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Original Article

Dentistry Section

Efficacy of Systemic Administration of Alpha Lipoic Acid and Scaling and Root Planning in Patients with Chronic Periodontitis and Type 2 Diabetes Mellitus-A Randomised Controlled Trial

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ABSTRACT

Introduction: Both diabetes and periodontitis are globally rampant diseases with common risk factors. Current evidence points to a bidirectional inter-relationship between diabetes and periodontitis and it has been hypothesised that inflammation, lipids and adipokines may mediate this relationship. Resistin is an adipokine whose levels are elevated in patients with insulin resistance. Oxidative stress has a pivotal role to play in the progression of both the diseases, and antioxidants like Alpha Lipoic Acid (ALA) and Non Surgical Periodontal Therapy (NSPT) may improve the disease outcome.

Aim: To evaluate the effect of systemic administration of ALA as an adjunct to Scaling and Root Planing (SRP) on serum resistin levels and Glycated Haemoglobin (HbA1c) in patients with chronic periodontitis and type 2 diabetes mellitus.

Materials and Methods: This study was a randomised interventional single blinded clinical trial conducted on 40 patients, 18 males and 22 females, aged between 35 and 60 years. Subjects with type 2 diabetes and chronic periodontal disease were recruited in the study. The samples were equally divided into groups A and B. A total of 20 patients in group A were administered ALA systemically, 600 mg thrice a day for three months after SRP, whereas 20 patients in group B underwent SRP only. Clinical parameters like Gingival Index (GI), Probing Pocket Depth (PPD), and Clinical Attachment Levels (CAL) as well as the HbA1c and serum resistin levels were measured at baseline and three months after NSPT. Intragroup comparison was done by paired t-test for continuous data and Wilcoxon signed rank test for score data and intergroup comparison was done by unpaired t-test for continuous data and Mann Whitney U test for score data. Data was analysed by Statistical Package for Social Sciences (SPSS) version 22.0.

Results: Both group A (test) and group B (control) showed significant improvement in relation to clinical parameters, as well as HbA1c and serum resistin levels, however when an intergroup comparison was made, patients in group A showed statistically significant results over group B.

Conclusion: ALA systemically administered after NSPT in the test group proved to be efficacious in improving the clinical parameters as well as in reducing the levels of serum resistin and HbA1c.

Keywords: Clinical parameters, Quantitative sandwich enzyme immunoassay technique, Spectrophotometric analysis

INTRODUCTION

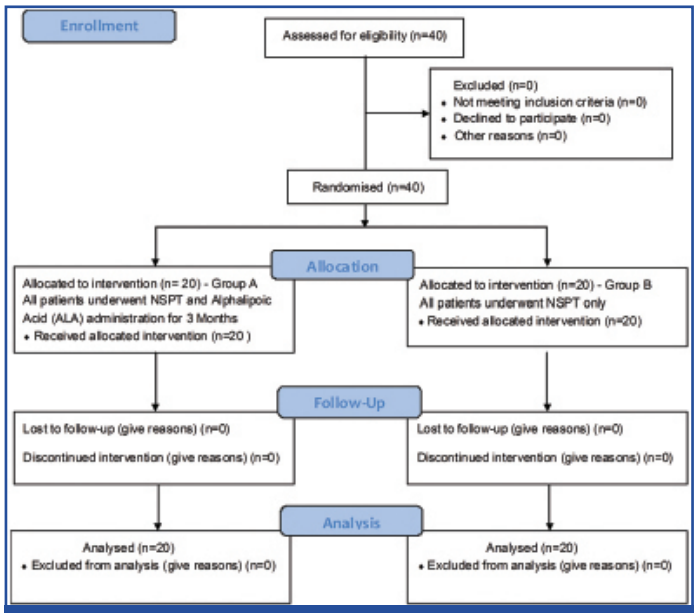
Periodontitis and diabetes mellitus are chronic inflammatory diseases with common risk factors. Periodontitis is initiated when the host response is unable to ward off the attack by putative microorganisms which thrive in the plaque biofilm.

