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Effect Of Non-Surgical Periodontal Therapy On Plasma Chemerin And Interleukin-18 Levels In Diabetic And Non-Diabetic Patients With Chronic Periodontitis: A Clinical And Biochemical Study

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Abstract: Aim of the study: To evaluate the effect of non-surgical periodontal therapy on plasma chemerin and interleukin-18 levels in diabetic and non-diabetic patients with chronic periodontitis. **Materials and Methods:** 60 subjects who met the inclusion criteria were enrolled in the present study. These subjects were allocated into two groups. Group A (Diabetic) included 30 subjects with chronic periodontitis and type II diabetes mellitus. And Group B (Non-Diabetic) included 30 subjects with chronic periodontitis and without type II diabetes mellitus. After recording a detailed case history, all the subjects underwent complete periodontal examination and the following clinical parameters were recorded: a) Pocket probing depth; b) Clinical attachment level; c) Periodontal index (Russel in 1956). Thereafter, venous blood samples were collected and transferred to EDTA coated tubes. Plasma samples were procured by centrifugating these blood samples at 2000-2500 rpm for 10 min. The plasma samples were then transferred to Eppendorf tubes and sent to the laboratory for analysis. Human Chemerin ELISA kit and Human Interleukin-18 ELISA kit were used to evaluate plasma chemerin and interleukin-18 levels. Scaling and root planning was performed after recording the clinical parameters and blood sample collection. Subjects were recalled after 4 weeks from the baseline visit and all the clinical parameters were re-evaluated and blood plasma samples were collected to evaluate post intervention plasma chemerin and IL-18 levels. **Result:** Non-surgical periodontal therapy lead to statistically significant decrease in clinical parameters like Pocket probing depth, Clinical attachment level and Russel's periodontal index in both, diabetic as well as non-diabetic patients with chronic periodontitis after 1 month follow up; with significant improvement in non-diabetic patients. **Conclusion:** Within the limitations of this study, it may be concluded that the clinically successful non-surgical periodontal therapy tends to reduce periodontal inflammation and the concentration of some circulating cytokines, that is Chemerin and interleukin-18, which could be important for patients with type II diabetes mellitus.

Keywords: NIL

Introduction

The term diabetes mellitus (DM) refers to a combination of metabolic diseases characterised by the inefficient management of glucose metabolism.1 This persistent hyperglycemic condition is linked to underlying ailments such as myopathies, vascular disease, neuropathy, nephropathy, delayed wound healing, and periodontitis.1,2 In periodontitis, which is a chronic inflammatory disease, cytokines, chemokines, and inflammatory mediators are produced as tissue defense mechanisms attempt to fight off microbiologic invaders.3 A plathora of studies have shown evidence of a bidirectional link between DM and periodontitis.4 Alterations in the microflora and neutrophil management, along with delayed wound healing, indicate that DM increases the chances of periodontal disease.5 On the other hand, it is also seen that periodontitis makes it difficult for the body to manage DM, but that periodontal treatments can result in healthier glycemic control. Research done to evaluate the efficacy of non-surgical periodontal treatments for patients with DM indicates a healthier periodontal condition and improvements in glycemic control.6-8 Periodontitis and DM seem to have numerous pathological features in comman. For instance, in presence of both, there is an increase in immuno-inflammatory responses with similar biologic mediators.9 The progression of DM and periodontitis occours when there is an an increase in plasma and gingival crevicular fluid (GCF) levels of pro-inflammatory markers such as C-reactive protein, tumor necrosis factor (TNF)-a, cytokines (interleukin [IL]-1b), IL-6, and prostanoids.10 Within this environment, proteins (adipokines) produced by the adipose tissue and the tissue defense cells, are likely to play a role in any kind of inflammatory reaction. In addition, the adipocytes generate inflammatory cytokines such as TNF-a and IL-6. Traditionally, the inflammatory cytokines were thought to have been generated by macrophages. They are, therefore, used to explain the connection between inflammation and resistance to insulin.11

Adipose tissue is an active endocrine organ, that produces a number of inflammatory cytokines, with the most important being adipokines. These cytokines influence insulin sensitivity, alter glucose and lipid metabolism, and impact inflammatory responses.12,13 These adipokines (leptin) play significant role in anti-inflammatory processes related to tissue defence. Others (resistin and visfatin) have a pro-inflammatory effect, and some (progranulin) play a pro-inflammatory and anti-inflammatory role at the same time.14,15 The relationship between proinflammatory and anti-inflammatory adipokines can lead to a low grade inflammatory conditions, similar to those occouring in periodontitis and DM.16,17 If levels of pro-inflammatory adipokines increase, patients may be vulnerable to periodontal disease.16 However, pro-inflammatory adipokine volumes can be lowered in patients with periodontitis and DM with non-surgical periodontal intervention.15,18

