

# Systemic lycopene as an adjunct to scaling and root planing in chronic periodontitis patients with type 2 diabetes mellitus

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## Abstract

**Background:** Patients with type 2 diabetes have an increased prevalence of periodontitis and, in turn, periodontitis adversely affects the diabetic status. Oxidative stress plays a key role in affecting the pathophysiology of both the diseases and adjunctive systemic antioxidant therapy may have beneficial effect on the treatment outcome. This study was planned to compare the efficacy of systemic antioxidant therapy with lycopene as an adjunct to scaling and root planing versus scaling and root planing alone in chronic periodontitis patients with type 2 diabetes mellitus. **Materials and Methods:** 40 diabetic subjects with periodontitis, attending the OP wing of the Department of Periodontics of a tertiary referral care hospital were randomized and equally divided into group A and group B. Diabetes status was recorded as per ADA guidelines and the periodontitis status as per American Academy of Periodontology (AAP) guidelines. Group A patients underwent scaling and root planing with administration of lycopene 8 mg and group B patients were treated with scaling and root planing alone. Clinical parameters like gingival index (GI), probing depth (PD), and clinical attachment level (CAL) were recorded. Serum markers, i.e. malondialdehyde (MDA) (TBARS assay) and C reactive protein (CRP) (ELISA), and glycated hemoglobin (HbA1c) levels were assessed at baseline and at 2 months and 6 months post-therapy. **Results:** Inter-group comparison showed group A giving statistically significant results in reducing mean serum MDA levels at 2 months and 6 months, and in reducing mean PD (mm) and mean HbA1c (%) levels at 2 months ( $P < 0.005$ ). **Conclusion:** Lycopene as an adjunctive treatment was effective in reducing oxidative stress and restoring altered glycemic levels. Further longitudinal studies with a larger sample size are required to establish the role of lycopene in the management of chronic periodontitis.

**Key words:** Antioxidant, diabetes, oxidative stress, periodontitis

## INTRODUCTION

Periodontitis has been identified as the sixth complication of diabetes<sup>[1]</sup> and its prevalence in type 2 diabetic patients is more than twice that in non-diabetic patients.<sup>[2-6]</sup> Diabetic patients display an increased

severity of disease, with the severity being related to diabetic control<sup>[7]</sup> but is unrelated to diabetic duration.<sup>[8]</sup> Periodontitis appears to have a reciprocating negative impact on diabetic status.<sup>[9,10]</sup>

Oxidative stress is an imbalance between the production of a reactive oxygen species and the antioxidant defense, leading to tissue damage. The produced reactive oxygen species, such as superoxide anion, hydroxyl radical, and peroxy radical, result in damage to many biological molecules (including DNA, lipids, and protein), and the prolonged existence of these reactive oxygen species promotes severe tissue damage and cell death.<sup>[11,12]</sup> It has been proposed that there is a causal relationship between insulin resistance, oxidative stress, and

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periodontitis, and that hyperglycemia is a major factor responsible for the activation of oxidative stress.<sup>[11,12]</sup>

Various antioxidants have been tried locally and systemically in periodontal diseases and have shown beneficial outcome. Lycopene is a hydrocarbon carotenoid that has received a lot of attention. It has a potential role in preventing prostate cancer,<sup>[13,14]</sup> cardiovascular disease,<sup>[15]</sup> and long-term diabetic complications in humans,<sup>[16]</sup> and has shown promising results in preeclampsia,<sup>[17,18]</sup> leukoplakia,<sup>[19]</sup> oral submucous fibrosis,<sup>[20]</sup> gingivitis<sup>[21]</sup> and chronic periodontitis.<sup>[22-24]</sup>

The present study was undertaken to evaluate the efficacy of scaling and root planing (SRP) with adjunctive systemic lycopene versus SRP alone based on the assessment of clinical parameters, lipid peroxidation serum marker malondialdehyde (MDA), and systemic inflammatory marker serum C reactive protein (CRP), in patients with both the chronic diseases, i.e., type 2 diabetes and chronic periodontitis.

## MATERIALS AND METHODS

Screening for patients commenced from January 2013. This was a randomized, controlled, double-blinded clinical trial which was carried out between March and August 2013 in the Department of Periodontics of a tertiary referral care hospital in Hyderabad. The protocol was approved by the institutional ethical committee.

