Original Article

Serum monocyte chemoattractant protein-1 is a biomarker in patients with diabetes and periodontitis

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ABSTRACT

Introduction: The role of serum Monocyte Chemoattractant Protein-1 (MCP-1) as a biomarker of periodontitis is well documented; however, its role in diabetic patients with periodontitis is unknown. **Aim**: This study was conducted to determine the presence and concentration of serum MCP-1 in diabetic patients with and without periodontitis and correlate it glycemic status with periodontitis. **Materials and Methods:** Adult diabetic patients were enrolled and grouped into group I, II, and III based on their glycemic status and serum MCP-1 estimated by ELISA. Linear regression and correlation tests were performed using *R* statistical software, Medcalc software to observe correlation between the serum MCP-1 and glycated hemoglobin level among different groups. **Results:** Serum samples obtained from 37 patients tested positive for MCP-1. Mean serum MCP-1 concentration was highest (482.3 pg/ml) in group III, lowest (149.3 pg/ml) in group I, and intermediate 398.8 pg/ml in group II. Correlation and regression analysis was done between HbA1c and serum MCP-1. A significant positive correlation ($P < 0.001$) was observed. Serum MCP-1 increased by 37.278 pg/ml for every 1% rise in HbA1c, and the levels were raised in group II and group III than in group I irrespective of their glycemic status. With an HbA1c range of 6.5-6.9% (group II), the serum MCP-1 values cluster around 380-410 pg/ml. Elevated levels of serum MCP-1 (>500 pg/ml) in three subjects corresponded to HbA1c values more than 12.2% (group III). **Conclusion:** To our knowledge, this is the first study to document serum MCP-1 levels in diabetic patients with periodontitis. Glycemic status influences serum MCP-1, and lack of glycemic control contributes to increased serum MCP-1 levels. Serum MCP-1 may thus serve as a biomarker of inflammation and disease progression in diabetes with periodontitis.

Key words: Glycemic control, periodontitis, serum Monocyte Chemoattractant Protein-1

Introduction

Diabetes of long duration results in irreversible functional and structural damage leading to several complications. One such complication is periodontal disease or periodontitis.[1] Diabetes is often associated with severe periodontal disease and is considered a risk factor for periodontal disease progression.[2] Analysis of the National Health and Nutrition Examination Survey (NHANES) III data set showed that the prevalence of diabetes in patients with periodontal disease is twice of that seen in non-periodontal disease patients (12.5% versus 6.3%).[1] In India, up to 70% of the adult population appears to have periodontal disease[3,4] and in the diabetic, this is estimated to be 82.7%.[5]

Inflammation is considered to be a major contributing factor in the development of complications.[6] Periodontal disease is caused by periodontal pathogens such as *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Campylobacter rectus* etc., Disease progression is mediated by the host inflammatory response.[7] Pro-inflammatory cytokines and chemical mediators are significantly increased in gingival inflammation and in periodontal disease progression.[8,9]

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Monocyte chemoattractant protein-1, a chemokine, is implicated in the pathogenesis of numerous complications of diabetes.[10] Various studies have documented the role of MCP-1 in periodontal disease.[11,12]

The role of MCP-1 has been studied in the pathogenesis of interstitial lung disease,[13] breast cancer cells,[14] rheumatoid arthritis,[15] cytomegalovirus encephalitis,[16] and small cell vasculitis.[17]

The over expression of MCP-1 is found to increase insulin resistance by initiating macrophage infiltration of the adipose tissue and thus predisposing to the onset of diabetes mellitus.[18] MCP-1 may play a role in the development of numerous complications of diabetes in angiopathy[19] and cause infiltration and activation of monocytes in the glomerulus, which leads to the diabetic nephropathy.[20] The increased level of MCP-1 in microglia and macrophages leads to the development of diabetic retinopathy.[21]

The role of serum MCP-1 as a biomarker of periodontitis is well documented; however, its role in diabetic patients with periodontitis is unknown. This study was conducted to determine the presence and concentration of serum MCP-1 in diabetic patients with and without periodontitis and to correlate it with glycemic status with periodontitis.