As the disease progresses, the host response is exaggerated, wherein there is an increased production of inflammatory cytokines, Matrix Metalloproteinases (MMPs), Reactive Oxygen Species (ROS) which in turn cause deleterious effects on the periodontium and alveolar bone [1,2]. Diabetes mellitus, a globally rampant disease, occurs when the body does not produce enough insulin to maintain optimal levels of glucose in the blood, resulting in hyperglycemia. Hyperglycemia initiates oxidative stress and also stimulates the Receptor Activator of Nuclear factor Kappa B Ligand (RANKL), Osteoprotegerin (OPG) pathway to cause immune dysfunction, cellular stress and cytokine imbalance. Advanced glycation end products which are formed due to the increased blood glucose levels aggravate the condition, resulting in enhanced tissue destruction and periodontitis [3,4]. Resistin is an adipokine whose levels are elevated in patients afflicted with diabetes [5,6,7]. Periodontitis can also initiate diabetes as the microorganisms dampen the immune response of the host, causing insulin resistance and thus diabetes [8]. Both the diseases stimulate the release of ROS which along with the MMPs and cytokines cause connective tissue and bone loss. SRP (NSPT) as a therapeutic option has been reported in many studies to improve the HbA1c levels and thus the diabetic status of the individual gets better [9-11]. Antioxidant therapy directed against the ROS has also been reported to improve the disease outcomes of both the diseases [12,13]. The aim of the present study was to assess the beneficial effects of NSPT and ALA administration on HbA1c and resistin levels in patients with both diabetes and periodontitis.

MATERIALS AND METHODS

This was a randomised interventional single blinded clinical trial which was carried out in Department of Periodontics of Panineeya Mahavidyalaya Institute of Dental Sciences and Research Centre in collaboration with Mohan's Diabetic Centre, Domalguda, Hyderabad, Telangana, India. The patients were selected from the outpatient ward of Mohan's Diabetic centre, and included both the sexes. The guidelines of Helsinki declaration of 1975 as revised in 2000, were strictly followed while conducting the

study. This study was approved by the Institutional Review Board and registered in clinical trials registry (NCT 02775266). A written informed consent form was signed by each patient before the start of the study. To get a mean difference of 8.20 in serum resistin levels between the test and control group with a standard deviation of 8.7, with power being 80% and level of significance 5%, the required sample size for each group was calculated to be 20 [6]. This study included 40 patients with uncontrolled diabetes mellitus (HbA1c levels >6.5 upto 10%) and generalised chronic periodontitis, aged between 35-60 years, with a mean age of 50.3 years, who were equally divided into group A (test) and group B (control) [Table/Fig-1].



[Table/Fig-1]: CONSORT 2010 flow diagram.

Inclusion Criteria

Patients recently diagnosed (<1 month) with Type 2 diabetes with HbA1c levels ≥6.5%. As per ADA (American Diabetes Association) criteria and taking metformin 500 mg/day by oral route, and chronic periodontitis as per American Academy of Periodontology (AAP) guidelines (which included presence of minimum of 15 natural teeth and at least four teeth with one or more sites with Probing Depth (PD) ≥5 mm, CAL ≥4 mm and Bleeding On Probing (BOP)) were included in the study [14,15].

Exclusion Criteria

Patients with systemic illness other than diabetes, smokers, pregnant and lactating women, patients who had undergone SRP and those who were on systemic antibiotics for the past three months were excluded from the study.

Selection Criteria: All the patients meeting the selection criteria were consecutively enrolled from December 2015 to February 2016. A total of 20 patients in group A (test group) underwent SRP after which ALA 600 mg was administered systemically thrice a day for three months [12]. In group B (control group), 20 patients underwent SRP only. The eligible samples were screened and randomly assigned by lottery method by investigator KRR into group A and group B. The treatment was performed by investigator SK who was blinded to the randomisation process.

