|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
Index Copernicus Value 2019: 79.34
Original Research Article
Volume 5, Issue 1; January: 2021; Page No. 14-18

EVALUATION OF SERUM INTERLEUKIN-10 LEVELS AS A BIOMARKER OF GLYCEMIC ALTERATION IN CHRONIC PERIODONTITIS AND TYPE 2 DIABETES MELLITUS: BIO-CHEMICAL STUDY

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Article Info: Received 20 November 2020; Accepted 2 January 2021
DOI: https://doi.org/10.32553/ijmbs.v5i1.1612
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Conflict of interest: No conflict of interest.

Abstract

Aim: Chronic periodontal disease (CPD) and type 2 diabetes mellitus (T2DM) share common pathogenic pathways. This study was aimed to estimate levels the of serum interleukin (IL-10), an anti-inflammatory cytokine also associated with T2DM and evaluate its association with hyperglycemia.

Materials and Methods: This investigation involved seventy five participants (55 males, 20 females, 30-55 age group) divided into three groups comprising 25 participants each: Group 1 (healthy controls), Group 2 (CPD patients) and Group 3 (T2DM patients with CPD) . Plaque index, gingival index, probing pocket depths (PPD), clinical attachment loss, bleeding on probing, random blood sugar, glycosylated hemoglobin (HbA1c), and serum IL-10 was measured.

Results: Interleukin-10 was detected in all three groups. Statistically significant ($P < 0.05$) differences were observed in most of the variables in all groups. IL-10 correlated significantly with PPD in Group 1 and with HbA1c in Group 3. IL-10 levels were lowest in Group 2.

Conclusion: Low IL-10 levels associated with high HbA1c. Pathogenic mechanisms of CPD seem to regulate IL-10. Serum IL-10 levels may be one of the predictors of hyperglycemia.

Key words: Chronic periodontitis, diabetes mellitus, glycosylated, hemoglobin A, interleukin-10, type 2 diabetes mellitus

Introduction

Chronic periodontal disease is an infectious inflammatory disease, and type 2 diabetes mellitus is a metabolic disease due to disrupted insulin action. Diabetes and periodontitis are complex chronic diseases with an established bidirectional relationship.[1] Non resolving chronic periodontal inflammation has an impact on diabetes control, beta cell function, insulin resistance and the development of and its complications.[2]Chronic periodontal disease may serve as an initiator or propagator of insulin resistance in a way similar to obesity, induce or perpetuate an elevated systemic chronic inflammatory state resulting in increased insulin resistance and poor glycemic control.[3,4]

Periodontitis may also have a negative impact on diabetes control while the periodontal therapy may lead to improvements in glycemia.[5] The mechanisms responsible for these outcomes in patients with diabetes are mainly related to their increased risk for infections, impairment of the synthesis of collagen and glycosaminoglycan by gingival fibroblasts, and increased gingival crevicular fluid collagenolytic activity.[6,7,8]

The relationship between these diseases represents a well-recognized example of a systemic disease predisposing to oral infection; if this infection actually occurs, it, in turn, exacerbates the systemic disease. Thus, the chronic Gram-negative infection of periodontal origin may be considered a potential focus of infection that aggravates metabolic control in patients who have diabetes.[9] In this context, the virulence of the sub-gingival bacteria present in the periodontium gains a greater significance. Effective immune responses against pathogenic microbes depend on the balance between pro and anti inflammatory reactions.

IL-10 inhibits cytokine synthesis by both T cells and natural killer (NK) cells due to its inhibitory effects on the macrophage–monocyte accessory cell. Additionally, IL-10 has a potent deactivating effect on granulocytes and dendritic cells. This inhibitory effect on cells of the macrophage-monocyte and dendritic cell lineages led to IL-10 being termed ‘‘macrophage deactivating factor’’ Other effects of IL-10 include inhibition of T-cell proliferation and IL-2 production and co-stimulation of B-cell growth and differentiation.[10]

Interleukin10 (IL-10) is essential in regulating this balance and has gained interest recently as a modulator of the response to infection at the Janus Kinase Signal Transducers and Activators of Transcription (JAK-STAT) signaling axis of host responses. Interleukin-10 is known to control or prevent production of TNF,IL-6 and other mediators .[11] A meta analysis has provided strong evidence that IL-10 is associated with risk of type II diabetes mellitus .[12] With regard to chronic periodontal disease, IL-10 levels

were higher in healthy controls as compared with chronic periodontitis patients and lower levels of IL-10 in aggressive periodontitis has been reported.[13,14]

The present study is being contemplated to estimate the serum levels of IL-10 and its association with glycemic status in chronic periodontal disease and type II diabetes mellitus and to evaluate the impact of an inflammatory state on glycemic status.