Chemerin, an adipose tissue–specific adipokine, plays an important role in adipocyte differentiation and development and also influences glucose and lipid metabolism, and inflammation levels.12,13 It is produced at several sites such as the adipose tissue, the liver, epithelial cells, endothelium, fibroblasts, and keratinocytes.19 Chemerin controls adipocyte differentiation and adipogenesis via the use of a receptor called chemokine-like receptor 1 (CMKLR1).13 The process is thought to be involved in both pro-inflammatory and anti- inflammatory responses.20 Chemerin supports the connection of macrophages to extracellular matrix proteins and adhesion molecules. This aids the union of macrophages to tissue endothelium.12 Along with pro-inflammatory characteristics, experimental study21 has shown evidence of the anti-inflammatory features of CMKLR1. In fact, an anti-inflammatory influence for chemerin/CMKLR1 was outlined in a mouse model for lipopolysaccharide- induced lung inflammation. In the research, the introduction of recombinant chemerin lowered lung tissue inflammation and alveolar infiltration by neutrophils.21 To summarize, research has found evidence to support the pro-inflammatory and anti-inflammatory influence of chemerin within immune cells.20 The links among chemerin, DM, and obesity have been thoroughly investigated.13,22,23 Altered chemerin levels were found in patients with obesity and type 2 DM (t2DM). It was also suggested that insulin resistance may be a forecaster of chemerin levels, but not necessarily in accordance with body mass index (BMI) or fasting insulin.22,24,25 Perhaps more significantly, chemerin has been associated with persistent micro and macro vascular complications.23 Although there is evidence to

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support the impact of chemerin on glucose homeostasis, the exact influence and participation is unknown. For instance, experiments with cultured 3T1-1–derived adipocytes have offered support for both the interruptive26 and stimulatory27 influence of chemerin on glucose uptake. Two studies19,28 investigated human chemerin levels during periodontal inflammation. The first study19 evaluated salivary levels of chemerin during periodontal inflammation and the second28 determined volumes of human chemerin within the GCF and tear fluid of patients with chronic periodontitis (CP) with and without t2DM. The studies19,28 indicated that human chemerin should be treated as a potential GCF and tear fluid marker of inflammatory activity in CP and DM.

Okamura et al discovered IL-18 with pro-inflammatory and tumor-suppressive properties in 199529 and was formerly termed as interferon-γ-inducing factor.30 IL-18 is a member of the IL-1 superfamily that is produced mainly by activated macrophages, dendritic cells, Kupffer cells, keratinocytes, intestinal epithelial cells, osteoblasts and adrenal cortex cells.30-33 It is potent in inducing both T helper 1 (Th1) and Th2 cytokines according to the immunological context 34. Furthermore, the control of Th1 and/or Th2 expression is fundamental to the immune regulation of periodontal disease.31,35 IL-18 levels are known to be elevated in various chronic diseases. 36 It plays a significant role in promoting activation of neutrophils37 and modulation of IL-1β production 38. Several studies demonstrate, a direct correlation between the severity of periodontal disease and level of IL-18.39-44 However, in few other studies, a significant difference in the concentration of IL-18 in GCF of periodontitis and healthy control group was not observed.45 Low-grade inflammation (micro-inflammation) occurs in patients with diabetes mellitus as well as those with cardiovascular diseases.46,47 Research indicates that high-sensitivity C-reactive protein (hs-CRP) 48 and pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, tumor necrosis factor (TNF), and IL-18 are elevated in patients with type 2 diabetes.49-52 The exact mechanism for elevation of serum IL-18 levels in type 2 diabetes remains unknown, but oxidative stress is a candidate.53 Activation of nuclear factor-β through oxidative stress induced by hyperglycemia, increases concentrations of circulating pro-inflammatory cytokines.47 Elevated levels of IL-18 have been identified as a strong predictor of mortality in patients with coronary artery disease54 and acute ischemic stroke.55 A major mechanism of cardiovascular events mediated by IL-18 is decreased stability of plaque. Carotid intima- media thickness (IMT) measured by carotid ultrasound is a useful tool for assessing cardiovascular diseases in diabetes,56 and a clinical study demonstrated that carotid IMT in patients with high IL-18 shows a greater thickness than in patients with normal IL-18.57 The last few years have seen an outburst of studies exploring various aspects of these unique cytokines, although its role in periodontal disease and effect of non-surgical periodontal therapy on these cytokines has received relatively scant attention.

Material and Methods

The present study was a clinical and biochemical study with a cross sectional experimental study design. The study protocol was approved by the ethical committee of Yogita Dental College and Hospital, Khed. A sample size of 60 is selected for the study, estimated by assessing the previous literature conducted in the area of research and keeping α=0.05 and power of study 80%. After satisfying the inclusion and exclusion criteria, 60 patients who visited the Departmnent of Periodontology, Yogita Dental College and Hospital, Khed; were recruited in the study. All the patients were given a detailed verbal and written description of the study, and written informed consent was taken prior to commencement of the study. These patients were divided into following groups:

Group A (Diabetic): 30 subjects with chronic periodontitis and type II diabetes mellitus. Group B (Non-Diabetic): 30 subjects with chronic periodontitis and without type II diabetes mellitus.

Inclusion criteria:

1. Age group: 20 - 60 years.
2. A minimum of 20 natural teeth present.
3. Chronic periodontitis patients with Pocket probing depth ≥4 mm.
4. Clinical attachment level (CAL) ≥4 mm.
5. Patients diagnosed with type II diabetes mellitus ≥1 year ago.

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6. Glycated hemoglobin (HbA1c) more than 6.5% and less than 8%.

Exclusion criteria:

1. Pregnant or lactating females.
2. Subjects undergoing antibiotic therapy.
3. Any systemic condition other than type II diabetes mellitus.
4. Use of orthodontic or prosthetic appliances.
5. Smokers or consumption of tobacco in any other form.
6. Alcoholics.

Withdrawal Criteria:

1. Failure to report for revaluation.
2. Non-Compliant Subjects.

Methodology:

A detailed case history of the subjects was recorded. All the subjects underwent complete periodontal examination and the following clinical parameters were recorded:

1. Pocket probing depth
2. Clinical attachment level
3. Periodontal index (Russel in 1956)

Venous blood samples were collected with disposable syringe (5ml), having 23-gauge needle. Thereby, the samples were transferred to EDTA coated tubes. Plasma was separated from blood by centrifugation at 2000-2500 rpm for 10 min. The plasma samples were then transferred to Eppendorf tubes and sent to the laboratory for analysis.