### Study population

Fifty-two subjects were screened for the study, out of which 12 subjects were excluded (8 did not meet the inclusion criteria and 4 refused to participate). Study sample consisted of 40 subjects (22 males and 18 females) aged between 35 and 50 years. Investigator KRR enrolled the participants and assigned them into two groups [CONSORT 2010 Flow Diagram]. Subjects with type 2 diabetes and chronic periodontal disease were recruited in the study. Patients who were known diabetics at least from the past 2 years were included.

### Inclusion criteria

- Type 2 diabetes as per American Dental Association (ADA) criteria, i.e. a fasting plasma glucose of >126 mg/dl
- Patients on oral hypoglycemic drugs with no modification in therapy from the past 12 months
- Chronic periodontitis as per American Academy of Periodontology (AAP) guidelines

- Minimum of 15 natural teeth
- At least four teeth with one or more sites with probing depth (PD)  $\geq 5$  mm, clinical attachment level (CAL)  $\geq 4$  mm, and bleeding on probing (BOP).

### Exclusion criteria

- History of antibiotic therapy within the previous 6 months
- History of anti-inflammatory drugs within the previous 3 months
- Pregnancy and lactation
- Use of contraceptives or any other form of hormone
- Usage of tobacco and tobacco-related products
- Periodontal treatment within 12 months.

Forty subjects were randomly allocated into two groups, group A and group B, by the investigator KRR and the treatment was performed by investigator AM who was blinded to the randomization process.

Group A comprised 20 subjects supplemented with systemic lycopene (Lycored soft gels; Jagsonpal Pharma, New Delhi, India) 8 mg daily for a period of 8 weeks along with SRP.

Group B was the control group consisting of 20 subjects who underwent SRP alone.

### Assessment of clinical parameters

Modified gingival index<sup>[25]</sup> (MGI), probing pocket depth (PPD), and clinical attachment level (CAL) were assessed for full mouth at six sites per tooth. Measurements were done with periodontal probe (Williams periodontal probe; Hu-Friedy, Chicago, USA).

### Assessment of serum markers

Blood samples were collected by venipuncture of antecubital vein. Two milliliters of blood was collected, with 1 ml in each test tube. One milliliter of whole blood was used for glycosylated hemoglobin (HbA1c) estimation. Ten minutes after collection, 1 ml blood was subjected to centrifugation at 3000 rpm for 10 min; the supernatant straw-colored fluid (serum) was separated and collected in two storage vials for serum MDA and serum CRP estimation.

### Assessment of serum MDA

MDA was assessed by spectrophotometric estimation of serum thiobarbituric acid substances<sup>[26]</sup> (TBARS). The

TBARS assay<sup>[27]</sup> measures MDA,<sup>[27]</sup> a reactive compound formed from lipid peroxides that are generated under conditions of oxidative stress. Oxidative modification of lipids occurs with aging and various diseases, and increased oxidative stress is associated with diabetes and its complications. MDA forms an adduct with thiobarbituric acid (TBA). Results are calculated from a standard curve constructed with authentic MDA.

**Assessment of serum CRP**

CRP assessment was done by ELISA kit [Alpha Diagnostic International (ADI), San Antonio, Texas, USA] method.

**Principle of the test**

Human CRP ELISA kit is based on simultaneous binding of human CRP from samples to two antibodies, one immobilized on the microtiter well plates and the other conjugated to the enzyme horseradish peroxidase. After a washing step, chromogenic substrate is added and color is developed. The enzymatic reaction (color) is directly proportional to the amount of CRP present in the sample. Adding stopping solution terminates the reaction. Absorbance is then measured on a microtiter well ELISA reader at 450 nm and the concentration of CRP in samples and control is read off the standard curve.

**Measurement of HbA1c**

Measurement of HbA1c (glycated hemoglobin) was done by spectrophotometric analysis using commercial kit (Bio Systems, Barcelona, Spain).

All these clinical, biochemical and inflammatory parameters were measured at baseline, 2 and 6 months post-therapy.

**Statistical analysis**

The observations recorded were subjected to independent sample *t*-test for statistical analysis for inter-group comparison.

**RESULTS**

**Drug adherence/safety**

No adverse effects were reported in this study with lycopene supplementation.