Materials and Methods

A prospective exploratory study was conducted in diabetic patients with and without periodontal disease, attending the out-patient clinic in a tertiary care hospital in sub-urban Chennai. The study was conducted between April 2011 and October 2011. The study protocol was approved by the Institution ethics committee, and informed consent was obtained. Sample size was determined based on the number of patients to be enrolled to obtain a meaningful data and was done in consultation with a statistician using convenient sampling.

Inclusion and exclusion criteria

Adult diabetic patients with (≥18 yrs) with type II DM who had not received any kind of dental treatment or prophylaxis in the past six months were included and the patients with hypertension,[22] cardiovascular disorders,[23] abnormal hepatic function,[24,25] hemoglobinopathies, renal failure, retinopathy,[21] pregnancy, patients on current antibiotic treatment or prophylaxis and other endocrine disorders such as hypothyroidism, hypo-parathyroidism, Addison's disease, Cushing's syndrome, and thyroid cancer, which would influence serum MCP-1 levels, were excluded from the study. Patients who were smokers, pan chewers, as well as habitual consumers of alcohol were also excluded.

Assessment of glycemic status

Subjects with HbA1c <7% were considered to have well controlled diabetes and poorly controlled/uncontrolled diabetes if HbA1c ≥7%.[13] Fasting blood sugar (FBS) level, post-prandial blood sugar (PPBS) level, MPG, lipid profile, and routine urine analysis were also recorded.

Oral health assessment

Periodontal status of the study population was assessed by oral examination by a qualified dentist. Patients were enrolled for oral hygiene index (OHI-S), evaluation of bleeding on probing (BOP), periodontal probing depths (PPD), and clinical attachment loss (CAL). Presence of BOP, PPD >5 mm, and CAL >3 mm[26] were considered diagnostic criteria for periodontal disease.

Categorization of the study population

Patients were categorized into three groups based on their glycemic control and periodontal status. Subsequently, the demographic details, general health conditions, oral hygiene behavior, and periodontal evaluation were analyzed.

Group I: Consists of diabetic patients with good glycemic control with no signs of periodontal disease

Group II: Consists of well-controlled diabetic patients with evidence of periodontal disease

Group III: Consists of diabetic patients with poor glycemic control and showed evidence of periodontal disease.

Collection of clinical specimens

Four milliliter of blood was collected in a sterile vacutainer (BD diagnostics, Franklin Lakes, USA) and immediately transferred to the laboratory. The samples were centrifuged at 3500 rpm for 15 min and were aliquotted and stored at -70°C until the time of assay.

Determination of MCP-1 concentration in serum

Serum MCP-1 levels were determined using a quantitative sandwich enzyme-linked immunosorbent assay (Human CCL2 (MCP-1) ELISA kit, Bioscience, Inc., Catalogue Number: 88-7399).[27] The sensitivity of the assay was 7 pg/ml-1000 pg/ml for MCP-1. The kit has been calibrated with National Institute for Biological Standards and Control (NIBSC); the co-efficient of variation of this assay is 3.3%.

The absorbance (OD) was measured at 450 nm by the ELISA plate reader (Multiskan EX primary EIA V.2.3). The concentration of MCP-1 was estimated using the reference calibrated standard curve.

The mean and range of MCP-1 concentrations and HbA1c values groups were calculated. Simple linear regression and correlation tests were performed using R statistical software (version 2.11.0), Medcalc software (version 12.6.1) to observe correlation between the serum MCP-1 and glycated hemoglobin level. The age and gender analysis were analyzed only after the completion of the study.

Results

The study group comprised of 37 adult diabetic patients; majority (62%) were females (n = 21) and 18.9% were males (n = 16).

Both group I and group II consisted of well-controlled diabetic patients with a mean HbA1c of 6.2% and a range of 5.2-6.9%. In diabetic patients with poor glycemic control (group III), the mean HbA1c was 9.5% with a range of 7.8-13.1%. [Table 1] Group I patients were younger with a mean age of 26.86 years [Table 1].

All 37 diabetic patients' serum samples tested positive for the presence of MCP-1, with concentrations that ranged from 135.6-543.5 pg/ml. In diabetics with good glycemic control and no evidence of periodontal disease (group I), the mean serum MCP-1 concentration was 149.3 pg/ml (range: 135.6-160.4 pg/ml).

