



Assessment of Resistin Level Using Azithromycin as an Adjunctive to Non-Surgical Treatment of Periodontitis Patients with Type II Diabetes Mellitus

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ABSTRACT

Purpose: This study was designed to evaluate the resistin levels in gingival crevicular fluid (GCF) of patients suffering from periodontitis and type II diabetes mellitus (TIIDM) after non-surgical periodontal therapy and Azithromycin (AZM) as adjunctive therapy. **Subjects and Methods:** 48 patients with periodontitis their age ranging between (20-50) years old were selected for this study were divided into three groups: (group I): healthy patients with periodontitis, (group II): controlled TIIDM patients with periodontitis, and (group III): controlled TIIDM patients with periodontitis who were received AZM. All patients received non-surgical periodontal therapy (NSPT) and were examined with the following clinical periodontal parameters which are plaque index (PI), gingival index (GI), probing depth (PD) and clinical attachment level (CAL) at baseline, 1 month and 3 months. Collection of GCF samples was done in all patients at baseline, 4 weeks and 6 weeks. Following the periodontal therapy. Quantification of resistin in human samples was measured using resistin ELISA test. **Results:** NSPT was found to show relative improvement in all clinical parameters as well as a decline in resistin levels. In addition, GCF levels of resistin, GI and PI showed greater reduction after non-surgical treatment in group III than group I and II with non-significant difference. **Conclusion:** NSPT is found to be effective in the management of periodontitis patients with and without diabetes mellitus and also GCF resistin can be a potential biomarker to detect the periodontal disease condition. Also, adjunctive use of AZM showed clinical benefit to patients with periodontitis by its role on host response modulation.

KEYWORDS

*Periodontitis, Diabetes Mellitus,
Resistin, Azithromycin.*

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INTRODUCTION

Periodontal disease was described as a chronic multifactorial inflammatory disease attributed with dysbiotic biofilms and grown specifically by gradual destruction of the supporting apparatus manifested by clinical attachment loss (CAL), radiographically evaluated alveolar bone loss, periodontal pocketing and gingival bleeding⁽¹⁾.

One of the medical conditions that exaggerate the host antibacterial defense mechanisms is diabetes mellitus. One of the major oral symptoms of diabetes is periodontal disease. Periodontal condition is at high risk in patients with undiagnosed or poorly controlled diabetes mellitus⁽²⁾. The most fundamental characteristic of DM and periodontal disease pathogenesis is inflammation. Pathways that increase inflammation, oxidative stress and apoptosis which are triggered by hyperglycemia. The onset of Type II DM can be predicted using serum IL-6 and C-reactive protein (CRP) levels. Insulin resistance and Type II DM are associated with such high CRP levels^(3,4).

A two-way pathway is established for periodontitis and diabetes, so periodontal assessment is a must to be part of the clinical evaluation of diabetes patients and if diagnosed, periodontal treatment should be effective to avoid exacerbation of diabetes complications in addition to enhancing glycemic control in these individuals⁽⁵⁾. Non-surgical periodontal treatment (NSPT) is the cornerstone of periodontal treatment and the first recommended strategy to manage periodontal disease. As refers to as "Cause-related therapy"⁽⁶⁾.

Therefore the concept of host modulation therapy was proposed that targets particular aspects of the inflammatory response aimed at altering the host response by reducing the harmful aspects or encouraging the inflammatory response regenerative/healing mechanism.⁽⁷⁾

Although in periodontics, host modulation therapy is still limited to a few FDA approved agents

such as sub-antimicrobial dose of doxycycline (SDD) in NSPT and locally administered Enamel matrix derivative (Emdogain®) and Growth-factor Enhanced Matrix (GEM 21S®) in the surgical approach. Currently approved medications are associated with periodontal therapy, which can enhance clinical responses, lessen disease progression and assist in more predictable patient management⁽⁸⁾.

There is evidence supporting the triple role of azithromycin in periodontal therapy through suppression of periodontopathogens, anti-inflammatory activity and enhancement of healing as azithromycin persists at low levels in periodontal tissue macrophages and fibroblasts and is concentrated in neutrophils, macrophages and particularly fibroblasts⁽⁹⁾.

