How to Cite:
Shetgaonkar, K. A., Suragimath, G., Varma, A. S., Zope, S. A., & Ashwinirani, S. R. (2022). Effect of non-surgical periodontal therapy (NSPT) on salivary and serum levels of a disintegrin-like and metalloproteinase with thrombospondin-1 (ADAMTS-1). *International Journal of Health Sciences*, *6*(S1), 13395–13407. https://doi.org/10.53730/ijhs.v6nS1.8348

Effect of non-surgical periodontal therapy (NSPT) on salivary and serum levels of a disintegrin-like and metalloproteinase with thrombospondin-1 (ADAMTS-1)

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***Abstract*---**Objectives*:* A Disintegrin -like and Metalloproteinase with Thrombospondin-1 (ADAMTS-1) is a protease with structure similar to Matrix metalloproteinase. ADAMTS-1 has role in wound healing, fibroblast migration, tissue modeling, vasculogenesis and development of neuronal system. The levels of ADAMTS-1 vary in periodontal health and disease. To evaluate the effect of Non-Surgical Periodontal Therapy (NSPT) on salivary and serum ADAMTS-1 levels in generalized periodontitis patients. Methodology: Forty-five subjects suffering from generalized periodontitis were selected and periodontal parameters were assessed using periodontal probing depth (PPD) and clinical attachment level (CAL). Salivary and serum ADAMTS-1 levels were assessed using enzyme-linked immunosorbent assay. NSPT was performed involving scaling and root planning, followed by oral hygiene instructions. The patients were recalled after three months, periodontal parameters and ADMATS-1 levels were analyzed. Pre-NSPT levels of periodontal parameters and ADAMTS-1 levels were compared with post NSPT. Descriptive statistics and paired t-test were applied to compare the variables. P-value < 0.05 was considered

statistically significant. Results: Serum ADAMTS-1 levels pre NSPT was 119.45ng/L and elevated post NSPT to 143.43ng/L. The salivary ADAMTS-1 at baseline was 157.81 and post NSPT 161.53 ng/L and both the values were statistically significant post NSPT. There was statistically significant improvement in clinical parameters, pre NSPT PPD (4.91mm), CAL (4.21mm) and post NSPT PPD (4.15mm), CAL (3.19mm). Conclusions: NSPT improved the patient's periodontal health by reducing PPD and gaining CAL. Salivary and serum ADAMTS-1 levels elevated post NSPT and ADAMTS-1 may be used as a diagnostic marker to assess the periodontal status.

***Keywords*---**ADAMTS-1, Clinical attachment level, Non-Surgical Periodontal Therapy, Periodontitis, Probing pocket depth, Saliva, Serum.

Introduction

A Disintegrin -like and Metalloproteinase with Thrombospondin - 1 (ADAMTS-1) is a protease with structure similar to Matrix metalloproteinase (MMP). ADAMTS-1 is known for its novel dual action, which could be physiologic as well as pathologic to the system.[1] The source of ADAMTS-1 has been suggested to be of multiple cell types. The macrophages are considered primary cells to produce ADAMTS-1 in early and late phase of inflammation. Fibroblasts and keratinocytes also synthesize ADAMTS-1, which are involved in cell differentiation, and turnover.[1] ADAMTS-1 helps in tissue modeling and vasculogenesis, antitumor activity, development of the neuronal system, heart, adrenal glands, adipose tissue, muscle and liver. ADAMTS-1 has a role in tumor metastasis, organogenesis, ovarian folliculogenesis, blood or lymph vessel formation, ovulation and extracellular matrix (ECM) remodeling.[2-8] The ADAMTS-1 can be assessed using Enzyme Linked Immunosorbent Assay (ELISA) in various body fluids such as serum, saliva, gingival crevicular fluid (GCF), etc. Literature mentions that levels of ADAMTS-1 have been altered in gingival health and disease such as gingivitis and chronic periodontitis (CP). ADAMTS-1 is considered as one of the possible factors in the pathogenesis of periodontitis as variation in their levels is associated with periodontal inflammation.

Periodontal disease is a complex inflammatory disease with interplay between bacterial infection and host response to the bacterial challenge. The chemical mediators of inflammation play a fundamental role in the loss of connective tissue and the supporting alveolar bone that act as biochemical markers of periodontal inflammation and tissue degradation. The severity of disease is determined by the variation in concentration of biochemical markers and their presence or absence might be associated with disease progression.