Human Chemerin ELISA kit and Human Interleukin-18 ELISA kit (Human chemerin ELISA

96 wells Mfg: Kinesis Dx, USA; Human IL-18 ELISA, 96 wells Mfg: Krishgen Biosystems,USA-India) was used to evaluate plasma chemerin and interleukin-18 levels.

Scaling and root planning was performed after recording the clinical parameters and blood sample collection. Subjects were recalled after 4 weeks from the baseline visit and all the clinical parameters were re-evaluated and blood plasma samples were collected to evaluate post intervention plasma chemerin and IL-18 levels.

Assay Procedure for Chemerin ELISA:

All reagents were brought to room temperature prior to use. All Standards and Samples were run in duplicates or triplicates. A standard curve was required for each assay. Standards Dilution: Standards were prepared as per the table given below using the provided standard Concentration and standard diluent.

6400ng/ml	Standard No.5	120µl Original Standard (12800ng/ml) + 120µl Standard diluent
3200ng/ml	Standard No.4	120µl Standard No.5 + 120µl Standard diluent
1600ng/ml	Standard No.3	120µl Standard No.4 + 120µl Standard diluent
800ng/ml	Standard No.2	120µl Standard No.3 + 120µl Standard diluent
400ng/ml	Standard No.1	120µl Standard No.2 + 120µl Standard diluent

The number of strips required for the assay, were removed. 50 µl of Standards and 40 µl Samples were pipetted out into the respective wells as mentioned in the work list. 10 µl of Biotin Conjugate was pipetted into each sample well. 50 µl of Streptavidin-HRP Conjugate was pipetted into each sample and standards well. The plate was covered and incubated for 1 hour at 37 °C in the incubator. Plate was washed 4 times with 1X Wash Buffer and residual buffer was blotted by firmly tapping plate upside

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down on absorbent paper. Any liquid was wiped out from the bottom outside of the microtiter wells as any residue can interfere in the reading step.

All the washes were performed similarly. Substrate A 50 µl, followed by Substrate B 50 µl, was then added to each well including Blank well. Gently mixed, incubated for 10 min at 37℃ in dark. 50 µl of Stop Solution was pippetted. Wells turned from blue to yellow in colour. The absorbance was read at 450 nm within 15 minutes after adding the Stop Solution blanking on the zero standards.

Assay Procedure for Interleukin-18 ELISA:

All reagents were brought to room temperature prior to use. All Standards and Samples were run in duplicates or triplicates. A standard curve was required for each assay. 100µl/well of Standards and Samples was added to the plate. Six two-fold serial dilutions of the 2000pg/ml top standard, either within the plate or in separate tubes were performed. Thus, the Human IL-18 standard concentrations were 2000pgml, 1000pg/ml, 500pg/ml, 250pg/ml, 125pg/ml, 62.5pg/ml and 31.3pg/ml. Assay Diluent (1X) served as the zero standard (0pg/ml). Plate was sealed and incubated at Room Temperature for 2 hours. Plate was aspirated and washed 4 times with Wash Buffer (1X) and residual buffer was blotted by firmly tapping plate upside down on absorbent paper. Any liquid from the bottom outside of the micro-titer wells was wiped as any residue can interfere in the reading step. All the washes were performed similarly. 100µl of diluted Detection Antibody solution was added to each well, plate sealed and incubated at Room Temperature for 2 hours. Plate was washed 4 times with Wash Buffer (1X) as in step 3. 100µl of diluted Streptavidin-HRP solution was added to each well, plate sealed and incubated at Room Temperature for 30 minutes. Plate was washed 4 times with Wash Buffer (1X) as in step 3. For this final wash, wells were soaked in Wash Buffer for 30 seconds to 1 minute for each wash. This would help minimize background. 100µl of TMB Substrate solution was added and incubated in the dark for 15 minutes. Positive wells turned bluish in color. Reaction was stopped by adding 100µl of Stop Solution to each well. Positive wells turned from blue to yellow. Absorbance was read at 450 nm within 30 minutes of stopping reaction.

Statistical analysis

All the data were entered into Microsoft Excel 2010. Descriptive statistics were expressed as mean ± standard deviation (SD) for each group for various clinical parameter. For Age Frequency distribution and percentage were used. Discrepancy among groups and age distribution was calculated by Chi square Test. Discrepancy among groups and gender distribution was calculated by Fishers' Exact Test.

Before and After comparison among all groups for all clinical parameter was done by Paired 't' Test. Two groups (Diabetic group vs Non-diabetic Group) were compared for various parameter by Unpaired 't' Test (Independent t test)

For All the above test p value is considered statistically significant when it was <0.05. The software used was SPSS (Statistical package for Social Sciences) version 17.

Result

Table 1. Age Statistics among two groups

groups	N	Minimum	Maximum	Mean	Std. Deviation	**Fisher Exact Test p value**
Diabetic group	30	33	62	44.53	7.016	0.348*
Non Diabetic Group	30	21	56	36.13	9.073	

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The mean age among Diabetic group was 44.53 ±7.016 and among Non-Diabetic Group it was 36.13 ±9.073. There is statistically insignificant difference among two groups with p=0.