One such newly recognized marker is resistin, which is a protein rich in cysteine found in the inflammatory region⁽¹⁰⁾. Resistin upregulates the expression of proinflammatory cytokines such as TNF-alpha, IL-6, IL-12 and macrophages with monocyte chemoattractant protein (MCP)-1. In addition, circulatory resistin is associated in the general population and in individuals with T2DM with inflammatory and fibrinolytic markers such as CRP, TNF-alpha, and IL-6⁽¹¹⁾.

Thus, the aim of the present study was to evaluate the resistin levels in GCF in patients with periodontitis and T2DM after NSPT and adjunctive use of azithromycin.

SUBJECTS AND METHODS

Forty eight Patients were selected from those attended to the Outpatient Clinics of Oral Medicine, Periodontology, Oral Diagnosis & Radiology department, Faculty of Dental Medicine for Girls, Al-Azhar University, clinically diagnosed as having at least one site with CAL \geq 5mm. And ethical committee approval (Code: REC 18-084) was obtained before the study. The criteria for inclusion in the present study were including

patients systemically free from any conditions that affect periodontium or interfere periodontal treatment except controlled T1DM according to the modified Cornell Medical Index, non-smokers, did not receive any periodontal treatment in the past three months before the examination, and not receive antibiotics or anti-inflammatory therapy in the three months before the examination and for female patients, no pregnancy or lactation was included.

Patient grouping

The selected patients were divided into the following three groups:

Group I: Sixteen patients with periodontitis (systemically free).

Group II: Sixteen type II Diabetes Mellitus patients with periodontitis.

Group III: Sixteen type II Diabetes Mellitus patients with periodontitis who will receive azithromycin dosage is 250 mg/day for 5 days, after an initial dose of 500 mg one hour before NSPT ⁽¹²⁾.

All individuals were informed about the procedures of the study and benefits of their participation in the study. A satisfactory written consent was obtained from all the patients denoting they're convinced about the schedule research program design. Ethical committee meeting approved the study protocol.

Each patient's periodontal status was evaluated by measuring the plaque index (PI), gingival index (GI), probing depth (PD), clinical attachment loss (CAL); at the baseline, one month and at 3 month intervals by using Williams graduated periodontal probe. The deepest PD was selected.

Collection of Samples

Specimens were collected from gingival crevicular fluid (GCF) at the baseline, four weeks, and six weeks following periodontal therapy. The

samples were collected from the selected sites. The sample area was isolated with cotton rolls and cautiously cleaned supra-gingival with sterilized cotton pellets, then a sterile absorbent paper point was inserted into the gingival crevice until resistance and held in position for 30s. The samples were immediately put in Eppendorf tubes and rapidly delivered to the laboratory and stored at -80°C. The collected samples were analyzed by the enzyme-linked immunosorbent assay (ELISA) technique of human resistin kits.

Non-Surgical Periodontal Therapy

All patients in each group were treated with nonsurgical periodontal therapy, which included the following: supra-gingival and subgingival scaling and root debridement. They were performed with manual instruments and an ultrasonic device. Chlorohexidine mouthwash was prescribed twice daily for two weeks post periodontal therapy and oral hygiene instructions included teeth brushing using soft dental brush two times daily and suitable interdental aids once a day were prescribed.

Quantification of Human Resistin Using ELISA Technique

Quantification of resistin in human samples was measured using two human resistin ELISA kits which are an in-vitro quantitative assay based on the concept of competitive enzyme immunoassay for resistin peptide detection. The kit is suitable for testing a variety of sample types in vitro, such as serum, plasma, cell culture supernatants and urine and purchased from Sigma-Aldrich Co. US. The kit assayed resistin level in the sample, using a microplate which is pre-covered by anti-rabbit secondary antibody. Both peptide standard (targeted peptide) and biotinylated resistin peptide react competitively with the resistin antibodies after a blocking stage and plate incubation in samples using anti-resistin antibodies. The uncompetent biotinylated resistin

peptide then interacts with the catalyzed color reaction of Streptavidin-horseradish peroxidase (SA-HRP). The frequency of the colorimetric signal is inversely proportional to the amount of resistin peptide in the samples but directly related to the amount of biotinylated peptide complex SA-HRP. This is due to the competitive resistin antibody binding in standard or samples between the biotinylated resistin peptide and peptides. It is possible to identify a regular curve of identified resistin peptide levels and measure the resistin peptide concentration in the samples accordingly. So the concentration of resistin in the specimens is determined by comparing the curve to the O.D. In such samples.