Clinical Parameters

All patients were subjected to a periodontal clinical examination performed in six sites per tooth using William's periodontal probe. The clinical parameters assessed were the GI, PPD and CAL [16-18].

Biochemical Parameters

Collection of Blood Sample and Serum Separation

Random blood samples were collected by venepuncture of anticubital vein. Around 2 mL of blood was collected. About 1 mL was placed in each test tube and 1 mL of whole blood was used for HbA1c estimation. Also, 10 minutes after collection the other test tube containing 1 mL blood was subjected to centrifugation at 3000 rpm for 10 minutes. The supernatant straw colored fluid (serum) was separated into two storage vials for serum resistin.

Assessment of Serum Resistin

It was done at baseline and three months after NSPT by commercial kit (R and D systems a bio-techne brand USA) [19]. The assay employs the quantitative sandwich enzyme immunoassay technique [Table/Fig-2].

[Table/Fig-2]: Human resistin ELISA kit.

Assessment of Glycosylated Haemoglobin

Assessment of HbA1c was done at baseline and three months by using spectrophotometric analysis (Erba chem 5 plus v2, Transasia Biomedicals Limited, Mumbai) [Table/Fig-3] [20].

[Table/Fig-3]: Spectrophotometer for assessment of HbA1c.

Primary and Secondary Outcome Measures

The Primary outcome measures assessed were the serum resistin and HbA1c levels and the secondary parameters assessed were the GI, PPD and CAL.

STATISTICAL ANALYSIS

Data was analysed by SPSS version 22.0. Data was summarised by mean±Standard Deviation (SD) for continuous data and median±IQR (InterQuartile Range) for score data. Data was summarised by Percentages for categorical data. The comparison between baseline and three months was done by paired t-test for continuous data and Wilcoxon signed rank test for score data. The comparison between two groups was done by unpaired t test for continuous data and Mann Whitney U test for score data. The association between two groups was done by chi-square test/Fishers exact test for categorical data. All p-values less than 0.05 were considered as statistically significant.

RESULTS

The intragroup comparison in group A (test group) showed that there was a statistically significant difference pertaining to all the clinical (GI, PPD, CAL) and biochemical parameters (HbA1c and serum resistin) from baseline to three months with p<0.001 [Table/Fig-4]. In group B (control group) also, there was a statistically significant difference pertaining to all the clinical (GI, PPD, CAL) and biochemical parameters (HbA1c and serum resistin) from baseline to three months p<0.001 [Table/Fig-5].

Parameters*	Assessment	n‡	Range	Mean	SD†	p-value
GI	Baseline	20	2.2-3.0	2.6	0.3	<0.001
	3 months	20	0.6-1.3	1.0	0.2	
PD	Baseline	20	7-9	8.1	0.6	<0.001
	3 months	20	3-4	3.8	0.4	
CAL	Baseline	20	5-7	6.1	0.6	<0.001
	3 months	20	1-2	1.7	0.5	
HbA1c%	Baseline	20	9.3-10.7	9.9	0.3	<0.001
	3 months	20	6-7	6.3	0.3	
Serum resistin (ng/mL)	Baseline	20	20.3-36.7	27.2	5.4	<0.001
	3 months	20	8.5-29	16.7	8.0	

[Table/Fig-4]: Intragroup comparison in group A (test group) of clinical and biochemical parameters.
*Clinical and biochemical parameters: GI: Gingival index; PD: Probing depth; CAL: Clinical attachment levels; HbA1c%: Glycated haemoglobin percentage and serum resistin levels.
†SD: Standard deviation
‡n: Number of patients
Paired t-test was done for GI, HbA1c%, serum resistin (ng/mL) and Wilcoxon signed rank test was used for PD and CAL.