Nonsurgical periodontal therapy (NSPT) is the cornerstone of periodontal therapy, which is first treatment modality to manage the periodontal disease. NSPT includes scaling and root planning, habit counseling, local drug delivery, low level laser therapy, photodynamic therapy, etc. Periodontal treatment with NSPT has

shown to improve the periodontal status by down regulation of inflammatory mediators and reduction in inflammation.

The role of ADAMTS-1 in periodontal health and disease is not yet ascertained. We intend to elucidate the level of ADAMTS-1 pre and post NSPT to better understand its application for future research. With this background the current study was designed to assess the levels of ADAMTS-1 pre and post NSPT in saliva and serum of patients with generalized periodontitis.

Methods

Study design: Forty five patients in the age group of 32-68 years, suffering from generalized periodontitis stage II Grade B were selected according to AAP 2017 Classification. The study was conducted during the time period from February 2021 to December 2021, in Department of Periodontology, School Of Dental Sciences, Krishna Institute Of Medical Sciences "Deemed to be University" (KIMSDU), Karad, Maharashtra, India. The design and consent for this study was approved by Institutional Ethical Committee of KIMSDU (Ref No. KIMSDU/IEC/07/2019, dated on December 30, 2019). The objectives of the study were explained and a written informed consent was obtained from each patient before enrolling them. A flowchart representing recruitment and allocation of study population is given as shown in figure 1.