Statistical analysis

Values have been presented as values of mean and standard deviation (SD). Data for normality was evaluated using the Kolmogorov-Smirnov normality test. The findings of the Kolmogorov-Smirnov test showed that CAL and PD data were normally distributed (parametric data), so one way variance analysis (ANOVA) was used for comparative purposes. This was followed by the post hoc test by Tukey where the gap was considered to be significant. Data for GI and PI were non-parametric, therefore Kruskal Wallis test was used for comparison between groups, while Friedman test and Wilcoxon signed Rank test were used to study the effect of time. The difference by time was calculated as: Value after-value before the percent change by time was calculated by the formula

$$\frac{\text{Value after-value before}}{\text{Value before}} \times 100$$

Kruskall Wallis test was used for comparison between groups regarding difference and percent

change by time. The level of significance was set at $p < 0.05$. With SPSS 18.0 (Statistical Package for Research Projects, SPSS, Inc., Chicago, IL, USA) for Windows, statistical analysis was done.

RESULTS

Table (1) showed the changes in the clinical parameters measurements and resistin at baseline, 1-month and 3-months after NSPT in each group. In all groups, the highest mean value of each PI, GI, PD and CAL was recorded at baseline and a decrease was revealed in all parameters in the following observation times. The highest improvement was recorded in Group I, followed by Group III and the least improvement was in Group II in PD and CAL parameters, with no significant difference between Group I & III. Whereas Group III recorded the highest improvement in GI and PI. Regarding resistin, the highest mean value of resistin level was recorded at baseline and a statistically significant decrease was revealed at 1-month and 3-months respectively. However, no statistically significant difference between each the 1-month and 3-months observation times.

Figure (1) illustrated resistin changes throughout the study. The highest mean value was recorded in Group III, whereas the lowest mean value was recorded in Group II, with no significant difference between groups at baseline. Whereas at 1-month, the highest mean value was recorded in Group III, and the lowest mean value was recorded in Group I, with no significant difference between groups. While at 3-months the highest mean value record was in Group II where the lowest record was in Group III with no significant difference between groups.

Table (1) Changes of PI, GI, PD, CAL and Resistin between groups throughout the study (effect of time) [ANOVA and Friedman test]

	Time	Group I			Group II			Group III		
		Mean	Std. Dev	P value	Mean	Std. Dev	P value	Mean	Std. Dev	P value
PD	Baseline	5.56	.60		5.21	1.10		4.56	1.22	
	1 month	4.63	.56	0.00*	4.71	.96	0.00*	3.89	1.02	0.00*
	3 months	3.50	.52		4.00	.78		3.00	.97	
GI	Baseline	2.38	.50		2.29	.47		2.22	.43	
	1 month	1.38	.50	0.00*	1.43	.51	0.00*	1.38	.49	0.00*
	3 months	.63	.72		.86	.66		.56	.70	
PI	Baseline	2.25	.68		2.29	.47		2.11	.58	
	1 month	1.38	.50	0.00*	1.29	.47	0.00*	1.22	.43	0.00*
	3 months	.63	.72		1.00	.78		.33	.49	
CAL	Baseline	3.38	.50		4.79	.96		4.89	.93	
	1 month	2.44	.48	0.00*	4.21	1.24	0.00*	4.06	1.04	0.00*
	3 months	1.50	.52		3.71	1.44		3.11	.90	
Resistin	Baseline	21.44	12.63		19.68	6.37		22.38	4.37	
	4 weeks	14.91	2.43	0.00*	15.40	5.34	0.00*	15.65	3.23	0.00*
	6 weeks	12.34	1.96		14.05	4.71		12.03	2.58	

Significance level $p < 0.05$, * significant

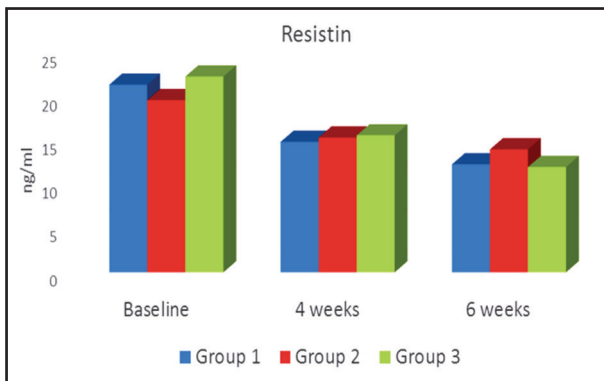


Figure (1) Bar chart showing mean Resistin level in different groups

DISCUSSION

There is significant evidence that the risk of dysglycaemia and insulin resistance is high in people with periodontitis which is also associated with an increased risk of diabetes incidence. Mechanistic associations between periodontitis and diabetes include elevations in the ratio of IL-1-β, TNF-alpha, IL-6, receptor activator nuclear factor-kappa B

ligand (RANKL)/osteoprotegerin(OPG), oxidative stress and toll-like receptor (TLR) expression⁽¹³⁾.