Parameters*	Assessment	n‡	Range	Mean	SD†	p-value
GI	Baseline	20	2.2-3.0	2.6	0.2	<0.001
	3 months	20	0.8-1.9	1.3	0.3	
PD	Baseline	20	6-10	8.0	1.3	<0.001
	3 months	20	3-6	4.6	0.8	
CAL	Baseline	20	4-8	6.0	1.2	<0.001
	3 months	20	1-4	2.6	0.8	
HbA1c %	Baseline	20	7.1-10.3	8.6	1.1	<0.001
	3 months	20	6.3-9.5	7.4	0.7	
Serum resistin (ng/mL)	Baseline	20	22-35.9	27.2	4.6	<0.001
	3 months	20	20.1-32.5	24.9	3.7	

[Table/Fig-5]: Intragroup comparison in group B (control group) of clinical and biochemical parameters.
*Clinical and biochemical parameters: GI: Gingival index; PD: Probing depth; CAL: Clinical attachment levels; HbA1c%: Glycated haemoglobin percentage and serum resistin levels.
†SD: Standard deviation
‡n-Number of patients
Paired t-test was done for GI, HbA1c%, serum resistin (ng/mL) and Wilcoxon signed rank test was used for PD and CAL.

However, when an intergroup comparison was made it was observed that all the clinical and biochemical parameters showed better and statistically significant results in group A (systemic ALA+NSPT) when compared to group B (NSPT only) [Table/Fig-6].

Parameters*	Groups	n‡	Range	Mean	SD†	p-value
GI	Control 3 months	20	0.8-1.9	1.3	0.3	0.002
	Test 3 months	20	0.6-1.3	1.0	0.2	
PD	Control 3 months	20	3-6	4.6	0.8	0.0005
	Test 3 months	20	3-4	3.8	0.4	
CAL	Control 3 months	20	1-4	2.6	0.8	<0.001
	Test 3 months	20	1-2	1.7	0.5	
HbA1c%	Control 3 months	20	6.3-9.5	7.4	0.7	<0.001
	Test 3 months	20	6-7	6.3	0.3	
Serum resistin (ng/mL)	Control 3 months	20	20.1-32.5	24.9	3.7	0.0002
	Test 3 months	20	8.5-29	16.7	8.0	

[Table/Fig-6]: Intergroup comparison of clinical and biochemical parameters at three months.
*Clinical and biochemical parameters: GI: Gingival index; PD: Probing depth; CAL: Clinical attachment levels; HbA1c%: Glycated haemoglobin percentage and serum resistin levels
†SD: Standard deviation
‡n: Number of patients
Unpaired t-test was done for GI, HbA1c%, serum resistin (ng/mL) and Mann Whitney U test for PD and CAL.

DISCUSSION

Periodontitis is a complex polymicrobial disease in which inflammation in the periodontal tissues is stimulated by the long term presence of the subgingival plaque. The inflammatory response is characterised by dysregulated secretion of host derived mediators of inflammation and tissue breakdown. The most extensively studied include IL-1β, IL-6, Prostaglandin E2 (PGE2), TNF-α, RANKL, and the MMP's particularly MMP-8, MMP-9 and MMP-13, as well as T cell regulatory cytokines (e.g., IL-12, IL-18) and the chemokines [21]. The etiology of type 2 diabetes appears to be multifactorial. A genetic component contributes to individual susceptibility for the development of type 2 diabetes. Metabolic syndrome, the characteristics of which are impaired glucose tolerance, obesity, hypertension and dyslipidemia, is associated with an increased risk for the development of diabetes by a factor of 2.99 and may be considered a 'pre diabetic' state. Type 2 diabetes and the 'pre diabetic' metabolic syndrome are associated with obesity, physical inactivity and a high glucose, high fat, low fibre diet. Both the diseases are interlinked and one disease may lead to the other [22]. Many studies have given conclusive evidence about diabetes worsening periodontitis and vice versa [23-26].