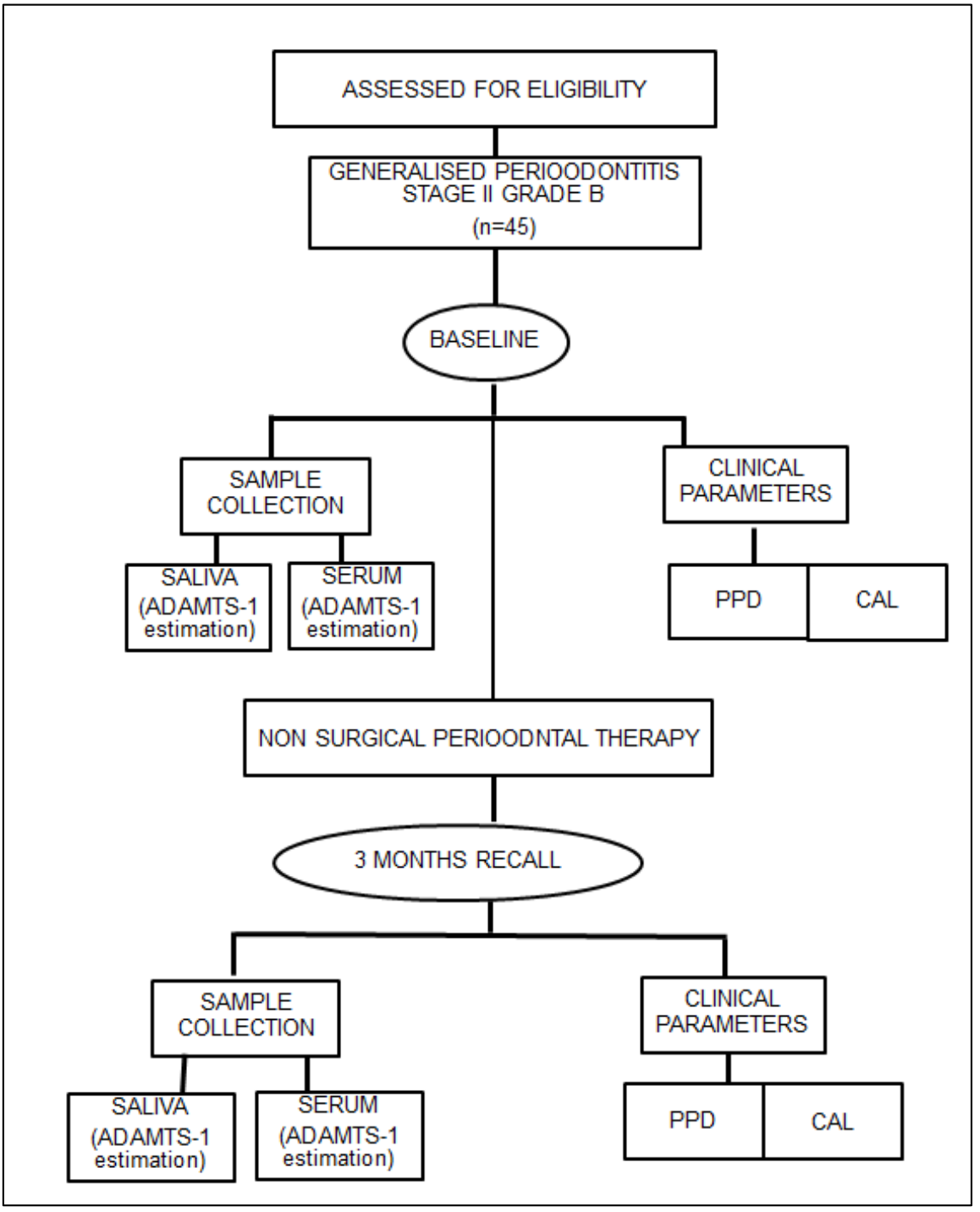

Figure 1: Flowchart representing recruitment and allocation of study population

Inclusion, exclusion criteria and periodontal examination: The inclusion criteria were considered, after radiographic and full mouth clinical periodontal examination including Pocket probing depth (PPD) and Clinical attachment level (CAL). The diagnosis was arrived based on AAP 2017 Classification, where the subjects with PPD < 5mm, CAL 3 to 4 mm and BOP >10% sites were included in the study. The subjects suffering from systemic diseases such as diabetes, hypertension, bleeding disorders, polycystic ovarian disorder (PCOD), cardiovascular diseases (CVD), rheumatoid arthritis (RA), and osteoarthritis were excluded. The patients with recent infections, pregnant and lactating females, tobacco users, patients who had undergone periodontal therapy or taking medications within six months were not considered. The basic demographic data and periodontal parameters were recorded at baseline and post NSPT after three months by a single trained and calibrated operator.

Saliva collection: Unstimulated saliva sample was collected in morning from 10am to 12 pm, two hours after the last meal to standardize the collection according to the circadian rhythm. Under aseptic conditions two ml of saliva was collected by modified draining method into a test tube and centrifuged at 4,000 rpm for ten minutes to remove cell debris. Supernatant of 0.5 ml was transferred into a 1.5 ml plastic vial and stored at –80°C till further analysis.

Serum collection: The blood samples were collected in a red vacutainer by venipuncture method from antecubital fossa and were allowed to clot at room temperature for 30 minutes. The vacutainers were centrifuged at 3,000 rpm for five minutes to extract the serum sample. The desired volume of 0.5 ml of the extracted serum was then stored in a labeled plastic vial, at –80°C until further analysis.

Non-surgical periodontal therapy: The NSPT was carried out post collection of blood and saliva samples by a single trained operator under the guidance of a senior periodontist. In the present study, NSPT comprised of combination of a single sitting scaling using piezo-electric ultrasonic scaling unit (The Netherland's SONIC flex air scalers, KaVo Biberach, Germany) and root planning using Standard Gracey Curretes (HuFriedy, Chicago, IL, USA) followed by self-performed plaque control measures, as per oral hygiene instructions given by the operator.

Recall visit: The subjects were scheduled for recall after three months post NSPT and clinical examination and periodontal evaluation was carried out. The blood and saliva samples were collected and stored by similar procedure conducted at baseline.

Measurement of ADAMTS-1: The levels of serum and salivary ADAMTS-1 were determined using Alliaz Bio® ELISA kit as per manufacturer's instructions (Figure 2). The values of ADAMTS-1 were obtained on ELISA reader (Lisa Quant TS, Tulip Diagnostics Pvt. Ltd., Goa, India) at 450nm absorbance. The salivary and serum ADAMTS-1 levels were calculated using quadratic regression equation.

Figure 2: Components of ELISA kit

Statistical analysis: The data obtained was compiled and arranged in Microsoft Excel 2010. All the analysis were performed using SPSS (Statistical Package for the Social Sciences) software version 26. The p-value < 0.05 was considered statistically significant. The descriptive statistics were expressed as mean ± standard deviation (SD) for serum and salivary ADAMTS-1 levels. The PPD, CAL measurements for pre and post-NSPT were compared using paired t-test.

Results

Gender distribution and Age statistics: A total of 45 patients were included in the study, with mean age of 43.2 years and a male to female ratio 1:1.2. (Table 1)

Table 1: Age and gender distribution of study subjects

	Frequency (N)	Percentage (%)	Minimum	Maximum	Mean	SD
Combined	45	100%	32	68	43.2	8.99
Male	20	44.4%	32	65	46.1	10.23
Female	25	55.6%	32	68	40.88	7.27

Biochemical findings: Significant elevation in serum ADAMTS-1 levels was observed from baseline (119.45 ng/litre) to three months post-NSPT (143.43 ng/litre), which was statistically significant ($p<0.05$). (Table 2)

Table 2: Comparison of serum ADAMTS-1 levels pre and post NSPT.

