EFFECTS OF NON-SURGICAL PERIODONTAL THERAPY ON GLYCEMIC CONTROL AND SYSTEMIC INFLAMMATION IN PERIODONTITIS STAGE II WITH SIMILAR DISEASE SEVERITY AND MODIFIED GRADE SCORE.

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Abstract-

Aim: To analyze how non surgical periodontal therapy affects the levels of serum glycated hemoglobin levels (HbA1c%, mmol/mol), C- reactive protein(CRP mg/l), interleukin 1beta(IL-1 β pg/ml) in periodontitis stage II with similar severity of disease and recognized risk factors, diabetes mellitus type 2(DM2) presenting modified grade score.

Materials and Methods: 40 subjects, aged 25-60 years comprising of healthy individuals and patients diagnosed with periodontitis stage II according to the 2017 classifications were examined. A modified-grade level was assigned to the patients according to their HbA1c in DM2**.** The subjects were equally divided into healthy individuals (H), grade A (NDM+P), grade B (ADM+P), grade C (IDM+P).Plaque index (PI), gingival index (GI), probing pocket depth (PD mm)and clinical attachment level (CAL mm), serum HbA1c%, mmol/mol, CRP mg/l and IL-1β pg/ml were estimated at baseline and 3 months after scaling and root planning (SRP).

Results: The difference in pre to post mean change in PI, GI, APD and CAL has showed significant ($p< 0.001$) among all the groups. The pre to post mean change showed statistically significant in both HbA1c% mmol/mol and CRP mg/l ($p< 0.001$) among the groups but not in IL-1β pg/ml ($p = 0.552$). However, it did not differ between the groups and found to be statistically insignificant. ($p> 0.05$)

Conclusion: Non surgical periodontal therapy helps in reducing systemic inflammation and glycemic levels which in turn lowers the likelihood of developing diabetes and its complications among high risk patients.

Keywords: stage II periodontitits, diabetes mellitus, serum HbA1c, CRP, IL-1beta, non-surgical periodontal treatment

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1. Introduction

Periodontitis and DM are complex chronic diseases, linked by an established bidirectional relationship with each having negative impacts on the other. Molecular mechanism is marked by double sword inflammatory processes initiated by microbial insult; brought on by the activation of innate immunity and the subsequent host inflammatory response.[1,2,3,4]Host response to periodontal infections produces acute inflammatory phase mediators such as CRP, Interleukin -6(IL-6), plasminogen activator-1(PAI-1) and fibrinogen. These acute phase reactant helps in neutralizing the pathogens but also involves in repair and regeneration of the tissues.[2 ,5]

Van dyke proposed a unifying concept of Inflammation-Mediated Polymicrobial-Emergence and Dysbiotic-Exacerbation (IMPEDE) model that integrates the role of systemic inflammation not localized to periodontium as a driving force for the emergence of opportunistic polymicrobial infection.[6] The concept also complements the 2017 world workshop classification of periodontitis which included a multidimensional staging and grading system. Staging (I-IV) defines the extent and severity of periodontitis. [7,8] Gradingis a key aspect that accounts for variability in the rate of periodontitis progression. Modified Grading system also relies on recognized risk factors for periodontitis progression and individual patients' systemic diseases such as DM that increases the risk for further progression. Furthermore, a risk factor (smoking or diabetes) shift the grade score to a higher value independently of the radiographically calculated primary criterion represented by the rate of progression. In this context, diabetic individuals would be diagnosed as modified Grade C if their glycated hemoglobin HbA1c% ≥7 and as Grade B if their HbA1c %<7. [7,8,9].

