Original Article

Association of Serum Interleukin-10 Level with Glycemic Status to Predict Glycemic Alteration with Periodontitis: A Cross-Sectional, Observational Study

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Abstract

Background and Aim: Studies showed bidirectional relationship between chronic periodontitis (CPD) and diabetes. This study was conducted to estimate the levels of serum interleukin (IL)-10 in patients with CPD and type 2 diabetes mellitus (T2DM) to evaluate the association of serum IL-10 levels with glycemic status and to evaluate the influence of periodontal inflammation on glycemic control. **Setting and Design:** A cross-sectional observational study. **Materials and Methods:** Eighty patients were divided into four groups consisting of 20 patients in each group. Group 1: healthy control, Group 2: T2DM without chronic periodontitis, Group 3: chronic periodontitis only (CPD), and Group 4: T2DM with chronic periodontitis (CPD). Plaque index, gingival index, pocket probing depth, clinical attachment loss, random blood sugar, and glycated hemoglobin (HbA1c) level were recorded for categorizing patients into aforestated groups. Serum IL-10 level was measured by ELISA kit. **Statistical Analysis Used:** ANOVA statistics and *post hoc Tukey's* test were performed for comparing individual groups. **Results:** IL-10 was detected lowest in Group 3 followed by Group 4. Highest level of IL-10 was found in the healthy group then in Group 2. **Conclusion:** IL-10 levels have an inverse relationship with HbA1c. Lowest level of IL-10 in CPD dictates periodontal inflammation itself influences in regulating serum IL-10 level and poor glycemic control. Serum IL-10 level may be one of the predictors of glycemia.

Keywords: *Chronic periodontitis, diabetes mellitus, glycated hemoglobin, interleukin-10*

Introduction

Periodontitis is an inflammation of teeth-supporting tissues caused by specific microorganisms resulting progressive destruction of alveolar bone with pocket formation or both.[1] Several modifiable factors such as smoking, poor oral hygiene, female hormonal changes, diabetes mellitus, stress, and certain medications along with nonmodifiable factors such as age, and hereditary factors may lead to periodontal disease.[2] Among these, diabetes is a chronic metabolic disease characterized by chronic hyperglycemic state or elevated blood glucose with disturbances of carbohydrate, fat, and protein metabolism.

Authors suggest "two-way" relationship between diabetes and periodontitis that not only diabetes is a risk factor for periodontitis, but periodontitis may also influence on glycemic control.[3]

Periodontitis is associated with increased systemic inflammatory markers such as cytokines which play an important role in pathogenesis and progression of the disease. The host inflammatory response to periodontal microorganism is mediated by B and T lymphocytes, monocyte, and neutrophil which are triggered to produce inflammatory mediators such as cytokines, chemokines, arachidonic acid metabolites, and proteolytic enzymes.[4] That's why cytokines in serum, plasma, gingival crevicular fluid (GCF), and saliva can be used as biomarkers of chronic periodontitis or identified as inflammatory indicators of periodontal disease.[5] Further on, diabetes negatively affects periodontal structure. Bacterial toxins, endotoxins, cell membrane products challenge host, activates an inflammatory cascade with synthesis of some inflammatory mediators including cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1 β.

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The balance between the pro-inflammatory and anti-inflammatory cytokines balances between disease progression and health. The prolonged and excessive production of pro-inflammatory cytokine and other mediators leads to inflammation and clinical signs of periodontitis and diabetes. IL-10 is a pleiotropic cytokine with its immunosuppressive properties. It suppresses tissue destruction by its dual role, suppressing immunoinflammatory responses as well as B-cell activation. IL-10 has strong deactivating properties on the inflammatory host response mediated by macrophages and lymphocytes and potently inhibits the production of pro-inflammatory cytokines such as IL-6 and TNF-α.[6] Therefore, several authors suggested that apart from regulating the duration and extent of inflammatory response of periodontitis, IL-10 may play an important role in maintaining glycemic status.[7]

We, therefore, propose low IL-10 production capacity is associated with periodontitis and type 2 diabetes mellitus (T2DM). Again, study showed severe periodontitis at baseline was associated with increased risk of poor glycemic control (glycated hemoglobin [HbA1c] >9.0%) at minimum 2-year follow-up suggesting periodontitis as a risk factor for developing chronic hyperglycemic state. As there is bidirectional relationship between diabetes and periodontitis and low level of IL-10 has been suggested by various authors in diabetic and periodontitis patients, we conducted the study to estimate serum IL-10 and its association with glycemic status in T2DM and chronic periodontitis and to evaluate the influence of periodontal inflammatory state on glycemic status.