Serum ADAMTS-1	Mean	SD	Mean Difference ± S.E	Paired 't' test value	p value, Significance
Pre (n=45)	119.45	86.75	23.98 ± 78.88	t = -2.039	p = 0.047*
Post (n=45)	143.43	36.95			

*p<0.05 – significant difference

Significant elevation in salivary ADAMTS-1 levels was noted from baseline (157.81 ng/litre) to three months post-NSPT (161.53 ng/litre), which was statistically significant (p<0.05) (Table 3)

Table 3: Comparison of salivary ADAMTS-1 levels pre and post NSPT.

Salivary ADAMTS-1	Mean	SD	Mean Difference ± S.E	Paired 't' test value	p value, Significance
Pre (n=45)	157.81	10.82	4.35 ± 1.41	t = 3.085	p = 0.004*
Post (n=45)	161.53	10.79			

*p<0.05 – significant difference

Clinical findings: There was improvement in the clinical parameters (PPD and CAL) from baseline to post-NSPT, which showed significant differences with p-value < 0.001 (Table 4).

Table 4: Comparison of PPD and CAL pre and post NSPT.

	Mean	SD	S.E	Minimum	Maximum	p value, Significance
Pre PPD (n=45)	4.91	0.38	0.05	4.11	5.7	p < 0.001
Post PPD (n=45)	4.15	0.75	0.11	1.7	5.13	p < 0.001
Pre CAL (n=45)	4.21	0.26	0.04	4	4.19	p < 0.001
Post CAL (n=45)	3.19	0.52	0.07	2.1	4	p < 0.001

Discussion

Periodontal disease includes inflammatory conditions that affect the supporting structures of the teeth; periodontium. The periodontal disease initiates and propagates through a dysbiosis of the commensal oral microbiota (dental plaque),

which further interacts with the host immune defense leading to inflammation and tissue breakdown.[2] Even though the periodontal destruction is triggered by bacterial infection, the major role is played by the host's immune response, which is implicated in the pathological process leading to periodontal tissue destruction.

ADAMTS-1 is proven to stimulate pro-tumorigenic changes like elevated tumor cell proliferation, inhibition of apoptosis and altered vascularization.[3] It has a significant role in peritumoral remodeling of the extracellular matrix environment to promote tumor progression and metastasis, but there is contradictory literature that suggests ADAMTS-1 is a tumor suppressor. Initially, ADAMTS-1 was designated to be a mediator of inflammation but its actions has also been recognized in organogenesis, ovarian folliculogenesis, blood or lymph vessel formation, ovulation, follicle development and gametogenesis.[2-10] ADAMTS proteases play major roles in organ development and tissue homeostasis by regulating extracellular matrix (ECM) formation, remodeling and homeostatic adaptation.[11] During physiological events, ADAMTS-1 aids in remodelling the ECM through the proteolytic degradation of key substrates such as chondroitin sulfated proteoglycans and collagen.[12-18] ADAMTS-1 also has a key role in inhibition of angiogenesis by sequestration of proangiogenic stimulus, Vascular epithelial growth factor (VEGF) and prevention of its interaction with its receptor.[4,19] The dysregulation of ADAMTS-1 leads to pathological manifestations of altered ECM and/or vascular density.[20-26] The studies have highlighted functional activity of ADAMTS-1 during tumorigenic transformation.[20-30] ADAMTS-1 dysregulation is linked to four of the most commonly diagnosed cancers, but conflicting reports currently surround its expression in cancer, as different studies have shown both up- and down regulated expression of ADAMTS-1 in primary tumors compared with healthy tissue controls. [27,28,31-38] ADAMTS-1 has been ascribed to have both pro- and anti-tumorigenic activities with poor understanding of the specific mechanisms it mediates to promote or inhibit tumorigenesis. Irrespective of the direction of regulation, perturbations in ADAMTS-1 expression are commonly associated with the transition to malignancy and changes in the peritumoral environment, tumor vascularity and tumor cell behavior. [4,27-29,39,40] The novel dual function of ADAMTS-1 in fibroblast migration is as follows at lower concentrations of ADAMTS-1, it stimulates fibroblast migration via its proteolytic activity and in high concentrations, it inhibits fibroblast migration because of binding to fibroblast growth factor-2 (FGF-2), which subsequently inhibits its promotogenic activity.[1] ADAMTS-1 also has a role in keratinocyte differentiation and migration of fibroblasts and endothelial cells.[41] The role of ADAMTS-1 in periodontal pathogenesis is said to be through the regulation of inflammation and vascularization and its levels are associated with tissue inflammation.[40]

Nonsurgical periodontal therapy (NSPT) which is the "Cause-related therapy," is the first recommended approach to the control of periodontal infections.[42] In the current study, NSPT performed included complete supragingival and subgingival scaling and root planning followed by oral hygiene instructions, patient motivation and reinforcement. The study employed saliva sample due to its non-invasive method of collection and also the study anticipated to expand the horizon of salivary biomarkers to be used in assessment of periodontal status. The

collection of serum sample elucidates an overall indication of effect of the biomarker on the oral and systemic health.