**Other results**

The mean values for PD in group A (lycopene + SRP) and group B (SRP only) were  $5.46 \pm 0.47$  and

$5.39 \pm 0.44$  mm, respectively, at baseline [Table 1]. At 2 months follow-up [Table 2], the PPD reduced to  $2.12 \pm 0.45$  and  $2.63 \pm 0.38$  mm, respectively. From baseline to 2 months, the PD reduction was 3.34 mm in group A and only 1.76 mm in group B, which showed statistically significant ( $P < 0.001$ ) difference in group A [Figure 1]. At 6 months follow-up [Table 3], the PD was  $2.67 \pm 0.39$  and  $3.17 \pm 1.41$  mm, respectively, which was not statistically significant between the groups.

The mean values of serum MDA in group A (lycopene + SRP) and group B (SRP only) were  $1.36 \pm 0.30$  and  $1.29 \pm 0.25$  nmol/ml, respectively, at baseline [Table 1]. At 2 months follow-up, the MDA values reduced to

**Table 1: Baseline parameters**

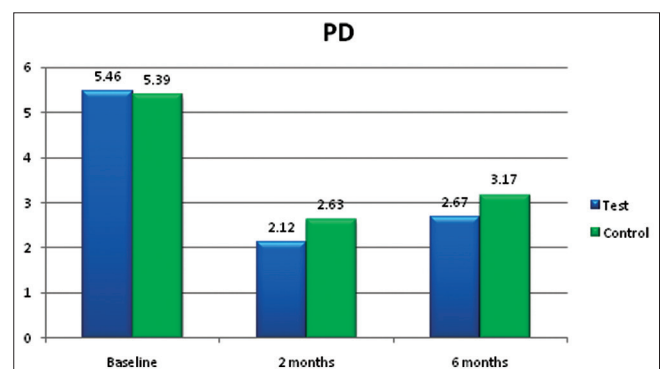
Parameter	Mean±SD		P
	Group A	Group B	
MGI	2.28±0.39	2.35±0.37	-
Mean PPD (mm)	5.46±0.47	5.39±0.44	-
Mean CAL (mm)	5.65±0.35	5.62±0.45	-
MDA (nmol/ml)	1.36±0.30	1.29±0.25	-
HbA1c (%)	7.58±0.88	7.80±0.98	-
CRP (ng/ml)	10,471.65±1830.04	10,531.30±2052.71	-

MGI=Modified gingival index, PPD=Probing pocket depth, CAL=Clinical attachment level, MDA=Malondialdehyde, HbA1c=Glycated hemoglobin, CRP=C reactive protein

**Table 2: Inter-group evaluation (post-treatment at 2 months)**

Parameter	Mean±SD		P
	Group A	Group B	
MGI	0.81±0.39	0.88±0.27	-
Mean PPD (mm)	2.12±0.45	2.63±0.38	<0.001*
Mean CAL (mm)	2.99±0.67	3.30±0.54	-
MDA (nmol/ml)	0.68±0.08	0.84±0.20	0.003*
HbA1c (%)	6.10±0.56	6.84±0.65	<0.001*
CRP (ng/ml)	4588.05±648.57	4910.65±824.67	-

MGI=Modified gingival index, PPD=Probing pocket depth, CAL=Clinical attachment level, MDA=Malondialdehyde, HbA1c=Glycated hemoglobin, CRP=C reactive protein. \*Statistically significant ( $P \leq 0.05$ )



**Figure 1:** Probing depth (in mm)

0.68 ± 0.08 and 0.84 ± 0.20 nmol/ml, respectively, and at 6 months follow-up, the values were 1.17 ± 0.22 and 1.38 ± 0.26 nmol/ml, respectively. Both at 2 months follow-up (*P* = 0.003) and 6 months follow-up (*P* = 0.01), these reductions were statistically significant in group A (lycopene + SRP) compared to group B [Tables 2 and 3, Figure 2].

The mean values of HbA1c in group A (lycopene + SRP) and group B (SRP only) were 7.58 ± 0.88 and 7.80 ± 0.98%, respectively, at baseline [Table 1]. At 2 months follow-up [Table 2], the HbA1c values reduced to 6.10 ± 0.56 and 6.84 ± 0.65%, respectively, and at 6 months follow-up [Table 3], the values were 6.82 ± 0.61 and 7.12 ± 0.41%, respectively. From baseline to 2 months, these reductions were statistically significant (*P* < 0.001) in group A (lycopene + SRP) when compared to group B, but there was no difference between the groups at 6 months [Figure 3].