Clinical evidences of a pro inflammatory cytokine, IL-1β also provides its significance in the pathogenesis of periodontal diseases, participating in inflammatory- immune regulation and bone resorption. It has been verified that periodontitis leads to excessive production of IL-1β locally in gingival crevicular fluid, saliva and systemically via serum. [10] The elevated circulating levels of these inflammatory mediators are reported to be risk indicators for the development of various metabolic disorders and exacerbate the progression of diabetes mellitus.[11] Conversely, elevated levels of pro inflammatory cytokines in DM can reach the periodontal tissues and increases risk for periodontal disease by three-fold in people with diabetes compared to individuals. Several reports have demonstrated elevated serum HbA1c%, CRP levels in patients with periodontitis compared with healthy controls and some clinical studies have suggested that successful non-surgical periodontal treatment can reduce these levels in systemically healthy subjects. [11,12,13,14] It has been suggested that adequate periodontal treatment in diabetic patients may be beneficial in reducing diabetic complications. [15,16]

The purpose of this study was to analyze the effects of non surgical periodontal therapy on the levels of serumHbA1c%, CRP, IL-1 β in periodontitis stage II with similar severity of disease and recognized risk factors presenting modified grade score.

2. Materials and Methodology

This observational study was conducted with samples derived from Indian population who presented with chronic periodontitis with or without diabetes mellitus type 2. The study design followed the guidelines of STROBE statement. [Figure1]The study protocol and written informed consent were approved by the Ethical Committee, Sardar Patel Post graduate Institute of Dental and Medical Sciences, Lucknow (UP), India.

Out of 245 patients assessed for eligibility, only 40 subjects, aged 25-60 years, healthy volunteers and patients visiting the outpatient department of Periodontology were enrolled. The samples were equally divided into apparently healthy individuals (H, n=10), patients with periodontitis stage II grade A (NDM+P, n=10), periodontitis stage II grade B (ADM+P, n=10), periodontitis stage II grade C (IDM+P, n=10). [Figure1]

Inclusion criteria were patients suffering from Periodontitis stage II with regard to extent and severity and modified-grade level was assigned to the patients according to their HbA1c% in DM2 as follows:

1. The patients with at least 6 sites with PD ≤ 5mm and interdental CAL 3-4 mm and BOP in at least 15 teeth, excluding third molars and no previous history of tooth loss.[8]
2. Grade A was assigned with no risk modifiers, modified grade B with DM2 (HbA1c <7.0%) and modified grade C with DM2 with (HbA1c ≥ 7.0%). [8]

Exclusion criteria included were known medical disorders that required antibiotic prophylaxis; having received SRP in the last 6 months and history of medications that affect periodontal tissues and serum cytokine levels in the last 6 months, pregnancy and smokers.

2.2 Study Parameters:

At screening, PI [18], GI [19], PD and CAL were estimated to evaluate the periodontal status. Blood samples were collected to estimate biochemical parameters, namely serum HbA1c (%, mmol/mol), CRP (mg/l) and IL-1β (pg/l). Estimation of serum IL-1beta was performed at CSIR-Central Drug Research Institute, Lucknow. PI was estimated by Sillness and Loe method and GI by Loe and Sillness method. [18,19] Calibrated UNC 15 mm probe was used to measure the probing pocket depth. Probing measures were made measured from gingival margin to the base of pocket. CAL was measured between the cementoenamel junction (CEJ) and the gingival margin using the UNC 15 mm probe.

HbA1c was estimated by Glycohaemoglobin ion exchange resin method using the Transasia Biomedical kit, India CRP by Turbi latex agglutination assay kit, Spectrum Medical Industries Pvt. Ltd. Kit, India and IL-1β by Human interlekin-1β ELISA kit, Thermo Scientific kit, U.S.A.

The periodontal clinical parameters and biochemical parameters were estimated at baseline and 3 months after scaling and root planning nonsurgical periodontal therapy. The patients were recalled for examination of oral hygiene maintenance 1 month after the baseline visit and reinstructed if necessary.

2.3 Statistical analysis

Clinical and Biochemical parameter analyses were performed on SPSS software (Windows version 22.0). Continuous pre and post groups were compared by paired t test. Comparison among the groups were evaluated by one factor analysis of variance (ANOVA) and the significance of mean difference between (inter) the groups was done by Tukey's HSD (honestly significant difference) post hoc test after ascertaining normality by Shapiro-Wilk's test and homogeneity of variance between groups by Levene's test. Discrete groups were compared by chi-square (χ^2) test. A two-tailed (α=2) $p < 0.05$ was considered statistically significant.