Chart 1. Age Statistics among Two groups

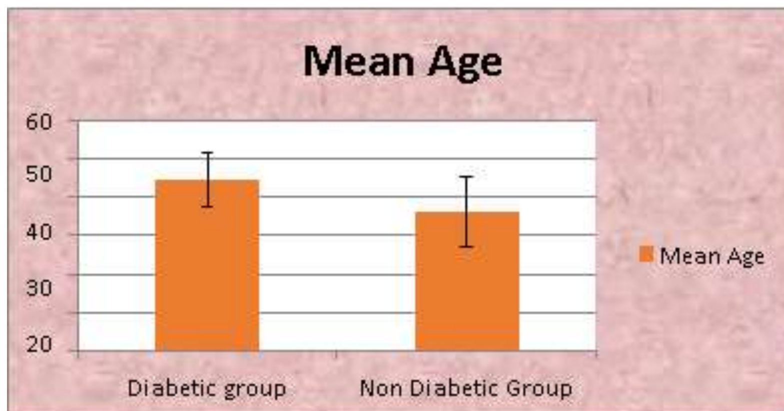

Table 2. Gender Statistics among two groups

groups		Frequency	Percent	Valid Percent	Cumulative Percent	**Chi square Test P value**
Diabetic group	Male	16	53.3	53.3	53.3	0.796
	Female	14	46.7	46.7	100.0	
	Total	30	100.0	100.0		
Non Diabetic Group	Male	15	50.0	50.0	50.0	
	Female	15	50.0	50.0	100.0	
	Total	30	100.0	100.0		

Chart 2. Gender Distribution among Two groups

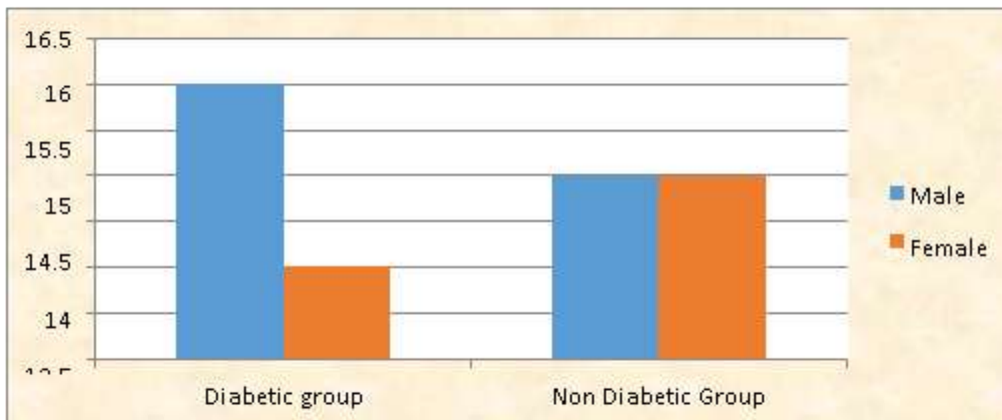

Table 3. Inter and Intra group comparison of Chemerin among diabetic and Non- Diabetic groups by Unpaired t-test and Paired t-test respectively

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Chemerin	(Diabetic group) (n=30)		(Non-Diabetic Group) (n=30)		P-value
	Mean	SD	Mean	SD	(Inter-Group)
Before	142.0000	11.32691	118.0567	14.44727	<0.001*
After	138.0013	13.03516	113.1287	12.47239	<0.001*
P-value (Intra-group)					
Pre-op v 1-month	<0.001*		0.002*		
P-values (Inter-Group) by independent sample t test. P-value (Intra-Group) by Paired t test. P-value<0.05 is considered to be statistically significant. *P-value<0.05, **P-value<0.01, ***P-value<0.001, NS-Statistically non-significant.					

Intra-Group by Paired t-test

There is statistically significant difference among baseline chemerin (142.0±11.32691) and post Intervention chemerin (138.0013±13.03516) among Diabetic Group with p<0.001.

There is statistically significant difference among baseline chemerin (118.0567 ±14.44727) and post Intervention chemerin (113.1287 ±12.47239) among Non-Diabetic Group with p=0.002.

Inter-Group by independent sample t-test

There is statistically significant difference at baseline chemerin Diabetic (142.0±11.32691) and non diabetic (118.0567 ±14.44727) with p<0.001*

There is statistically significant difference at Post intervention chemerin Diabetic group (138.0013±13.03516) and non diabetic group (113.1287 ±12.47239) with p<0.001*

Graph 3. Inter and Intra group comparison of Chemerin among diabetic and Non- Diabetic groups by Unpaired t-test and Paired t-test respectively.

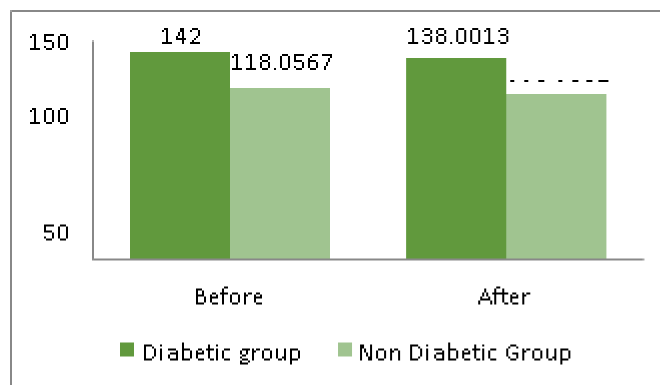

Table 4. Inter and Intra group comparison of IL 18 among diabetic and Non-Diabetic groups by Unpaired t-test and Paired t-test respectively

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IL 18	(Diabetic group) (n=30)		(Non-Diabetic Group) (n=30)		P-value
	Mean	**SD**	**Mean**	**SD**	**(Inter-Group)**
Before	.3349	.09340	.2129	.11213	<0.001*
After	.3224	.09969	.1993	.11229	<0.001*
P-value (Intra-group)					
Pre-op v 1-month	0.009*		0.001*		
P-values (Inter-Group) by independent sample t test. P-value (Intra-Group) by Paired t test. P-value<0.05 is considered to be statistically significant. *P-value<0.05, **P-value<0.01, ***P-value<0.001, NS-Statistically non-significant.					