Materials and Methods

The present study was conducted in the Department of Periodontology in Lucknow, India. An ethical clearance (CPGIDSH/22/38 dated January 15, 2022) was obtained from the institutional ethical committee conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. An informed written consent was obtained from all participants. A total of 80 participants (49 males and 31 females) were included in the study. The inclusion criteria were patients with age range between 25 and 60 years and the presence of at least 20 natural teeth. Patients with probing pocket depth ≥5 mm found in minimum four teeth and clinical attachment loss (CAL) ≥2 mm, presence of bleeding on probing (BoP), and radiographic evidence of bone loss defined chronic periodontitis. The glycemic status of patients who gave a history of T2DM was confirmed by random blood sugar (RBS) level >180 mg/dL and HbA1c ≥6.5% with no major diabetic complications.

Patient who requires prophylactic antibiotics before dental treatment; any medication that increases risk of bleeding; any other systemic disorder that could compromise safe participation; patients that underwent antibiotic treatment in the last 6 months; patients on immunosuppressants; pregnant women and lactating mothers; smokers (≥10 cigarettes/day), alcoholics, and chewing tobacco users; and individual with body mass index (BMI) >30 were excluded from the study. Dental and medical history were recorded for categorization of the participants into four groups. A single examiner conducted the intraoral examination. Plaque index (PI), pocket probing depth (PPD), CAL, BoP, BMI, HbA1c levels (measured by – Variant II Turbo, Bio-Rad, USA), and RBS levels were recorded. The selected participants were then divided into four groups of 20 each: Group 1 (healthy control) included nondiabetic and systemically and periodontally healthy individuals; Group 2 (T2DM) were type 2 diabetic without chronic periodontitis; Group 3 (CPD) were nondiabetic and systemically healthy and diagnosed with periodontal disease; and Group 4 (T2DM+CPD) were diagnosed with type 2 diabetes with periodontal disease. Blood samples were collected from each participant and were allowed to clot for serum extraction. Patient's serum was then stored in −70°C until samples from all participants were collected. Serum IL-10 level was then estimated by commercially available ELISA *kit* (Diaclone, France).

Statistical analysis

D'Agostino and Pearson test was performed to check the normality of the distribution of variables. As all the data were distributed normally, one-way ANOVA was performed for comparing all four groups. For comparing individual groups, *post hoc Tukey's* test was performed. $P < 0.05$ will be considered statistically significant. Statistical analysis was performed using SPSS software (Windows, Version 26.0. Armonk, NY:IBM Corp).

Results

The mean values of all the variables of the four groups were expressed as mean ± standard deviation [Table 1] and consolidated pairwise comparison (*P* Value) between the four groups for PI, gingival index (GI), PPD, CAL, HbA1c, RBS, and IL-10 ($P < 0.05$) expressed in Table 2. Intergroup comparisons (*P* Value) between the four groups for PI, GI, PPD, CAL, HbA1c, RBS, and IL-10 ($P < 0.05$) are summarized in Table 2. There is no statistically significant difference ($P > 0.05$) in probing pocket depth and attachment loss in between healthy groups (Group 1 and Group 2) and in between periodontally compromised groups (Group 3 and Group 4). Statistically significant difference was observed in HbA1c levels between Group 1 and Group 2 and between Group 1 and Group 4.

IL-10 was detected (pg/mL) in all the four groups, highest (182.99 ± 75.93) in Group 1 and lowest (83.41 ± 51.81) in Group 3. Group 2 and Group 4 had 123.30 ± 72.87 and 90.84 ± 45.93, respectively. The difference in IL-10 level between Group 1 and other groups is statistically significant. Group 3 and Group 4 have lower

Table 1: Mean±standard deviation values of plaque index, gingival index, clinical attachment loss, glycosylated hemoglobin %, random blood sugar, and interleukin-10 in four groups

Group	PI	GI	PPD	CAL	HbA1c %	RBS	IL-10 level
1	0.88±0.18	0.83±0.20	2.23±0.13	0	5.44±0.47	120.10±17.80	182.99±75.94
2	1.22±0.32	1.08±0.25	2.27±0.17	0	7.20±0.69	202.35±18.75	123.30±72.87
3	2.00±0.27	1.91±0.31	5.04±0.80	6.33±1.71	5.25±0.48	122.45±16.56	83.42±51.81
4	2.18±0.35	2.31±0.32	4.86±0.70	5.62±1.64	7.94±1.10	222.55±44.10	90.84±45.94