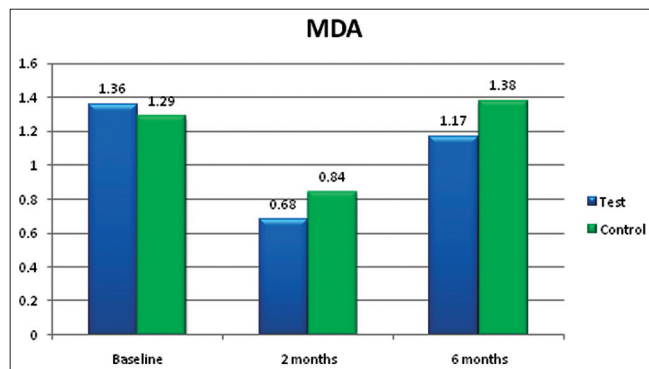
## DISCUSSION

One of the common pathological mechanisms linking periodontitis and diabetes is oxidative stress; others are activation of innate immunity and inflammation.

**Table 3: Inter-group evaluation (post-treatment at 6 months)**

Parameter	Mean±SD		P
	Group A	Group B	
MGI	1.19±0.29	1.30±0.30	-
Mean PPD (mm)	2.67±0.39	3.17±1.41	-
Mean CAL (mm)	3.57±0.58	3.61±0.45	-
MDA (nmol/ml)	1.17±0.22	1.38±0.26	0.01*
HbA1c (%)	6.82±0.61	7.12±0.41	-
CRP (ng/ml)	7266.50±1181.92	7107.15±1722.33	-

MGI=Modified gingival index, PPD=Probing pocket depth, CAL=Clinical attachment level, MDA=Malondialdehyde, HbA1c=Glycated hemoglobin, CRP=C reactive protein. \*Statistically significant (*P*≤0.05)



**Figure 2:** Serum malondialdehyde (MDA) in nmol/ml

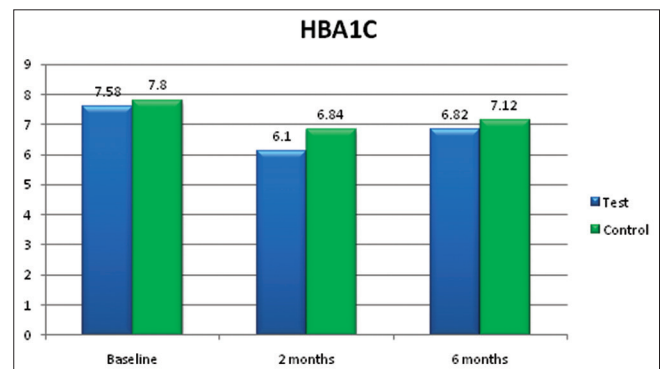
Oxidative stress is an imbalance between the production of reactive oxygen species and antioxidant defense, leading to tissue damage. With regard to diabetes, advanced glycation endproducts (AGEs) present in diabetic gingiva may be associated with a state of enhanced oxidative stress, a potential mechanism for accelerated tissue injury.<sup>[28]</sup> The reactive oxygen species produced, such as superoxide anion, hydroxyl radical, and peroxy radical, result in damage to many biological molecules including DNA, lipids, and protein, and prolonged existence of these reactive oxygen species promotes severe tissue damage and cell death.<sup>[28]</sup> Therefore, treating this aspect of oxidative stress by means of systemic antioxidant therapy improves the symptoms of both the diseases.

In this study, systemic lycopene in physiological doses, i.e. 8 mg daily for 2 months, was used as an adjunct to SRP and compared with SRP alone.

Lycopene is a hydrocarbon carotenoid that has recently received a lot of attention. Although similar in structure to the much studied β-carotene, lycopene does not have provitamin A activity. Di Mascio *et al.*<sup>[29]</sup> showed that lycopene had the strongest singlet oxygen-quenching capacity of several carotenoids, with α-carotene, β-carotene, and lutein ranking next in capacity.

In the present study, the oxidative stress marker assessed was serum MDA, a marker of lipid peroxidation. A recent study by Trivedi *et al.*<sup>[30]</sup> found that serum MDA levels were high in both chronic periodontitis patients and chronic periodontitis patients with diabetes.