Intra-Group comparison of plasma IL-18 levels by Paired t-test

There is statistically significant difference among baseline plasma IL-18 levels (0.3349±0.09340) and post Intervention plasma IL-18 levels (0.3224±.09969) among Diabetic Group with p=0.009.

There is statistically significant difference among baseline plasma IL-18 levels (0.2129±.11213) and post Intervention plasma IL-18 levels (0.1993±0.11229) among Non- Diabetic Group with p<0.001.

Inter-Group comparison of plasma IL-18 levels by independent sample t-test

There is statistically significant difference at baseline plasma IL-18 levels in diabetic (0.3349±0.09340) and non-diabetic (0.2129±.11213) with p<0.001*.

There is statistically significant difference at Post intervention plasma IL-18 levels in diabetic group (0.3224±.09969) and non-diabetic group (0.1993±0.11229) with p<0.001*.

Graph 4. Inter and Intra group comparison of IL-18 among diabetic and Non-Diabetic groups by Unpaired t-test and Paired t-test respectively.

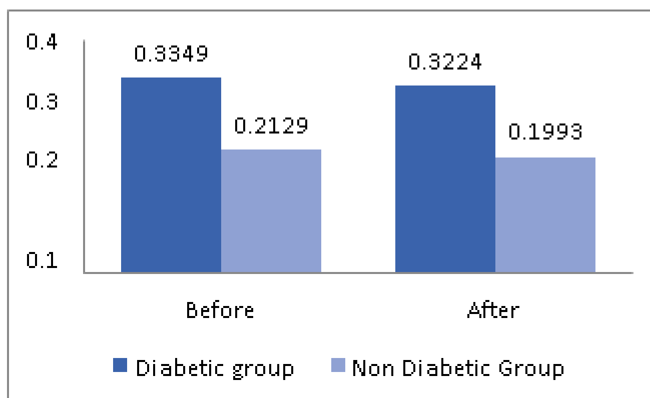

Table 5. Inter and Intra group comparison of Probing Depth among diabetic and Non- Diabetic groups by Unpaired t test and Paired t test respectively

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Probing Depth	(Diabetic group) (n=30)		(Non-Diabetic Group) (n=30)		P-value
	Mean	**SD**	**Mean**	**SD**	**(Inter-Group)**
Before	5.13	.730	4.40	.814	0.001*
After	4.17	.699	2.73	.691	<0.001*
P-value (Intra-group)					
Pre-op v 1-month	<0.001*		<0.001*		
P-values (Inter-Group) by independent sample t test. P-value (Intra-Group) by Paired t test. P-value<0.05 is considered to be statistically significant. *P-value<0.05, **P-value<0.01, ***P-value<0.001, NS-Statistically non-significant.					

Intra-Group comparison of Probing Depth by Paired t test

There is statistically significant difference among baseline Probing Depth (5.13±0.730) and post intervention Probing Depth (4.17±0.699) among Diabetic Group with p<0.001*.

There is statistically significant difference among baseline Probing Depth (4.40±0.814) and post intervention Probing Depth (2.73±0.691) among Non-Diabetic Group with p<0.001*.

Inter-Group comparison of Probing Depth by independent sample t test

There is statistically significant difference at baseline Probing Depth in diabetic (5.13±0.730) and non-diabetic (4.40±0.814) with p=0.001*.

There is statistically significant difference at Post intervention Probing Depth in diabetic group (4.17±0.699) and non-diabetic group (2.73±0.691) with p<0.001*.

Graph 5. Inter and Intra group comparison of Probing Depth among diabetic and Non- Diabetic groups by Unpaired t-test and Paired t-test respectively

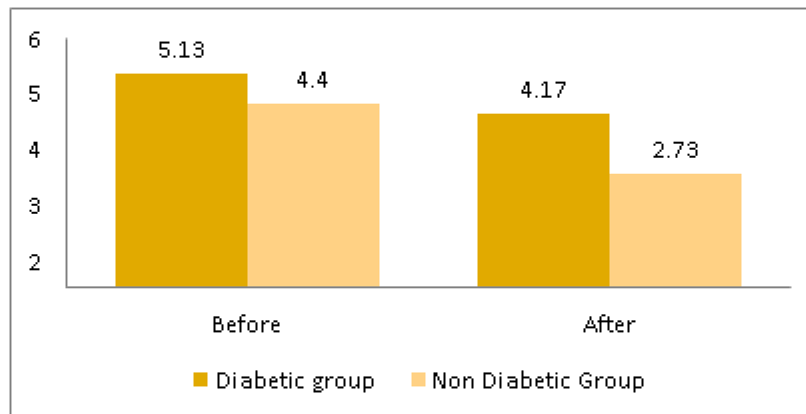

Table 6. Inter and Intra group comparison of Clinical Attachment Loss (CAL) among diabetic and Non-Diabetic groups by Unpaired t-test and Paired t-test respectively

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CAL	(Diabetic group) (n=30)		(Non-Diabetic Group) (n=30)		P-value
	Mean	SD	Mean	SD	(Inter-Group)
Before	6.73	.944	5.60	.675	<0.001*
After	5.13	.730	4.40	.814	0.001*
P-value (Intra-group)					
Pre-op v 1-month	<0.001*		<0.001*		
P-values (Inter-Group) by independent sample t test. P-value (Intra-Group) by Paired t test. P-value<0.05 is considered to be statistically significant. *P-value<0.05, **P-value<0.01, ***P-value<0.001, NS-Statistically non-significant.					