In a study conducted by Alshehri FA, and Javed F, 50 pre diabetic patients were enrolled and divided equally into two groups. The test group (25 patients) received SRP along with oral doxycycline 100 mg, whereas the control group (25 patients) received SRP only. In both the groups the clinical parameters and fasting blood glucose levels were assessed at baseline and after six months. It was observed that both groups showed an improvement in the clinical parameters after six months, however there was no improvement in the fasting blood glucose levels after six months in both the groups [27].

In this study also there was a statistically significant difference in all the clinical parameters in both the groups. However the results were more significant in group A (SRP+ALA 600 mg thrice daily for three months) when compared to group B (SRP only).

In a study to examine if HbA1c levels are elevated in patients with periodontitis, 70 subjects with periodontitis and 70 healthy controls were enrolled. It was observed that the HbA1c levels in patients with periodontitis were significantly higher than the control group. The resultant hyperglycaemic state may increase the risk for diabetes [28]. There are conflicting reports related to the improvement in HbA1c levels in diabetic patients after SRP. In a meta analysis which was conducted in 2005, gathering reports from ten interventional studies, done to examine the effects of periodontal treatment on HbA1c levels in diabetic patients, it was concluded that HbA1c levels decreased by 0.38% for all the studies, which was not statistically significant [29]. However, some of the studies conducted later concluded that there was an improvement in the HbA1c levels in the test group (diabetic patients with periodontitis who underwent SRP) [Table/Fig-7] [30-34].

In this study it was observed that the HbA1c levels reduced in both the groups after SRP, however, highly significant results were obtained in group A (9.9 to 6.3%) (p<0.001) when compared to group B (8.6 to 7.4%). Oxidative stress (which is an imbalance between reactive species and antioxidants produced by the body) pays a pivotal role in the etiopathogenesis of most diseases and diabetes is no exception. The hyperglycaemic state induces the production of free radicals and impairs the endogenous antioxidant

Author (Year)	Country	Sample size	Inclusion criteria for diabetic patients-HbA1c%	Inclusion criteria for chronic periodontitis patients	Intervention	Duration of study	Changes in HbA1c levels after intervention
Koromantzos PA et al., (2011) [30]	Greece	60 Test=30 Control=30	Type 2 DM HbA1C levels (7%-10%) Initial HbA1c: T=7.0-9.9 C=7.0-10.2	Having at least 16 teeth present with at least eight sites (PPD) >6 mm and four sites with CAL >5 mm, distributed in at least two different quadrants.	T=SRP+OHI C=Delayed treatment	6 months	HbA1c changes within the 1st 3months T=0.73±0.66 C=0.18±0.59 HbA1c changes after 6th month T=0.72±0.93 C=0.13±0.46
Engebretson SP et al., (2013) [31]	USA	50 Test=25 Control=25	Type 2 DM HbA1c level (7.0%-9.0%) Initial HbA1c: T=7.84 (0.65) C=7.78 (0.60)	A minimum of 16 natural teeth. CAL/PD >5 mm in two or more quadrants of the mouth. No periodontal treatment in the prior six months.	T=SRP+OHI C=OHI	6 months	Mean change of HbA1c (95% CI) at 3rd month T=0.14 (0.02-0.27) C=0.11 (-0.02 to 0.24) Mean change of HbA1c (95% CI) at the end of 6th month T=0.15 (-0.01 to 0.30) C=0.09 (-0.06 to 0.25)
Kanduluru A and Naganandini S (2014) [32]	India	70 Test=35 Control=35	Type 2 DM HbA1c level Initial HbA1c: T=8.49±1.50 C=8.04±0.70	Pocket Depth [PD] 4-6 mm involving >30% sites Generalised moderate periodontitis	T=SRP+OHI C=OHI	3 months	HbA1c Changes after 3rd month T=8.47±0.89 C=8.27±0.63
Gay IC et al., (2014) [33]	USA	126 Test=66 Control=60	Type 2 DM HbA1c level (4.0-15.0%) Initial HbA1c: T=9.0±2.3 C=8.4±2.02. nonsmoker	No systemic antibiotic therapy within six months of recruitment. The presence of localised or generalised severe chronic periodontitis	T=SRP+OHI C=OHI	4 months	HbA1c Changes after 4th month T=8.4±1.9 C=8.1±1.8
Kaur PK et al., (2015) [34]	India	100 Test=50 Control=50	Type 2DM Initial HbA1c: T=8.17±2.49 C=7.87±2.562	Presence of ≥12 teeth, clinical diagnosis of moderate and severe periodontitis. Moderate periodontitis: ≥2 interproximal sites, not on the same tooth, with an attachment loss ≥4 mm, or PD ≥5 mm. Severe periodontitis: ≥2 interproximal sites, not on the same tooth, with an attachment loss ≥6 mm, and one or probing depth ≥5 mm	T=OHI+SRP C=No treatment	3,6 months	HbA1c changes in the end of 3rd month. T=7.49±1.83 C=7.96±2.65 HbA1c changes in the end of 6th month. T=7.29±1.61 C=8.06±2.72