In group II (well-controlled diabetes with periodontal disease), the mean MCP-1 concentration was 398.8 pg/ml (range: 330.4-435.1 pg/ml). In diabetics with poor glycemic control and periodontal disease (group III), the mean serum MCP-1 concentration was 482.3 pg/ml (range: 460.9-543.5 pg/ml). The mean serum MCP-1 concentration was highest (482.3 pg/ml) in group III and lowest (149.3 pg/ml) in group I [Table 1].

Correlation between serum MCP-1 and glycated hemoglobin

Simple linear regression and correlation analysis performed to observe the relation between glycated hemoglobin (HbA1c) levels and serum MCP-1 concentrations suggests a linear progression [Figures 1b and c] in group II and group III. The linear progression was more marked in group III [Figure 1c], and the correlation was highly significant with a $P < 0.001$, suggesting that serum MCP-1 levels are markedly elevated as the glycated hemoglobin levels increase in poorly-controlled diabetic patients (HbA1c ≥7%) with periodontal disease. In group III, in three patients with serum MCP-1 concentrations above 530 pg/ml, the corresponding HbA1c values were found to be above 12.1%.

In group II [Figure 1b], serum MCP-1 concentrations of 320-380 pg/ml clustered around HbA1c of 6%; serum MCP-1 was higher >410 pg/ml when the HbA1c levels were in the range of 6.5-6.9%. Two subjects with good glycemic control (HbA1c <6%) in group II had elevated levels of serum MCP-1 (>410 pg/ml), which may be due to the severity of the periodontal disease. The correlation between HbA1c and serum MCP-1 was not significant in group I (diabetic patients with good glycemic control and no periodontal disease) [Figure 1a].

From the linear regression analysis performed on all study subjects [Figure 2], it was found that a 1% rise of HbA1c resulted in 37.278 pg/ml increase of serum MCP-1 concentration, which was statistically significant. ($P < 0.001$).

Serum MCP-1 levels in different study groups

When we analyzed the serum MCP-1 concentrations of each patient in the different groups, we found that the MCP-1 values tend to cluster based on HbA1c levels [Figure 3]. For example, in group I, the serum MCP-1 values clustered below 200 pg/ml. MCP-1 values in the range of 350-450 pg/ml clustered around group II (HbA1c <7%). In group III, the values clustered around 460-550 pg/ml.

The serum MCP-1 concentrations in diabetic patients with periodontal disease were above 300 pg/ml irrespective of

Table 1: Descriptive statistics of the study groups showing mean, median, standard deviation, and range for age, glycated hemoglobin (HbA1c), and serum MCP-1 levels

Parameters	Group	No. of subjects	Mean	Median	SD	Minimum	Maximum
Age (yrs)	Gr-1	7	26.86	24	7.82	18	39
	Gr-2	15	54.8	55	7.69	44	66
	Gr-3	15	51.1	52	8.9	31	64
HbA1c (%)	Gr-1	7	6.186	6.5	0.601	5.3	6.9
	Gr-2	15	6.213	6.2	0.47	5.2	6.9
	Gr-3	15	9.46	8.7	1.87	7.8	13.1
Serum MCP-1 (pg/ml)	Gr-1	7	149.3	150.9	9.78	135.6	160.4
	Gr-2	15	398.8	418.8	35.704	330.4	435.1
	Gr-3	15	482.3	471.4	29.085	460.9	543.5