Intra-Group comparison of Clinical Attachment Level by Paired t-test

There is statistically significant difference among baseline Clinical Attachment Level (6.73±0.944) and post Intervention Clinical Attachment Level (5.13±0.730) among Diabetic Group with p<0.001*.

There is statistically significant difference among baseline Clinical Attachment Level (5.60±0.675) and post Intervention Clinical Attachment Level (4.40±0.814) among Non- Diabetic Group with p<0.001*.

Inter-Group comparison of Clinical Attachment Level by independent sample t-test There is statistically significant difference at baseline Clinical Attachment Level in diabetic (6.73±0.944) and non-diabetic (5.60±0.675) with p<0.001*.

There is statistically significant difference at Post intervention Clinical Attachment Level in diabetic group (5.13±0.730) and non-diabetic group (4.40±0.814) with p=0.001*.

Graph 6. Inter and Intra group comparison of CAL among diabetic and Non-Diabetic groups by Unpaired t-test and Paired t-test respectively.

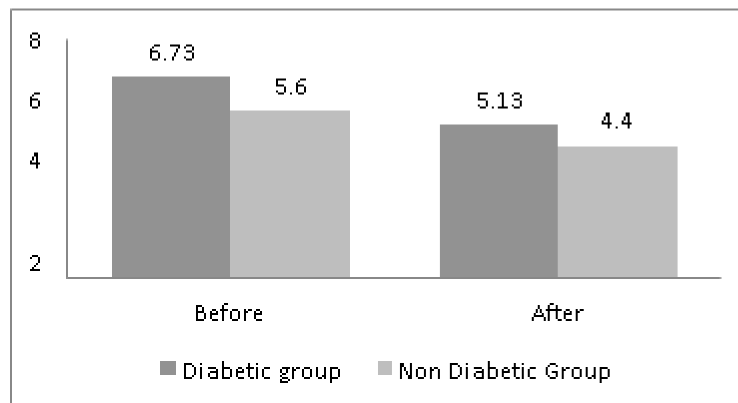

Table 7. Inter and Intra group comparison of Russell's Periodontal Index (RPI) among diabetic and Non-Diabetic groups by Unpaired t-test and Paired t-test respectively

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RPI	(Diabetic group) (n=30)		(Non-Diabetic Group) (n=30)		P-value
	Mean	**SD**	**Mean**	**SD**	**(Inter-Group)**
Before	2.1113	.29372	1.5323	.27843	<0.001*
After	1.8603	.27679	1.1217	.18534	<0.001*
P-value (Intra-group)					
Pre-op v 1-month	<0.001*		<0.001*		

P-values (Inter-Group) by independent sample t test. P-value (Intra-Group) by Paired t test. P-value<0.05 is considered to be statistically significant. *P-value<0.05, **P-value<0.01, ***P-value<0.001, NS-Statistically non-significant.

Intra-Group comparison of Russell's Periodontal Index scores by Paired t-test

There is statistically significant difference among baseline Russell's Periodontal Index scores (2.1113±0.29372) and post Intervention Russell's Periodontal Index scores (1.8603±0.27679) among Diabetic Group with p<0.001*.

There is statistically significant difference among baseline Russell's Periodontal Index scores (1.5323±0.27843) and post Intervention Russell's Periodontal Index scores (1.1217±0.18534) among Non-Diabetic Group with p<0.001*.

Inter-Group comparison of Russell's Periodontal Index scores by Unpaired sample t-test There is statistically significant difference at baseline Russell's Periodontal Index scores in diabetic (2.1113±0.29372) and non-diabetic (1.5323±0.27843) with p<0.001*.

There is statistically significant difference at Post intervention Russell's Periodontal Index scores in diabetic group (1.8603±0.27679) and non-diabetic group (1.1217±0.18534) with p<0.001*.

Graph 7. Inter and Intra group comparison of RPI among diabetic and Non-Diabetic groups by Unpaired t-test and Paired t-test respectively.

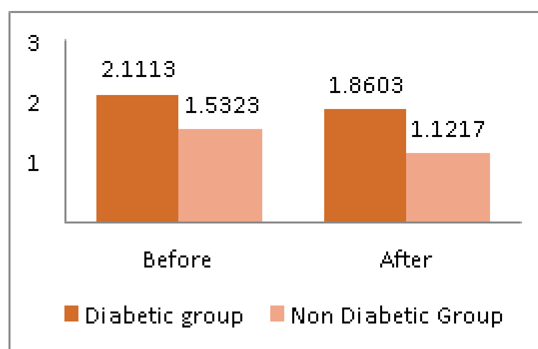

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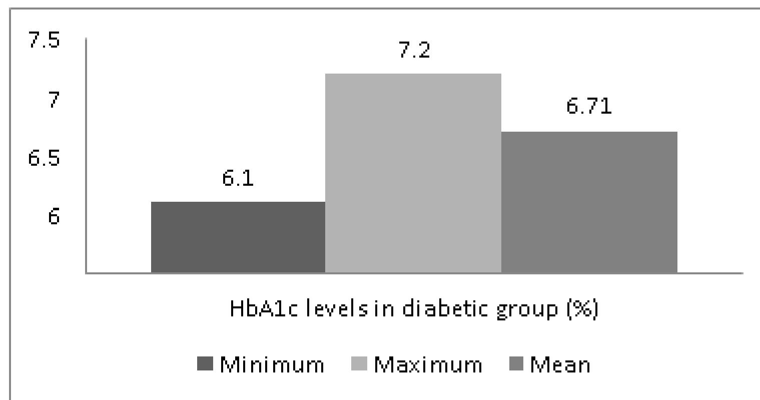
Table 8. Descriptive Statistics for HbA1c among Diabetic Group