PI: Plaque index; GI: Gingival index; PPD: Probing pocket depth; BoP: Bleeding on probing; CAL: Clinical attachment loss; HbA1c: Glycosylated hemoglobin; RBS: Random blood sugar; IL-10: Interleukin-10

Table 2: Consolidated pairwise comparison (*P*) between the four groups for plaque index, gingival index, probing pocket depth, clinical attachment loss, glycosylated hemoglobin, random blood sugar, and interleukin-10 (*P*<0.05)

Group (*n*=20)	PI	GI	PPD	CAL	HbA1c %	RBS	IL-10
1							
2	0.003*	0.022*	0.997	10.000	0.000*	0.000*	0.021*
3	0.000*	0.000*	0.000*	0.000*	0.855	0.993	0.000*
4	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
2							
1	0.003*	0.022*	0.997	10.000	0.000*	0.000*	0.021*
3	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0.204
4	0.000*	0.000*	0.000*	0.000*	0.012*	0.090	0.378
3							
1	0.000*	0.000*	0.000*	0.000*	0.855	0.993	0.000*
2	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0.204
4	0.259	0.000*	0.710	0.130	0.000*	0.000*	0.982
4							
1	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*
2	0.000*	0.000*	0.000*	0.000*	0.012*	0.090	0.378
3	0.259	0.000*	0.710	0.130	0.000*	0.000*	0.982

*Statistical significant (*P*<0.05). PI: Plaque index; GI: Gingival index; PPD: Probing pocket depth; BoP: Bleeding on probing; CAL: Clinical attachment loss; HbA1c: Glycosylated hemoglobin; RBS: Random blood sugar; IL-10: Interleukin-10

level of serum IL-10 than other groups but difference among Group 3 and Group 4 is not statistically significant. The variation of the serum IL-10 level has been depicted through box plot in Figure 1.

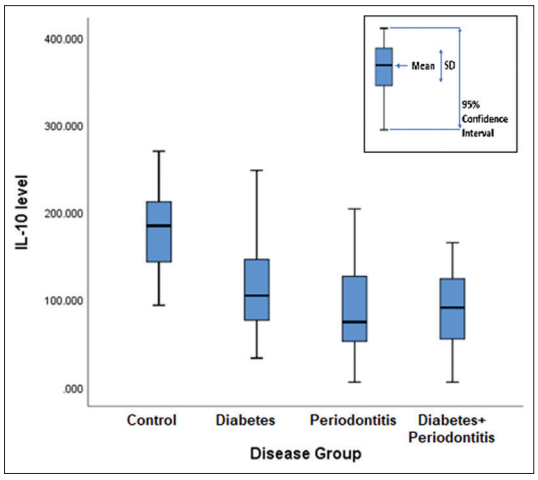

Figure 1: Box plot representing the variation of the serum IL-10 level (mean ± SD and 95% CI). CI: Confidence interval, SD: Standard deviation, IL: Interleukin

Discussion

Periodontitis is a peripheral chronic inflammatory disease,[8] has some common etiopathogenesis with type 2 diabetes that is linked to elevated inflammatory markers such as C-reactive protein, fibrinogen, and pro-inflammatory cytokines such as IL-6 and TNF-α.[7,9,10] IL-10 has strong deactivating properties on the inflammatory host response inhibiting the production of pro-inflammatory cytokines such as IL-6 and TNF-α.[6] Therefore, it was suggested that IL-10 might have an important regulatory role in limiting the duration and extent of the inflammatory response[7] and low IL-10 production capacity is associated with periodontitis and T2DM. Hence, this study was conducted to correlate the serum IL-10 level with periodontal inflammation and glycemic status and to predict the possible impact of periodontitis on glycemic alteration.

PI was recorded to assess the patients care about oral hygiene. GI was used to assess the severity of gingival inflammation, whereas pocket depth and clinical attachment loss (CAL) were recorded to categorize the patient based on periodontal destruction. Both PI and GI in this study were higher in T2DM with chronic periodontitis group that is consistent with other studies.[4,11,12]