SD: Standard deviation

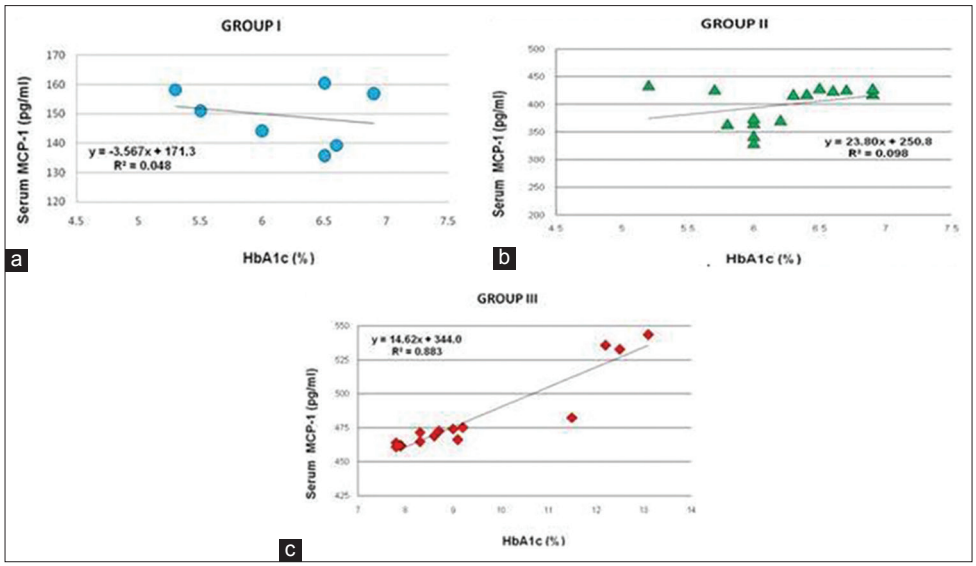

Figure 1: (a-c) Correlations of glycated hemoglobin levels (HbA1c) with serum MCP-1 in groups I, II, and III respectively. The intercept values were -3.568, 23.81, and 14.62, respectively. The values are not significant in group I and group II, whereas in group III, it is significant

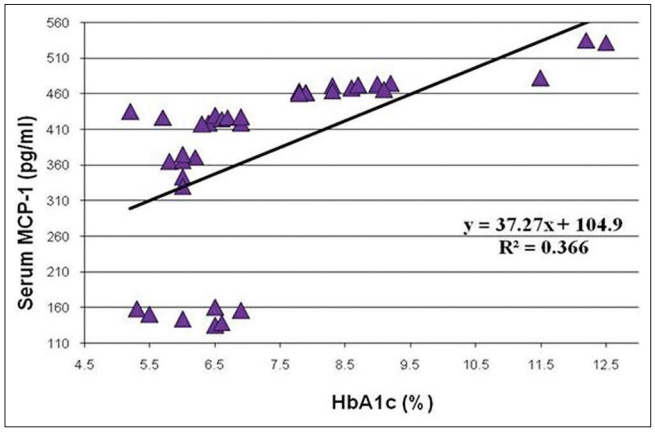

Figure 2: Linear Regression Analysis between HbA1c (%) and serum MCP-1 (pg/ml) in all the study subjects shows a significant intercept value of 37.278

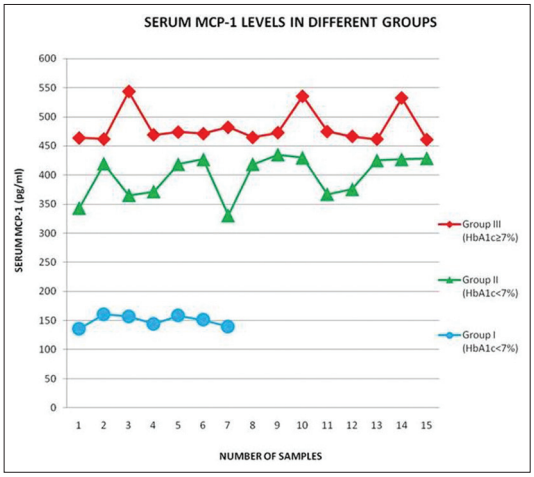

Figure 3: Projection of serum MCP-1 levels in all the three study groups

their glycemic status (group II and group III). However, the serum MCP-1 levels were above 460 pg/ml in diabetic patients with poor glycemic control and periodontal disease (group III), whereas it was only below 450 pg/ml in group II (well-controlled diabetic patients with periodontal disease). The power of the study is 0.0014.