3. Results

3.1 Periodontal parameters

The pre and post mean periodontal parameters showed significant improvement in all the groups ($p< 0.001$) except group (H) which showed insignificant change ($p > 0.05$).Further, comparing the pre to post mean change in periodontal parameters among groups, ANOVA showed significantly different change in PI (F=21.12, $p< 0.001$), GI (F=44.84, $p< 0.001$), PD (F=88.81, $p< 0.001$) and CAL (F=104.30, $p< 0.001$) among the groups. [Table 1]

Moreover, comparing the difference in pre to post mean change in periodontal parameters between the groups, Tukey test showed significantly ($p< 0.001$) different parameters of Group (NDM+P), Group (ADM+P) and Group (IDM+P) as compared to Group (H). However, it did not differ ($p> 0.05$) among the above first three group. Moreover, the pre to post mean change in both PD and CAL showed significant difference ($p< 0.01$) and higher improvement in Group (ADM+P) as compared to Group (IDM+P). [Table 1]

3.2 Biochemical parameters

Comparing the pre and post mean biochemical parameters, paired t test showed significant decreased ($p< 0.001$) in all the groups except healthy (H) group($p > 0.05$). Further, comparing the pre to post mean change in biochemical parameters among groups, ANOVA showed significantly different change in both HbA1c (F=148.60, $p< 0.001$) and CRP (F=20.28, $p< 0.001$) among the groups but not in IL-1β (F=0.71, $p = 0.552$). [Table 2]

Further, comparing the difference in pre to post mean change between the groups, Tukey test showed significantly ($p< 0.001$) different and highest pre to post mean change in HbA1c of Group (IDM+P) followed by Group (NDM+P) and Group (ADM+P). However, it did not differ between the groups and found to be statistically insignificant. ($p> 0.05$) [Table3]

Conversely, the pre to post mean change in CRP of Group (NDM+P), Group (ADM+P) and Group (IDM+P) was found significantly ($p< 0.001$) different and higher as compared to Group (H) but not differ ($p> 0.05$) between Group (NDM+P) and Group (ADM+P), and Group (IDM+P). In contrast, the pre to post mean change in IL-1β was found similar ($p> 0.05$) among all the four groups. [Table 3]

4. Discussion

The two-way relationship between periodontal disease and DM has been extensively studied, not only as DM is a risk factor for periodontitis, but also because periodontitis could have a negative effect on glycemic management. [20,21] DM has been conclusively linked to the development of periodontal diseases;[22]and diabetic patients have a threefold higher chance of developing periodontitis than non-diabetics do.[23] When compared to

individuals with DM2 without periodontitis, Taylor et al. showed a six-fold greater risk of poor glycemic control in patients with severe periodontitis [24]. Although the majority of research on the connection between these two disorders has been on the potential mechanisms via which glycemic metabolic may cause periodontal damage. [21-25]

Recent studies have put forward a converse relationship between the two diseases, which is marked by bidirectional inflammatory processes due to activation of innate immunity and advanced glycation end product (AGE) playing a significant role in its pathogenic pattern. Both diseases can modulate host immune response, such as upregulation of inflammatory cell phenotype, elevation of pro inflammatory cytokines and initiation of tissue damage leads to outcome of activation of the low grade inflammatory response.[20] Therefore, In the 2017 classification, the modified grade of periodontitis has been included to analyzed additional information about the biological characteristics of the disease based on the risk factor involved for the assessment of the risk of further progression and an analysis of possible poor outcomes of treatment.[8]

The results of the present study highlighted positive impact of non surgical periodontal therapy in the glycemic control, serum CRP levels and IL-1β in periodontitis stage II with modified grade score diabetic patients. PI, GI, PD and CAL have shown improvement after SRP in all the groups. Further, the difference in pre to post mean change has showed significant ($p< 0.001$) in periodontal parameters between the Group (NDM+P), Group (ADM+P) and Group (IDM+P) as compared to Group (H). However, it did not differ ($p> 0.05$) among the above three group. Moreover, the pre to post mean change in both PD and CAL showed significant difference ($p< 0.01$) and higher improvement in Group (ADM+P) as compared to Group (IDM+P) as shown in Table 1.