[Table/Fig-7]: Studies conducted to assess the effect of scaling and root planing on HbA1c levels.
T: test; C: Control; OHI: Oral hygiene instructions; DM: Diabetes mellitus

defence system of the host [35]. Resistin is an adipokine whose levels are elevated in inflammatory conditions. This enzyme causes insulin resistance and is often associated with diabetes and obesity [36,37]. A study was carried out to investigate the relationship between periodontal conditions and serum levels of resistin and adiponectin in elderly Japanese. It was demonstrated that both circulating resistin levels and total leukocytes and neutrophil counts were significantly elevated in subjects with periodontitis when compared with controls [37].

A total of 40 subjects were enrolled in another study of whom 20 were healthy (control group) and 20 had chronic periodontitis (test group). Periodontal parameters Plaque Index (PI), GI, Bleeding Index (BI), PPD, CAL together with serum resistin levels were assessed at baseline and between 6-8 weeks following NSPT for subjects. Clinical parameters and serum resistin levels were assessed both at baseline and 6-8 weeks after NSPT in samples in the test group and only at baseline in the control group. There was a statistically significant difference in the clinical parameters at baseline between the groups and significant improvement in the test group after SRP. Though, the serum resistin levels were higher in the test group when compared to the control group at baseline, the values were not statistically significant. Moreover, 6-8 weeks after scaling also, serum resistin levels decreased in the test group and no significant difference was found in their levels between baseline and postintervention [38].

The present study showed elevated resistin levels at baseline in both the test and control groups; however, it was observed that there was a reduction in resistin levels in group A (27.2 to 16.7ng/mL) as well as in group B (27.2 to 24.9 ng/mL) three months after SRP. However, the reduction in resistin levels were highly significant in group A (p=0.0002) when compared to group B.

ALA is a powerful antioxidant that is able to scavenge a number of free radicals, such as superoxide radicals, singlet oxygen, hydroxyl radicals and hypochlorous acid. It occurs with a chelate of Fe^{2+} and Fe^{3+} in both hydrophilic and lipophilic environments. The ALA present in nature is always covalently bonded and not readily available from dietary sources. It is able to cross the blood brain barrier without any serious side effects and has been shown to improve glucose metabolism in diabetic patients [39].

Drug Adherence/Safety: No adverse effects were reported in this study with ALA administration.

LIMITATION

ALA could have been administered for a longer period of time. The sample size could have been larger to better validate the results.

Many studies have already been done on the beneficial role of ALA supplementation in diabetic patients; however, the effect of ALA administration on patients with both diabetes and chronic periodontitis has not been assessed. Thus, in future many more such studies can be done to throw light on the benefits of ALA supplementation.

CONCLUSION

This study shows that ALA as an adjuvant after SRP has a beneficial role both in combating oxidative stress induced tissue destruction

and restoring glycaemic control in patients with chronic periodontitis and type 2 diabetes mellitus, however many more studies have to be done to assert its positive effects on the periodontium.

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