Discussion

The process of tissue destruction (connective tissue and alveolar bone) in periodontitis results from the interaction of bacteria or bacterial substances with host cell as well the host response to bacterial invasion. Bacterial plaque is responsible for inducing host inflammatory processes followed by secondary colonization of periodontal pathogens such as *Porphyromonas gingivalis, Actinobacillus actinomycetemcomitans, Prevotella intermedia,* and others.[28] The number of monocytes/macrophages are more in progressing periodontal lesions as compared to non-progressing periodontal lesions[29] and may be closely related to the pathogenesis and progression of periodontitis. The role of MCP-1 has been studied in periodontal health and disease. MCP-1 is synthesized in inflamed gingiva by mononuclear phagocytes, endothelial cells, and osteoblasts.[30] Increased levels of MCP-1 have been reported in gingival biopsies of patients with periodontal disease[31] and in the gingival crevicular fluid (GCF) of periodontal patients.[32] The recovery of periodontal pathogens has been studied in saliva and varying rates of detection *Tanerella forsythensis* (56.9%), *Treponema denticola* (38.2%), and *Porphyromonas gingivalis* 35.4%[33] reported.

Periodontal disease is considered as potential risk factor for progression of various systemic diseases, also increased

levels of serum MCP-1 due to periodontal disease may be a risk factor for systemic diseases.[2] The association between periodontal disease and cardiovascular diseases is well established; the role of serum MCP-1 has also been assessed.[34] However, the role of MCP-1 in periodontal disease and uncontrolled diabetes mellitus has not been studied.

In our study, serum MCP-1 was detectable in all 37 diabetic patients. Serum MCP-1 levels were raised in diabetic patients with good glycemic control having periodontal disease (group II) when compared with well-controlled diabetic patients without periodontal disease (group I), with even higher levels of serum MCP-1 in diabetic with poor glycemic control having periodontal disease (group III). Circulating levels of MCP-1 are known to be elevated in diabetic patients[35] and may contribute to the development of complications in diabetics.[36,37]

Diabetic patients with good glycemic control and no periodontal disease (group I) were much younger (mean age of 26.86 yrs) when compared with group II and group III. The patients were enrolled in to the different group based on their glycemic status, and it was incidental finding that patient with good glycemic controls were younger. Aging does increase circulating levels of MCP-1.[38] Experimental studies on rat model have stated that aging induces expression of MCP-1/CCL-2 receptors leading to age-associated arterial remodeling. However, age-related MCP changes are gradual and do not increase dramatically as seen in our study. We believe that MCP-1 differences cannot be dismissed because of age alone.

When the glycated hemoglobin levels were in a range of 5.2-6.9% indicating good glycemic control, the serum MCP-1 concentrations were found to be within acceptable limits[39] (<165 pg/ml in group I).

The concentration of MCP-1 in serum was increased by 37.278 pg/ml for every 1% rise in HbA1c. Regression analysis performed for group III was found to be significant, suggesting that poor glycemic control contributes to increase in serum MCP-1 levels. Even in the absence of any complications such as renal failure, retinopathy, and cardiovascular diseases among the patients enrolled in the study, the MCP-1 levels in the serum were elevated.

The serum MCP-1 levels clustered into specific ranges even without knowledge of HbA1c and periodontal status. Based on their glycemic status, the MCP-1 values were increased in group I (135 -160 pg/ml), group II (330-435 pg/ml), and in group III. (461-543 pg/ml) Thus, the determination of serum MCP-1 may be used to assess both the glycemic and periodontal status. This pattern clearly substantiates our categorization of diabetic patients into different groups. The clustering of serum MCP-1 values among the different groups of patients suggests that there may be threshold levels related to age, glycemic status, and periodontal disease. Further studies need to be conducted to support this. If indeed threshold values are established, it will definitely alert the clinician to take measures to pre-empt the progression of diabetes to various complications. To our knowledge, this is the first study to determine serum MCP-1 levels in diabetic patients with periodontal disease and correlate with glycemic control.

This is a prospective exploratory study conducted in 37 diabetic patients, and MCP-1 levels were estimated as a onetime assessment. Prospective studies need to be undertaken with serial estimation of MCP-1 to determine the progression to complications in larger group of patients.

Conclusion

A significant positive correlation between serum MCP-1 and glycemic status (HbA1c) has been documented. It has been found that 1% rise of HbA1c resulted in 37.278 pg/ml increase of serum MCP-1 concentration. Our findings suggest that glycemic status influences serum MCP-1 levels in diabetic patients with periodontal disease. Elevated serum MCP-1 levels could contribute to onset and progression of several complications in diabetes. Thus, serum MCP-1 may serve as a biomarker of inflammatory activity and helps in early detection and intervention of diabetic complications.

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