Materials and Methods

Seventy five participants (55 males and 20 females) including healthy volunteers and patients visiting the Department of Periodontolgy and implantology, D.J. College of Dental Sciences and Research were recruited in this study. An informed written consent was obtained from all the patients before their participation in the study. The inclusion criteria were patients in the age range of 30–55 years, presence of at least 20 natural teeth, minimum of 4 teeth with a probing pocket depth (PPD) ≥5 mm, and clinical attachment loss (AL) ≥2 mm, which were positive for bleeding on probing (BoP) and which showed radiographic evidence of bone loss when evaluated using the long cone technique, defined chronic periodontitis. The glycemic status of patients previously diagnosed with T2DM was confirmed by their glycosylated hemoglobin (HbA1c) ≥7% and random blood sugar (RBS) levels >200 mg/dl, with no major diabetic complications, a body mass index (BMI) <30 and total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG) within normal limits. All the groups were age and gender matched. The T2DM patients in this study were diagnosed with this disease for at least 1-year. They were on oral hypoglycemic agents/insulin as per the prescribed treatment regimen of their respective physician/endocrinologist, with no major alteration in the diabetes treatment in the past 1-year.

The exclusion criteria were smokers or those who chewed any form of tobacco, pregnancy or lactating females, immunosuppressed individuals, any condition requiring prophylactic antibiotics prior to dental treatment, prolonged bleeding as a result of any medication, any other systemic disorder that could compromise safe participation in the study and any participant who had undergone nonsurgical therapy for periodontal disease in the last 3 months or were on an antibiotic or/and anti-inflammatory drug regimen prior to the study. A dental and medical history was recorded for the selected participants, and a single examiner conducted the intraoral examination. On the basis of their plaque index (PlI), gingival index (GI),PPDs, clinical AL, BoP, BMI, radiographic evidence of bone loss, total cholesterol, TG, LDL, HDL, glycated hemoglobin (HbA1c) levels and RBS levels, the selected participants were then divided into three groups of 25 each: Group 1 (healthy controls) included individuals who were nondiabetic, systemically and periodontally healthy; Group 2 (CPD only) were nondiabetic and systemically healthy and diagnosed with periodontal disease and Group 3 (T2DM with CPD) were diagnosed as type 2 diabetes with periodontal disease. Blood samples were drawn from all participants and serum IL-10 was measured using a commercially available ELISA kit .

Result

This study was carried out on 75 participants. Participants (55 males, 20 females) in the study were aged between 30 and 55 years with the average age being 42.7 years. Participants were grouped into three groups i.e. group 1 (healthy/ control group), group 2 (patients with chronic periodontitis) and group 3 (patients with chronic periodontitis and T2DM)

Interleukin-10 was detected (pg/ml) in all the three groups, highest (15.45 ± 1.39) in Group 1 and lowest (10.36 ± 0.65) in Group 2. Group 3 has 11.35 ± 0.56 level of IL-10 (TABLE 1)

Table 1: Mean and SD values of IL-10 in the three groups

Groups	Mean value of IL-10	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	P value
				Lower Bound	Upper Bound			
Group I	15.45	1.398	0.279	14.87	16.03	13.25	17.92	0.001
Group II	10.36	0.656	0.131	10.09	10.63	9.02	11.11	Significant
Group III	11.35	0.569	0.113	11.11	11.58	10.38	12.28	

One Way ANOVA at p≤0.05 is significant

Hb1Ac was detected for all the patients. HbA1c value for control group (healthy individuals) should be below 5.7% for prediabetes HbA1c should be between 5.7% and 6.5% and HbA1c of 6.5% or higher are detected in diabetes patients. In the present study Hb1Ac value for group 1 (healthy/control) patients is 4.86±0.48, 5.78±0.28 for group 2 and highest for group 3 i.e. 8.96±0.38 indicating T2DM. (TABLE 2)

Table 2: Mean and SD value of HbA1c in three groups

Groups	Mean value of Hb1Ac	Standard deviation
Group 1	4.86	0.48
Group 2	5.78	0.28
Group 3	8.96	0.38