Descriptive Statistics[a]						
group		N	Minimu m	Maximu m	Mean	Std. Deviation
Diabetic Group	HbA1c levels in diabetic group (%)	30	6.10	7.20	6.7100	.30439
	Valid N (listwise)	30				

Graph 8. Descriptive Statistics for HbA1c among Diabetic Group



Discussion

Diabetes mellitus is a disease that is associated with several other conditions including dyslipidemia, visceral obesity, and hyperglycemia. Dyslipidemia is one of the most common causes of DM.[58,59] It is fair to argue that periodontitis facilitates its development within diabetic circumstances.[60] It is known that some active molecules that are affected and are elevated in periodontitis, are capable of disrupting the lipid metabolism, but the exact process is still not known. Unhealthy adipose tissue metabolism in t2DM patients is known to affect other organs, as a result of the creation of adipokines, TNF-a, IL-6, and other pro-inflammatory cytokines.[60,61] Chemerin is a new adipokine that participates in both metabolic and immune dysfunction.[62] Literature suggests that inflammatory cytokines play an important role in chemerin generation within the adipose tissue.[63] Abnormal production of chemerin might provoke or intensify the progression of t2DM and periodontitis.[64] Also, periodontitis could participate in the unhealthy expression of chemerin. This would eventually, accelerate unhealthy lipid metabolism in patients with DM. Several studies[58,65,66] have linked chemerin to various inflammatory markers in obesity and t2DM. An earlier investigation[67] found that plasma chemerin levels were greater among patients who are obese and overweight.

Another study established that chemerin levels are notably greater in men than in women. However, serum chemerin levels were lower in male individuals with t2DM.[68] The research proposed that chemerin levels are closely linked with glycemic status, after accounting for age, sex, and BMI.[68] Thus, for the present research, the impact of age and sex on chemerin levels was kept minimal by incorporating a balanced amount of males and females and only choosing participants aged 30 to 60 years. In recent years, researchers[69,70] have examined the link between serum chemerin levels in patients with t2DM. Chemerin serum levels were discovered to be higher within the serum of patients with t2DM than in those with normal glucose levels.[69] Some researchers have demonstrated a connection between higher strengths of circulating chemerin and insulin resistance for patients with both type 1 and type 2 DM.[70,71] In a similar study, chemerin levels in GCF were discovered to be greater in diabetic groups than in control (non-diabetic) groups within this study. The researchers evaluated chemerin levels in GCF,

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because GCF (which offers more data than indicators in saliva) is positioned close to the periodontal tissues in which periodontal disease occours.[63] O'zcan[72] evaluated chemerin levels during periodontal inflammation and found that salivary chemerin levels were notably greater among the periodontitis group than the healthy and gingivitis groups.

Okamura *et al.* was the first to discover IL-18 in 1995. It was originally identified as interferon- ϒ (IFN- ϒ)-inducing factor.[73] IL-18 is a pro-inflammatory and tumor-suppressive cytokine, that belongs to the IL-1 cytokine family, due to its structure, receptor family, and signal transduction pathways.[74,75] The last few years have seen an outburst of studies exploring various aspects of this unique cytokine, although its role in periodontal disease has received relatively scant attention. Nakamura et al. in 2005 conducted a study to demonstrate, that the serum level of IL-18 is a common predictor of nephropathy and atherosclerosis in patients with type 2 diabetes. It was found that serum and urinary IL-18 levels were significantly raised in patients with type 2 diabetes as compared with control subjects. It was concluded that serum levels of IL-18 might be a predictor of progression of diabetic nephropathy as well as cardiovascular diseases.[76] It is well known that the control of Th1/Th2 balance is central to the immune-regulation of periodontal disease.[77,78,79] It is also evident that IL-18 stimulates both Th1- and Th2-mediated responses.[80,81,82,83,84] In addition to its capacity to act as a potent co- stimulus for Th1 induction, and its ability to induce TNF-α and IL-1β in mononuclear cells, IL-18 is able to initiate a cytokine cascade with a concomitant increased expression of pro-inflammatory markers, such as chemokines, nitric oxide, adhesion molecules, and MMP-9.[85,86] These events also occur in chronic periodontal inflammation. Based on *in situ* hybridization studies of tissue extracts and gingival crevicular fluid, Page *et al.* suggested that periodontal health is characterized by low levels of pro-inflammatory cytokines (IL- 1β, TNF- α, IFN- ϒ), PGE2, and MMPs, and by high levels of tissue inhibitors of metalloproteinases and cytokines that suppress the immuno-inflammatory response (IL-10, TGF- α) [87] There have been several studies that related the up-regulation of IL-18 to human inflammatory and autoimmune diseases, including rheumatoid arthritis, psoriasis, type I diabetes, atherosclerosis, and chronic heart failure/coronary heart disease.[88,89,90,91,92,93] In some of these diseases, IL-18 clearly correlated with clinical severity.[75] Interestingly, periodontal disease has also been associated as a risk factor for some of these diseases.[94,95,96] Johnson and Serio (2005) have reported on the concentrations of IL-2, IL-4, IL-6, IL-10, IL-12, IL-18, and IFN- ϒ in the gingival tissues of Dominican Republic Hispanic individuals with healthy and diseased periodontium.[97] Diseased periodontal tissues displaying bleeding on probing were subdivided into 3, 4 to 6, and > 6 mm probing depths. Concentrations of all the cytokines adjacent to 4-6-mm diseased sites were greater than in healthy sites, where IL-12 concentrations were higher. IL-6 and IL-18 concentrations were greater adjacent to > 6 mm sites compared with healthy sites. IL-6 and IL-18 were positively correlated with deep probing depths, while IFN-ϒ and IL-12 demonstrated negative correlations. It was suggested that IL-18 and IL-6 accumulate within the gingiva, possibly contributing to a non-resolving hyper-inflammation mediated by a shift toward a Th2 phenotype.[97]