These findings can be attributed to the advantages of SRP and confirm the reciprocal relationship between these inflammatory conditions, including DM2 as a risk factor for periodontitis as well as delayed periodontal healing and repair events among diabetic patients with insufficient glycemic control who had periodontitis. The results also reveal that, in comparison to the group where the risk variables are not addressed, periodontitis stage II grade B responds favorably to SRP throughout the three-month follow-up. However, Periodontitis stage II grade C showed decrease improvement may be due to metabolic dysregulation, AGE generation as a result of poor glycemic management, and persistent hyperglycemia, which can lead to impaired microcirculation and slow wound healing.

The pre to post mean change in biochemical parameters among groups, showed significantly different change in both HbA1c and CRP ($p< 0.001$) among the groups but not in IL-1β ($p = 0.552$). Further, highest pre to post mean change in HbA1c of Group (IDM+P) followed by Group (NDM+P) and Group (ADM+P) ($p< 0.001$). However, it did not differ between the groups and found to be statistically insignificant. ($p> 0.05$)

The change in HbA1c in periodontitits stage II grade B with adequate glycemic control has shown a reduction (-0.30 ± 0.04 %) after SRP while remarkable reduction (-2.24 ± 0.11%) was observed among the periodontitits stage II grade C with poor glycemic control. Various studies have shown similar trend of reduction in HbA1c in diabetes mellitus patients suffering from periodontitis at 3months following the non surgical periodontal therapy [26]. Tsobgny-Tsague et al. in 2018[27] showed a massive improvement in glycemic control with a remarkable reduction in HbA1c post SRP. Quintero et al. 2018[28] reported that periodontal treatment generated a greater impact in the reduction of HbA1c in patients with higher levels of HbA1c>9% (0.31% vs 0.88%). According to Jain A et al.2019's systematic review, there is a decrease in HbA1c of 0.26% (P=0.17) when periodontal treatment is used as mono therapy at 3–4 months.[29] Simpson et al. 2015[30] Cochrane Collaboration reported a meta analysis and concluded that SRP does improve glycemic control with a mean percentage reduction of 0.29% in HbA1c at 3-4 months. Kaur et al.2015 also favors the result of the present study.[31]

The available evidence indicated a significant drop in HbA1c after periodontal therapy, which is relevant to the potential HbA1c decrease in diabetes patients following periodontal therapy. This has therapeutic significance since decreaseof 1% in HbA1c lowers mortality by 10% and reduces serious complications of diabetes by 35%.[32]

Local inflammatory chemical mediators such as tumour necrosis alpha (TNF-alpha) ,Interleukin - 1(1L-1)and CRP have been associated with periodontal disease progression and diabetic complications.[33]The current research measures the serum CRP levels of periodontitis stage II grade A without risk factor have shown increased levels of mean serum CRP levels (3.22 ± 0.13 mg/l) which

indicate systemic inflammation and the risk for development of metabolic disorders.[26] Moreover, the levels of serum CRP in both the periodontitis Stage II grade B and C patients have shown higher mean values of 3.76 ± 0.09 mg/l and 4.55 ± 0.15 mg/l at baseline respectively. Hence, this obvious signs of increase inflammatory marker explains the additional source of systemic pro-inflammatory mediators, and highlights the increase in cardiovascular risk and diabetic complications in grade C patients with uncontrolled glycemic control.[32]