Intergroup comparison

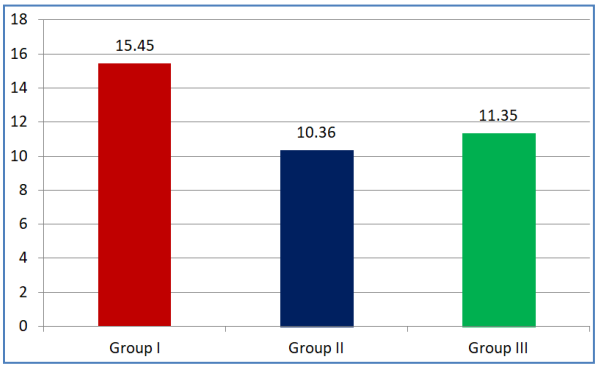
Intergroup comparisons of the clinical and biochemical parameters are summarized in Table 3. Statistically significant differences ($P < 0.05$) were observed in most of the comparisons.

The parameters for the groups, which were systemically healthy (Groups 1 and 2) revealed statistically significant differences ($P < 0.05$), also in group 1 (control group) and group 3 (chronic periodontitis with T2DM) patients significant differences ($P < 0.05$) were seen. No statistically significant results were observed ($P > 0.05$) among group 2 and group 3 (chronic periodontitis and chronic periodontitis with T2DM respectively) indicating that both have similar pathobiologic mechanisms. (TABLE 3)

Table 3: Consolidated pairwise comparison (*P* value) between the four groups for IL-10 (*P*<0.05)

Group	Mean Difference	Std. Error	Sig.	Significance
Goup I vs Group II	5.09	0.26884	0.001	Significant
Goup I vs Group III	4.10*	0.26884	0.001	Significant
Group II vs Group III	-0.989	0.26884	0.125	Non-Significant

Graph to show inter group comparison of IL-10



Mean value of IL-10 among three groups
Group 1: 15.45 pg/ml
Group 2:10.36 pg/ml
Group 3: 11.36 pg/ml

Discussion

This study was conducted to estimate and compare the concentration of IL-10 from the serum of healthy individuals and T2DM patients with and without CPD and to evaluate the relationship between an inflammatory state and glycemic status. Gingival index was selected for assessing the severity and quantity of gingival inflammation. A GI score of >1 indicated the presence of active periodontal disease[4] Periodontal pockets and subgingival inflammation give evidence of actual periodontal infection, whereas AL and bone loss are indicators of former periodontitis that has caused tissue destruction in the past.[5] Thus, PPD ≥5 mm, AL ≥2 mm and radiographic evidence of bone loss were considered as defining CPD[6]. Plaque index, GI and BoP were higher in the T2DM with CPD group (Group 3). This group had mean HbA1c level of 8.96 ± 0.38 which is comparable to the study by Duarte *et al.*[5],who reported two groups of periodontitis patients with HbA1c levels of ≤8 and ≥8, with mean PPD of 3.4 ± 0.6 and 3.7 ± 0.7 and mean AL 4.3 ± 0.8 and 4.3 ± 1, respectively.

Periodontitis is associated with increased HbA1c in individuals with and without T2DM. In people without diabetes, progression of periodontitis over 5–10 years was associated with increasing HbA1c and impaired glucose tolerance. The comparison of HbA1c levels was statistically significant in all groups in this study. Interleukin-10 is a prototypic anti-inflammatory cytokine that is produced in response to a multitude of pathogens that plays a central role in limiting host immune response to pathogens, thereby preventing damage to the host and maintaining normal tissue homeostasis, dysregulation of IL-10 is associated with enhanced immunopathology in response to infection as well as increased risk for development of many diseases. IL-10-mediated anti-inflammatory response (AIR) represents an essential homeostatic mechanism that controls the degree and duration of inflammation. It also inhibits the secretion of inflammatory cytokines, including interferon, TNF-α, IL-1, IL-2, and granulocyte-monocyte colony-stimulating factor (GM-CSF), as well as several chemokines.[12]

Van Exel *et al.*[15], proposed that high IL-10 levels prevent the development of T2DM and metabolic syndrome by limiting the effects of the inflammatory response that is, by counter regulating the effects of pro-inflammatory cytokines such as TNF-α and IL-6. They further proposed that IL-10 at least partly represents the effect of an AIR on T2DM and metabolic syndrome, based on another study that suggests IL-10 to be a key regulator and powerful

suppressor of the immune response.This hypothesis is partly derived from van Exel *et al*.[15], findings, which suggest that when the production capacity of IL-10 is taken into account, the production capacity of TNF-α adds little to markers of T2DM, such as TG and HbA1c. van Exel *et al*.[15], further reported that low IL-10 production capacity is associated with T2DM, wherein the IL-10 levels decreased with an increase in HbA1c levels.