For periodontal disease to occur, the relationship between the host response and the composition of the subgingival biofilm is not just the involvement of a single periodontal pathogen, but also the interplay where host factors and complex niches play an important role. In addition to the decreased inhibitory effect of commensal bacteria, there is an excess of immune-stimulating pathobionts and their virulence factors in dysbiotic biofilms, which results in an aggravated inflammatory response^(14,15).

Although NSPT is effective in improving clinical parameters such as PDs, it may not be sufficient, particularly in more susceptible patients, such as diabetes mellitus, to reduce excessive levels of several underlying destructive inflammatory mediators. Adjunctive use of the host modulatory agent could positively impact clinical outcomes in the management of periodontitis by down regulating different biological inflammatory mediators⁽¹⁶⁾.

Resistin, a putative signalling polypeptide derived from adipocytes, is named after its proposed insulin resistant function. This cysteine-rich molecule belongs to the adipokine group. However, very little resistin is expressed in adipocytes in human studies and is principally expressed in neutrophils, macrophages and monocytes. Human resistin also functions as a pro-inflammatory molecule and induces the synthesis and secretion of pro-inflammatory cytokines: TNF- α , IL-6, IL-12 and MCP-1⁽⁴⁷⁾. Hence, it has been shown that the levels of GCF resistin can be regarded as a biomarker for diagnosis/prognosis of the severity of periodontitis patients with/without diabetes mellitus⁽⁴⁸⁾.

The results of current study showed that by comparing clinical parameters demonstrated that there was an improvement in all clinical parameters (PD, GI, PI and CAL) in all groups with no significant difference between groups after a period of 3 months from NSPT. These results was in agreement with several studies that showed either NSPT alone or in conjunction with adjunctive therapy could improve the clinical outcomes with controlled T1DM periodontitis patients⁽¹⁹⁻³⁰⁾. Group III who received azithromycin showed the highest improvement in GI. These results could be explained by the fact that SDD could enhance the results of a number of mechanical nonsurgical interventions by inhibition of MMPs which is involved in periodontal tissue destruction⁽³¹⁾. In addition to the effect of azithromycin is due to highly uptake by fibroblasts and acute reactant cells, such as neutrophils, macrophages, monocytes, and lymphocytes which is increased in inflamed tissues⁽³²⁾. AZM has been shown to decrease proinflammatory cytokine expression such as IL-1 β , IL-6, IL-8 and TNF- α , growth factors such as granulocyte-macrophage colony-stimulating factor, and also increase the amount of alveolar macrophages actively phagocytosing⁽³³⁾. Down regulation of these cytokines would lead to its anti-inflammatory property⁽³⁴⁾.

In addition, GCF resistin levels are the highest in all groups' baseline. The rise in resistin secretion

could be due to the local inflammatory condition in the periodontium and a systemic inflammatory state due to hyperglycemia. GCF levels of resistin significantly decreased by time in all groups after SRP to reach the lowest mean value at 6 weeks. Also, at 3 month, the present study found that group III showed the greatest reduction in GCF levels of resistin. This could be due to that azithromycin could induce changes in the phenotype of the macrophage, resulting in the shift from the phenotype M1 to M2⁽³⁵⁾. The M2 phenotype displays a markedly different activation pattern and plays another role in steering a humoral response from Th2 and improving repair after the inflammatory reaction. As mentioned previously, resistin is mainly produced by macrophages. Reduction of inflammatory cytokine production by macrophages noted after administration of azithromycin⁽³⁶⁾.

CONCLUSION

NSPT resulted in a decrease of resistin level in all groups. Moreover, adjunctive use of azithromycin with NSPT resulted in more reduction in GI, GCF resistin in periodontitis T1DM patients compared to periodontitis patients with T1DM who did not receive azithromycin.

CONFLICT OF INTEREST

None declared.

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