HbA1c levels in Group II and Group IV are much higher than both Group I and Group III in this current study. Again, Group IV has elevated level of HbA1c than Group II but the difference is not statistically significant (P = ns). The healthy control subjects and the periodontitis subjects (Group III) did not show any significant difference (P = ns) in HbA1c level. Higher probing depth was found both in the periodontitis group and diabetes with the periodontitis group. Mohamed *et al*. revealed in their study that tooth mobility, furcation involvement, probing depth, and periodontal inflammation were more prevalent among T2DM patients than their nondiabetic-matched controls.[11] Costa *et al*. investigated the influence of HbA1c levels on periodontal disease progression. They showed in their study that the progression of periodontal disease is associated with an increase in HbA1c levels in hyperglycemic patients and the severity of periodontitis was also interlinked with increased HbA1c in individuals with and without type 2 diabetes.[13] Another study investigated progression of periodontitis over 5–10 years with increasing HbA1C and impaired glucose tolerance in nondiabetic people that supports widely discussed topic about the influence of diabetes on periodontitis.[14]

However, this study aims to search for influence of periodontal health on glycemic control, pertains to core parameter which was serum IL-10 level, and was detected in pg/mL in all four groups. IL-10 level is significantly lower in Group II (diabetic group) and Group IV (diabetes with periodontitis group) than in the control group (Group I). Acharya *et al.* also found maximum IL-10 level in the control group[12] that supports the previously described conclusions by van Exel *et al.* that IL-10 has strong deactivating properties on the inflammatory host response mediated by macrophages and lymphocytes and potently inhibits the production of pro-inflammatory cytokines such as IL-6 and TNF-α. Van Exel *et al.* further reported that low production capacity of IL-10 was associated with metabolic syndrome and type 2 diabetes.[15]

Fenol *et al*. analyzed IL-10 levels in GCF among three groups: healthy patients, patients with gingivitis, and patients with periodontitis.[16] Their study showed highest IL-10 level in patients with gingivitis (1128.19 ± 532.90 pg/mL). The mean IL-10 level in the control group (648.96 ± 505.75) was lower than that in the periodontitis (956.22 ± 475.49) group in their study which is opposite to our present study result. However, unlike our present study, they analyzed IL-10 levels in GCF. According to Passoja *et al*., IL-10 levels were higher in healthy controls as compared with chronic periodontitis patients.[17] They found negative association between the serum level of IL-10 and the extent of BoP, PPD, and CAL. There was significantly higher level of IL-10 in healthy controls compared to the subjects with BoP, PPD ≥4 mm, and attachment loss ≥4 mm. The adjusted associations between serum IL-10 level and the extent of periodontal disease, using the control group as a reference, indicated that the subjects in the control group had significantly higher levels of IL-10 than the subjects with any form of periodontitis and were inversely related to every tertial increase of attachment loss.

Lower IL-10 levels were found both in the periodontitis and diabetes groups that mentioned earlier implying the added influence of both diseases on IL-10 levels. We, therefore, anticipated lowest level of serum IL-10 in patients with T2DM+CPD than the other three groups. However, it is interesting that the mean level of IL-10 in CPD is lowest in our study. However, no significant difference in serum IL-10 level was found among CPD and diabetes or T2DM+CPD groups.

Overall, the present study showed that patients with T2DM and chronic periodontitis have low levels of serum IL-10, however, lowest in the CPD group justifies that the inflammatory mechanisms of CPD alone may have likely role in the regulation of IL-10 levels. IL-10 is independently associated with both T2DM and CPD. Demmer *et al*. reported a positive nonlinear association between baseline periodontal disease and incident type 2 diabetes and concluded that the baseline periodontal disease is an independent predictor of incident diabetes.[18] When they compared in between healthy participants and individuals with intermediate levels of periodontal disease, they found increased incidence of developing diabetes in individuals having periodontitis, and the odds of incidence of developing chronic hyperglycemia are reliant on severity of periodontitis. This may support the hypothesis that the lowest level of IL-10 in chronic periodontitis has a potential role as one of the predictors of the changes in glycemic status.

Conclusion

The present study was undertaken to interlink between IL-10 levels, CPD, and T2DM to appraise the influence of periodontal inflammatory state on glycemic status to obtain scientific evidence of the aforesaid interlink that may help in screening the probability of developing hyperglycemia in periodontitis patients followed by prevention of diabetes.

This study concludes that IL-10 levels have an inverse relationship with HbA1c. Again, low level of IL-10 in periodontitis patients dictates pathogenic mechanisms of CPD seem to have a potential role in the regulation of IL-10 and asserted possible influence of CPD on glycemic status. Hence, serum IL-10 levels can be one of the predictors of developing hyperglycemia.

This study pertains to ultimate goal to continue research on many faces of periodontitis that will establish scientific study, diagnose and treat hyperglycemia under an integrative framework in the future. However, longitudinal multicenter investigations involving larger samples are necessary.

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Conflicts of interest

There are no conflicts of interest.

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