In theory, higher levels of IL-10 should cause an upregulation of tyrosine kinase activity of the insulin receptor causing a decrease in lipolysis, by counter regulating the effects of TNF-α and IL-6.[16] Therefore, high IL-10 levels could provide protection against T2DM, whereas low IL-10 levels may predispose an individual to T2DM. However, in our study, the serum IL-10 levels exhibited a similar reported behavior in Group 2 and 3; it was significantly lower in the former as compared with the latter, implying the added influence of both the diseases on IL-10 levels.

Interleukin-10 levels were higher in healthy controls as compared with chronic periodontitis patients with a negative association between the serum level of IL-10 and the extent of BoP, PPD and AL according to Passoja *et al*.[17] They also proposed that the level of IL-10 was indicative of a dose-dependent association with chronic periodontitis. Górska *et al*.[18],examined the relationship between clinical periodontal variables and cytokine profiles in patients with chronic periodontitis. Their results indicate that IL-10 from inflamed gingival tissue samples and serum obtained from the periodontitis patients and healthy controls were generally low or even undetectable, and remained, on average, on the same level. However, the frequency of IL-10 (72%) was much higher in healthy gingival tissues.

In our study, IL-10 was the highest in the healthy group. IL-10 correlated and regressed significantly with PPD in Group 1 and with HbA1c in Group 3, which implies that IL-10 levels are predictable with PPD and HbA1c. Schmidt *et al*.[19], and Duncan *et al*.[20], reported that a variety of inflammatory markers, including white blood cell count, low serum albumin, α1-acid glycoprotein, fibrinogen, and sialic acid, predict the development of T2DM in a middle-aged population. An ongoing cytokine-induced acute-phase response or low-grade inflammation is closely involved in the pathogenesis of T2DM, and CPD is associated with changes in serum components consistent with an acute-phase response.

Almost 90% of all patients with T2DM show insulin resistance, which also precedes the first symptoms of diabetes. Subclinical chronic inflammation is implicated as an important pathogenic factor in the development of insulin resistance and T2DM. Surrogate markers for this low-grade chronic inflammation include CRP, IL-6 and TNF-α.

In the present study, IL-10 levels were lower in patients with T2DM and CPD when compared with patients with only T2DM. The levels were lowest in the patients with only CPD, which is interesting because the anticipated IL-10 levels in Group 3 having CPD plus T2DM should have been lowest considering the influence of both the diseases. But this does not seem to have an impact on the IL-10 levels, contradicting anticipated lower levels, with no statistically significant difference between Groups 2 and 3. We hypothesize with caution that the inflammatory mechanisms of CPD alone may have a likely role in the regulation of IL-10 considering that serum IL-10 levels were lowest in the group with CPD alone. IL-10 is independently associated with both T2DM and CPD.

Demmer *et al*.[21], reported a positive nonlinear association between baseline periodontal disease and incident type 2 diabetes in the National Health and Nutrition Examination Survey–I and its epidemiologic follow-up study. This association persisted regardless of the periodontal disease definition. When compared with healthy participants, individuals with intermediate levels of periodontal disease had a two-fold increased odds of incident diabetes, and the odds remained elevated among participants with the highest levels of periodontal disease. This may justify in part, our hypothesis that the lowest levels of IL-10 in CPD to have a potential role as one of the predictors for the changes

in glycemic status.

Conclusion

It is tempting to hypothesize a link between IL-10 levels, glycemic changes, CPD, and T2DM. Since no other cytokines were assessed in this study, it is a limitation that cannot definitively conclude a relationship between serum IL-10 levels and the glycemic status in association with other cytokines. However, we detected serum IL-10 in health, CPD, T2DM and in patients with both these diseases. Also, IL-10 levels have an inverse relationship with HbA1c in health and these diseases. Pathogenic mechanisms of CPD seem to have a potential role in the regulation of IL-10. Hence, serum IL-10 levels can be one of the predictors for glycemic alteration that may worsen glycemic control in T2DM. Longitudinal investigations involving larger samples are necessary.

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