Conversely, statistically significant reduction in the mean change of serum CRP level was observed following the SRP in all the groups periodontitis stage II Grade A patients (-0.71 ± 0.11mg/l), grade B (-1.01 ± 0.16mg/l) and Grade C(-1.23 ± 0.12mg/l) ($p< 0.001$). Meta analysis studies conducted by Baeza M. et al 2019 concluded that the conventional periodontal treatment can helps in reducing the serum CRP levels, HbA1c thereby decreasing the systemic inflammation and augments the glycemic control.[26]This finding adds to previous systematic reviews' findings about the possible impacts of periodontal therapy on the overall health of patients with DM2 and strengthens the twofold explanatory approach for lowering systemic inflammation, specifically, one road directly through the decrease of pro-inflammatory mediators like TNF-alpha, IL-1, and IL-6, which cause acute phase reactions with hepatic biosynthesis and high serum CRP levels, and the other path indirectly through the reduction of HbA1c itself as a result of the reduction of insulin resistance.[34]

Few evidences have reported the correlation of the serum inflammatory bio markers and periodontal status and the effect of periodontal treatment on salivary cytokine levels. In the present study, the serum levels of IL-1β in Grade C patients with inadequate glycemic control has shown significantly higher mean levels (10.47 ± 1.11 mg/l) at baseline as compared to Grade B with adequate glycemic control (8.25 ± 0.82mg/l) than the Grade A and systemically healthy subjects. Serum levels of IL-1β were reduced in all the groups post SRP.In contrast, no statistically significant reductions were observed in serum IL-1β level ($p> 0.05$) following the treatment, irrespective of glycemic status among the groups. These findings were in accordance with the study conducted by Teles et al. 2009 where no significant differences between subjects with periodontitis and controls were reported for IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IFN-γ, and TNF-α.[35]Similarly, Sexton et al. 2011.[36] Rabelo et al.2021[37] highlighted that salivary levels of IL-1β and TNF-α were significantly reduced following the treatment while the serum levels IL-1β had no significant impact.

Apart from various differing opinions regarding the impact of non surgical periodontal therapy on serum CRP, HbA1c and IL-1β levels in different glycemic status diabetic patients suffering from chronic periodontitis, it can be concluded that significant reductions in serum CRP and HbA1c were attained by diabetic patients suffering from periodontitis irrespective of glycemic status. However, stand out reductions of HbA1c level in periodontitis stage II grade C with inadequate glycemic control highlights greater impact of periodontal treatment. These aspects must be considered for future research and investigation. Nevertheless, the impact of periodontal treatment appears to have limited effect on serum inflammatory cytokine levels in chronic periodontitis patients with and without adequate glycemic control.

The present study provides strong evidences of improvement in periodontal conditions and metabolic glycemic control in periodontitis patient with diabetes as risk modifier. The benefits of non surgical periodontal treatment can be mentioned as decrease of the systemic inflammation which lowers the risk of developing cardiovascular events and diabetic complications. Hence, the benefits of non surgical periodontal treatment can be appreciated in hindering inflammatory driving forces by reducing both local and systemic inflammation and metabolic control thereby decreases the risk of developing diabetic complications, killing two birds with single stone. It is thereby important to incorporate the periodontal treatment protocols into the public health care for the comprehensive management of diabetic patients.

