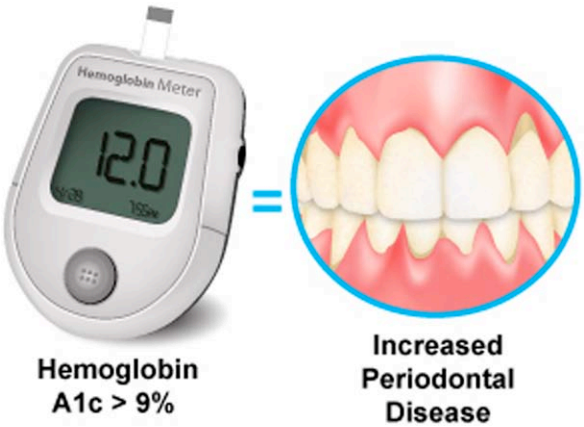
Table 8. Correlations between serum antibody levels of IgA, IgG, and IgM and clinical attachment level in Group 2 (poorly controlled diabetics).

Variable	IgA		IgG		IgM	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
CAL	0.45	0.006*	0.48	0.003*	-0.6	0.000**

*$p<0.01$
**$p<0.001$

respectively.The IgG levels were 1352.978 mg/dl, 1745.198 mg/dl, and 1364.978 mg/dl in Groups 1, 2, and 3, respectively. The IgM levels were significantly lower in Group 2 (59.96 mg/dl) as compared to Group 1 (103.358 mg/dl) and Group 3 (104.778 mg/dl) ($p<001$).

Table 8 shows a positive correlation between CAL and IgA and IgG, whereas no correlation was noted between CAL and IgM.



Discussion

This study provides evidence for an association between glycemic control and the increased severity of periodontal disease. Based on the findings reported by McCance et al.,[24] we used the level of glycemic control represented by HbA1c>9% as a cut-off point between poorly controlled diabetics and those patients with better-controlled diabetes.

Periodontal disease is a frequent complication of diabetes, and diabetic subjects often exhibit decreased immune response with increased susceptibility to infection.[15] The initial histological picture of the inflamed gingiva is characteristic of a local inflammatory reaction involving polymorphic nuclear leukocytes, vasculitis, and localized tissue loss. Subsequent changes in periodontal disease (mild gingivitis) show histological evidence of the involvement of the immune response in the initial accumulation of macrophages and lymphocytes devoid of surface-staining immunoglobulin.[25] As the disease progresses, a predominance of surface- and cytoplasmic-staining lymphocytes and plasma cells are observed (severe gingivitis and periodontitis).

Plaque index, bleeding index, and periodontal pocket depth showed no significant difference across the groups while loss of attachment varied significantly between Group 1 and Group 2 and between Group 2 and Group 3 (p-value<0.05). This finding is in agreement with Cutler et al.,[8] who found that periodontal attachment loss is more prevalent in subjects with either type 1 or type 2 diabetes mellitus, as compared to nondiabetic subjects. It is also in agreement with Novaes et al.[26] and Tsai et al.[18] These studies support the association between poorly controlled type 2 diabetes and severe periodontitis.

Estimation of total immunoglobulin (IgA, IgG, and IgM) showed that there was a significant difference between Groups 1 and 3 (p-value<0.001). We observed a higher level of IgG and IgA in Group 2 (poorly controlled diabetics) as compared to Group 1 (better-controlled diabetics) and Group 3 (control).

Patients with diabetes are often suspected of having antibody deficiency diseases. A reasonable strategy for screening those patients with suspected antibody deficiency would be to evaluate their total antibody levels by measuring IgA, IgG, and IgM. In the present study, total serum IgA and IgG antibodies were significantly increased in Group 2 when compared to Groups 1 and 3 (p-value<0.001), whereas the IgM antibody level was decreased in Group 2 when compared to Groups 1 and 3.

Immunoglobulin response is subject to immune regulation, which is considered to have a strong genetic component. It may be necessary to evaluate the immunoglobulin response to periodontium-specific antigens. Whether increased levels of immunoglobulin and the concurrent loss of collagen and resorption of alveolar bone seen in diabetic patients with periodontitis are indicative of a direct cause-and-effect relationship is still under debate. Further studies are needed to ascertain the exact role played by immunologic factors in type 2 diabetic patients with periodontal disease.