The results of the present study showed a significant increase in salivary and serum levels of ADAMTS-1 following NSPT which is in accordance with the findings observed in the study by Tayman et al where serum ADAMTS-1 in patients with Generalized Chronic Periodontitis was lower than healthy controls.[40] The elevated levels of ADAMTS-1 in healthy controls as compared to patients with generalized periodontitis suggest that level of ADAMTS-1 is higher in periodontal health as compared to periodontal disease. This explains the rise of ADAMTS-1 in our subjects after NSPT. The results indicate that NSPT improved the periodontal status of the patient from disease towards health. The raised levels of ADAMTS-1 post NSPT could be due to the widespread infiltration of inflammatory cells and migration of keratinocytes which is proven to appear after scaling and root planning. The keratinocytes and fibroblasts, may have contributed to increased production of ADAMTS-1 in the periodontal tissue post NSPT. The up regulation of ADAMTS-1 post NSPT will aid in wound repair by keratinocyte differentiation and fibroblasts migration. The fibroblasts in turn play a crucial role during periodontal wound healing.[2]

The assessment of periodontal disease using analysis with salivary diagnostic tests are primarily based on exploration of its molecular components, periodontal pathogens and DNA for assumed genetic risk.[43,44] The collection of saliva is advantageous as it is easy to collect and reflects the activity of all periodontal sites in the oral cavity.[45] This provides an indication of disease status in the mouth as a whole than at individual sites as with GCF analysis. To best our knowledge, this study is the first one to analyze the levels of ADAMTS-1 in saliva pre and post NSPT. The study by Tayman et al analyzed ADAMTS-1 in GCF and showed higher levels of ADAMTS-1 in healthy controls than patients with Chronic Periodontitis.[40] This could be owed to patients being systemically healthy and also suggested increase in ADAMTS-1 in GCF in healthy subjects could be due to lack of local tissue inflammation.

In our study, there was a significant improvement in all periodontal parameters following NSPT. There were reductions in PPD and gain in CAL three months after NSPT through the resolution of the periodontal inflammation. The results are in accordance with the study conducted by Teughels W et al and Deas DE et al, where improvement in periodontal status was observed following NSPT.[46, 47]

Our data suggests that changes in periodontal status and ADAMTS-1 levels may be attributed to reduction in the periodontal inflammation through NSPT. This implies that periodontal inflammation may down regulate the serum and salivary ADAMTS-1 levels in patients with generalized periodontitis Stage II Grade B. Hence, NSPT was successful in restoring the levels of ADAMTS-1 and periodontal health status.

Limitations

The small sample size and limited recall visit restricted the scope of our study. The inclusion of groups such as healthy controls could have enabled intergroup comparison.

Future perspective:

Longitudinal interventional studies should be conducted with large sample size to enhance the outcome and explore the role of ADAMTS-1 pre and post periodontal therapy.

Conclusion

NSPT improved the patient's periodontal health by reducing PPD and enabling an improvement in CAL. NSPT was able to alter salivary and serum ADAMTS-1 levels from disease to health of the periodontal tissues. The assessment of ADAMTS-1 levels in saliva could serve as biomarker to assess periodontal disease activity.

Ethics approval and consent to participate

The Ethical clearance for the study was obtained from the Institutional Ethical Committee (EIC) of KIMSDU, Karad, (Ref. No. KIMSDU/EC/06/2021, dated: 25/08/2021). The written informed consent was taken from the patient for research publication.

Availability of data and material

Data that support the findings of this study are available from the corresponding author and shall be produced upon reasonable request

Competing interests: None

Funding statement: This study was funded by Krishna Institute Of Medical Sceinces, Deemed-to-be-University, Karad, Maharashtra, India.

Authors' contributions

Kirti Shetgaonkar, Girish Suragimath: Conceptualization, data analysis, data visualization, methodology, writing, review, and editing. A. Siddhartha Varma, Ashwinirani SR: Review, Editing, data validation, methodology and review. Sameer A. Zope: Review, Editing, data validation, methodology and review.

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