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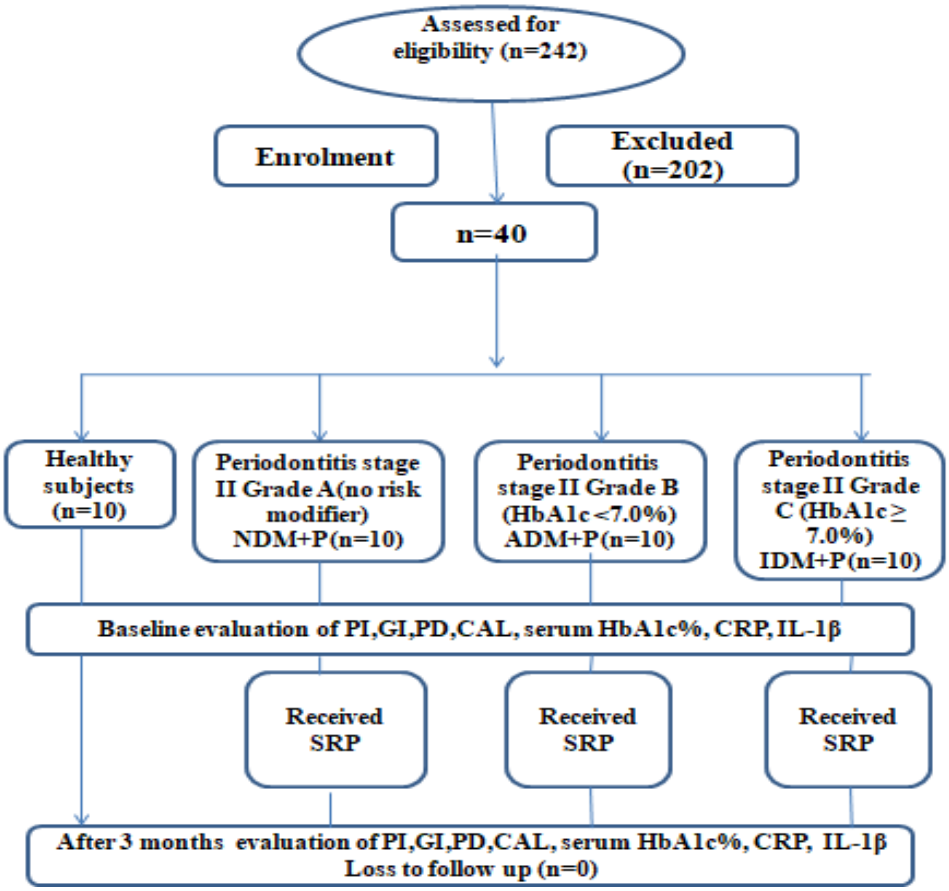

Figure 1: Study methodology following the STROBE statement

Table 1: Comparison of pre to post mean change in periodontal parameters of the groups

Variable	Group	Pre (n=10)	Post (n=10)	Change (Pre-Post)	t value	F value[§]	*p* value[k]
PI	Group H	0.88 ± 0.08	0.82 ± 0.09	-0.06 ± 0.03	2.00	21.12	0.077
	Group NDM+P	2.52 ± 0.25	1.12 ± 0.03	-1.40 ± 0.23	6.03		< 0.001
	Group ADM+P	2.54 ± 0.18	1.15 ± 0.02	-1.39 ± 0.17	8.21		< 0.001
	Group IDM+P	2.80 ± 0.11	1.13 ± 0.04	-1.68 ± 0.13	12.86		< 0.001
GI	Group H	0.15 ± 0.09	0.11 ± 0.06	-0.04 ± 0.03	1.31	44.84	0.222
	Group NDM+P	2.07 ± 0.20	0.10 ± 0.03	-1.97 ± 0.18	11.04		< 0.001
	Group ADM+P	2.14 ± 0.16	0.19 ± 0.05	-1.95 ± 0.15	13.44		< 0.001
	Group IDM+P	2.12 ± 0.19	0.31 ± 0.04	-1.81 ± 0.15	11.67		< 0.001
PD (mm)	Group H	1.26 ± 0.04	1.19 ± 0.07	-0.07 ± 0.05	1.29	88.81	0.229
	Group NDM+P	4.24 ± 0.09	2.66 ± 0.04	-1.58 ± 0.10	15.85		< 0.001
	Group ADM+P	4.66 ± 0.18	2.92 ± 0.12	-1.74 ± 0.08	22.35		< 0.001
	Group IDM+P	4.68 ± 0.05	3.32 ± 0.07	-1.35 ± 0.09	15.54		< 0.001
CAL (mm)	Group H	1.21 ± 0.04	1.19 ± 0.04	-0.02 ± 0.01	1.96	104.30	0.082
	Group NDM+P	4.39 ± 0.09	2.81 ± 0.08	-1.58 ± 0.10	15.85		< 0.001
	Group ADM+P	4.91 ± 0.21	3.17 ± 0.16	-1.74 ± 0.08	22.35		< 0.001
	Group IDM+P	4.97 ± 0.11	3.61 ± 0.07	-1.35 ± 0.09	15.54		< 0.001