It is known that diabetes mellitus alters the resistance of periodontal tissues and makes them prone to invasion by microorganisms.[16] The relationship between diabetes mellitus and periodontitis has been studied extensively, with contradictory results.[2] In the present study, elevated serum levels of IgG were observed in both the diabetic and nondiabetic patients, although values were close to the high upper limit of the normal range. Notably, the elevation of IgG was more pronounced and significant in the poorly controlled diabetic patients with periodontitis (Group 2) than in the nondiabetic patients (Group 3) and the better-controlled type 2 diabetic patients (Group 1). This finding is in agreement with the observations of Zambon et al.[27] This elevation in serum IgG may be due to increased antibody production designed to neutralize bacterial toxins.

Significantly high levels of serum immunoglobulin and complement have been reported in type 2 diabetes patients with periodontitis.[28] Fontana et al.[15] reported similar findings. In the present study, the concentrations of IgA and IgG in the serum of diabetic patients (Group 1 and Group 2) were found to be significantly increased as compared to the concentrations of the same parameters in control subjects. Even though there was an elevation in the levels of immunoglobulins in Group 1 diabetic subjects, this difference was not significant. However, tissue alterations caused by diabetes may create an environment that is less resistant to invasion by microorganisms.[29]

In this study, only patients with type 2 diabetes were selected. It was observed that serum IgA values were elevated in both groups of diabetic patients with periodontitis. The elevation in serum IgA observed in poorly controlled diabetic patients was significantly higher than in the better-controlled diabetics (Group 1) and nondiabetic control patients with periodontitis. This finding is in agreement with results reported by Ranney et al.[30] and Lai et al.,[31] who observed elevated levels of IgA in patients with periodontitis. In fact, the increased IgA content in the inflamed gingiva may be the reason for the apparent rise in serum IgA.[32] Bachrach et al.[33] also found that patients with periodontitis, regardless of their diabetic condition, expressed increased levels of total IgA in both whole and parotid saliva. However, the situation is changing in the case of diabetes, according to Anil,[17] who stated that IgG and IgA levels in periodontitis patients, both diabetic and nondiabetic subjects, were found to be significantly higher than those of healthy subjects. Significantly higher IgG and IgA levels were found in the diabetic group compared to the nondiabetic group with periodontitis.[17] Anil[17] concluded that these findings support the concept that the humoral immune response plays an important role in the pathogenesis of periodontal disease in diabetics. This elevation in IgG and IgA is significant, and perhaps the higher levels of immunoglobulin in the gingival tissues could be a protective mechanism against the increased bacterial challenge in diabetic subjects.

Conclusion

The results of this study revealed that periodontitis is associated with alterations in immune responses in both diabetic and nondiabetic subjects. Humoral immune responses are markedly altered in patients with poorly controlled diabetes (HbA1c>9%) with periodontitis. Furthermore, the mean CAL was significantly higher for Group 2 (patients with poorly controlled diabetes). IgA and IgG levels were found to be significantly higher in Group 2 as compared to Group 1 (patients with better-controlled diabetes) and Group 3 (control group). Additionally, poor glycemic control may be associated with the increase in IgG and IgA serum antibodies. Elevated antibody levels may explain why poorly controlled diabetes exacerbates periodontal disease.

Therefore, this study supports the importance of controlling the hemoglobin level. The observed changes in immune responses may be the cause or the effect of periodontal disease in diabetic patients. The increased incidence of periodontitis in diabetics suggests that the alteration in immune

response may be one of the factors contributing to the pathogenesis of periodontitis in cases of poorly controlled diabetes.

Clinical Significance

These findings demonstrate the importance of the immune system as well as good glycemic control, especially in patients diagnosed with periodontitis. The changes observed in immune response may be the cause or the effect of periodontal disease in diabetic patients. The increased incidence of periodontitis in diabetic patients suggests that the alteration in immune response may contribute to the pathogenesis of periodontitis in patients with poorly controlled diabetes.

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