Correa FOB et al. conducted a study in 2010 and found that the clinically successful non-surgical treatment lead to reduction in the markers of systemic inflammation and the cytokines measured.[98] Most of the differences did not reach statistical significance but some of the findings were relevant. TNF-α is known to play an important role in the pathogenesis of type 2 diabetes, [99] and the correlation of this cytokine with insulin resistance has also been shown in the metabolic syndrome.[100,101] The main finding of this prospective study was that the satisfactory clinical response to non-surgical periodontal therapy was followed by a reduction of circulating TNF-α concentration in T2DM patients. This is in accordance with studies that reported that mechanical periodontal therapy in association with local antibiotic delivery[102] or not[103] reduced circulating TNF-α. In contrast, some studies did not show changes in the TNF-α level in patients with diabetes following periodontal therapy.[104,105,106,107]

The present study aimed to evaluate the effect of non-surgical periodontal therapy on plasma chemerin and interleukin-18 levels in diabetic and non-diabetic patients with chronic periodontitis. Baseline periodontal parameters showed statistically significant difference in probing depth between

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diabetic (5.13±0.730) and non-diabetic (4.40±0.814) with p=0.001*. Similar findings were seen in relation to CAL and Russel's periodontal index. i.e, diabetic (6.73±0.944) and non-diabetic (5.60±0.675) with p<0.001* and diabetic (2.1113±0.29372) and non-diabetic (1.5323±0.27843) with p<0.001*; respectively. These findings are suggestive of greater amount of periodontal destruction in the diabetic group as compared to non-diabetic group.

Also, plasma chemerin and IL-18 levels showed a significant difference, diabetic group (142.0±11.32691) and non-diabetic (118.0567 ±14.44727) with p<0.001* and diabetic (0.3349±0.09340) and non-diabetic (0.2129±.11213) with p<0.001*, respectively. Statistically significant difference was seen in all periodontal parameters as well as plasma chemerin

{diabetic group (138.0013±13.03516) and nondiabetic group (113.1287 ±12.47239) with p<0.001*} and interleukin-18 {diabetic group (0.3224±.09969) and non-diabetic group (0.1993±0.11229) with p<0.001*} levels form baseline to post-intervention in both, diabetic as well as non-diabetic group.

Thereby it is seen that greater amount of reduction of plasma chemerin and interleukin- 18 levels is seen in non-diabetic group when compared to diabetic group. These findings are in accordance to the study done by Correa FOB et al. in 2010.[98] Post intervention intergroup comparison is done, knowing the fact that baseline values of both the biomarkers in both the groups were statistically significant.

Overall, in the present study, it is seen that non-surgical periodontal therapy is effective in reducing plasma levels of chemerin and interleukin-18 in both diabetic as well as non- diabetic patients with chronic periodontitis. Similar finding were seen when periodontal parameters are concerned. However, the non-diabetic group showed higher amount of reductions in clinical as well as biochemical parameters when compared to the diabetic group. The fact that higher amount of biomarkers are found in biological fluids of individuals with inflammatory and debilitating conditions, is already stated in literature. Hence, the related instance in present study can be considered as a confounding factor and a shortcoming of the present study.

Considering the number of comparisons made and the high biological variance among the subjects, it is clear that a larger study population would be needed to draw any final conclusions regarding the effect of periodontal treatment on plasma chemerin and interleukin- 18 levels. Hence, further research should be conducted in larger samples, adding a control group, in order to elucidate the effect of periodontal therapy on metabolic control and on parameters of systemic inflammation in T2DM patients.

Conclusion

The plasma levels of the evaluated biomarkers, that is Chemerin and interleukin-18 were significantly increased in the diabetic patients with chronic periodontitis when compared to non-diabetic individuals with chronic periodontitis. Non-surgical periodontal therapy in both diabetic as well as non-diabetic patients with chronic periodontitis, showed significant decrease in the plasma levels of chemerin and interleukin-18 after 1 month follow up. However, greater decrease in the plasma levels of these biomarkers after 1 month follow up was seen in the non- diabetic group, when compared to the diabetic group.

Non-surgical periodontal therapy lead to significant decrease in clinical parameters like Pocket probing depth, Clinical attachment level and Russel's periodontal index in both, diabetic as well as non-diabetic patients with chronic periodontitis after 1 month follow up; with significant improvement in non-diabetic patients.

Within the limitations of this study, it may be concluded that the clinically successful non-surgical periodontal therapy tends to reduce periodontal inflammation and the concentration of some circulating cytokines, that is Chemerin and interleukin-18, which could be important for T2DM patients.

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