ANOVA (F value) [§], paired t test [k](t value),significant difference ($p < 0.001$); healthy individuals (H), periodontitis stage II grade A (NDM+P),periodontitis stage II grade B (ADM+P), periodontitis stage II grade C (IDM+P);n- sample size; PI- plaque index, GI- Gingival index, PD- Probing depth, CAL- clinical attachment level

Table 2: Comparison of pre to post mean change in biochemical parameters among groups

Variable	Group	Pre (n=10)	Post (n=10)	Change (Pre-Post)	t value	F value[§]	*p* value[k]
HbA1c (%)	Group H	3.04 ± 0.06	3.01 ± 0.05	-0.03 ± 0.02	1.24	148.60	0.247
	Group NDM+P	4.22 ± 0.18	3.65 ± 0.14	-0.57 ± 0.11	5.40		< 0.001
	Group ADM+P	6.95 ± 0.12	6.66 ± 0.13	-0.30 ± 0.04	6.70		< 0.001
	Group IDM+P	9.09 ± 0.16	6.85 ± 0.11	-2.24 ± 0.11	19.59		< 0.001
CRP (mg/l)	Group H	1.46 ± 0.08	1.41 ± 0.09	-0.05 ± 0.03	1.84	20.28	0.100
	Group NDM+P	3.22 ± 0.13	2.51 ± 0.19	-0.71 ± 0.11	6.70		< 0.001
	Group ADM+P	3.76 ± 0.09	2.75 ± 0.12	-1.01 ± 0.16	6.43		< 0.001
	Group IDM+P	4.55 ± 0.15	3.31 ± 0.19	-1.23 ± 0.12	9.95		< 0.001
IL-1β (pg/ml)	Group H	4.99 ± 0.83	4.94 ± 0.82	-0.06 ± 0.04	1.26	0.71	0.240
	Group NDM+P	7.64 ± 1.27	5.91 ± 0.69	-1.73 ± 1.26	1.37		0.205
	Group ADM+P	8.25 ± 0.82	7.44 ± 0.67	-0.81 ± 1.00	0.81		0.439
	Group IDM+P	10.47 ± 1.11	8.16 ± 1.18	-2.30 ± 1.72	1.34		0.213

ANOVA (F value) [§], paired t test[k] (t value), significant difference ($p < 0.001$); healthy individuals (H), periodontitis stage II grade A (NDM+P), periodontitis stage II grade B (ADM+P), periodontitis stage II grade C (IDM+P);n- sample size;glycated haemoglobin -HbA1c (%), c-reactive protein- CRP (mg/l), interleukin 1beta- IL-1β (pg/ml)

Table 3: Comparison (p value) of difference in mean biochemical parameter between groups by Tukey test

Comparison	HbA1c (%)		CRP (mg/l)		IL-1β (pg/ml)	
	Mean diff	*p* value	Mean diff	*p* value	Mean diff	*p* value
Group H vs. Group NDM+P	0.54	< **0.001**	0.66	< 0.01	1.67	> 0.05
Group H vs. Group ADM+P	0.27	> 0.05	0.96	< **0.001**	0.75	> 0.05
Group H vs. Group IDM+P	2.21	< **0.001**	1.18	< **0.001**	2.25	> 0.05
Group NDM+P vs. Group ADM+P	0.28	> 0.05	0.30	> 0.05	0.92	> 0.05
Group NDM+P vs. Group IDM+P	1.67	< **0.001**	0.52	< 0.05	0.58	> 0.05
Group ADM+P vs. Group IDM+P	1.94	< **0.001**	0.22	> 0.05	1.50	> 0.05

significant difference($p < 0.001$); healthy individuals (H), periodontitis stage II grade A (NDM+P), periodontitis stage II grade B (ADM+P), periodontitis stage II grade C (IDM+P); n- sample size; glycated haemoglobin -HbA1c (%), c-reactive protein- CRP (mg/l), interleukin 1beta- IL-1β (pg/ml)