Neyestani *et al.*<sup>[16]</sup> treated type 2 diabetic patients with 10 mg lycopene daily for 2 months, which resulted in increased total antioxidant capacity (TAOC) to MDA and enhanced serum immunoglobulin M (IgM) levels at 2 months follow-up. This is in accordance with



**Figure 3:** Glycated hemoglobin (HbA1c) in %

the present study results wherein lycopene + SRP treated group A (0.68 and 1.17 nmol/ml) showed statistically significant reduction of serum MDA at 2 months and 6 months follow-up ( $P$  value 0.003 and 0.01, respectively) [Figure 2] compared to SRP alone group B (0.84 and 1.38 nmol/ml, respectively) [Tables 2 and 3].

A meta-analysis by Valero *et al.*<sup>[31]</sup> analyzed the possible role of lycopene on type 2 diabetes mellitus. Results showed that lycopene decreased the MDA and lipid peroxidation and was inconclusive for glycemic control, but in the present study in addition to decrease in MDA, lycopene + SRP treated group A (6.10%) also showed statistically significant reduction ( $P < 0.001$ ) in HbA1c levels at 2 months follow-up [Figure 3] compared to SRP alone group B (6.84%) [Table 2].

There is no published data regarding systemic lycopene associated glycemic control in chronic periodontitis patients with type 2 diabetes mellitus. This is the first study showing positive effect of lycopene on glycemic control in patients with both the diseases, i.e. chronic periodontitis and type 2 diabetes mellitus. This may be due to the reduction in oxidative stress and periodontal inflammation, which together may have controlled the insulin resistance resulting in glycemic control.

In this study, the immunological parameter CRP did not show any statistically significant difference between (lycopene + SRP) group A and (SRP alone) group B at 2 months and 6 months follow-up [Tables 2 and 3, Figure 4]. In a recent study by Arora.<sup>[24]</sup> it was observed that the immunological marker serum tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) did not show statistically significant reduction in the test (lycopene) group compared to placebo group at 2 months follow-up. In both studies, systemic lycopene as an adjunct to SRP has not shown any additional effect on improvement of serum inflammatory markers.

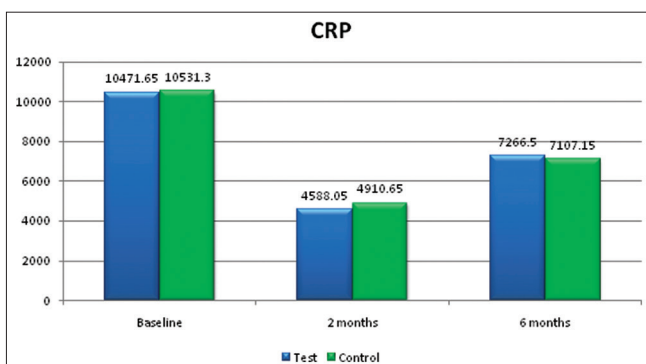


Figure 4: Serum C reactive protein (CRP) in ng/ml

Chandra *et al.*<sup>[21]</sup> and Arora *et al.*<sup>[24]</sup> concluded in their studies that systemic lycopene and oral prophylaxis showed statistically significant reduction in gingival index, compared to placebo oral prophylaxis group. In both the studies, patients were followed up for 2 weeks in gingivitis patients and 2 months in chronic periodontitis patients, respectively. In the present study also, gingival index [Figure 5] was reduced in (lycopene + SRP) group A compared to (SRP only) group B, but this was not statistically significant at 2 months and at 6 months [Tables 2 and 3].

PD reduction [Figure 1] was statistically significant ( $P < 0.001$ ) in (lycopene + SRP) group A (2.12 mm) than in (SRP alone) group B (2.63 mm) at 2 months [Table 2] in the present study. This finding was contradictory to the study finding of Nupur *et al.*<sup>[24]</sup> which showed no statistically significant reduction in the lycopene group.

CAL [Figure 6] did not show any difference between both the groups in the present study [Tables 2 and 3].

The present study differs from the previous studies as it was done on patients with two chronic diseases, i.e., periodontitis and type 2 diabetes mellitus. These patients had been evaluated for 6 months. In addition to decrease in oxidative stress marker MDA with lycopene therapy, it was also found in the present study that systemic lycopene played a role in the glycemic control of diabetic patients.

Based on the results of the study, it can be emphatically said that systemic antioxidant therapy with lycopene has an effective role in reducing oxidative stress in chronic periodontitis patients with type 2 diabetes mellitus.

### Limitations of the study

Although lycopene is generally recognized as safe (GRAS) drug, there are no studies with the drug

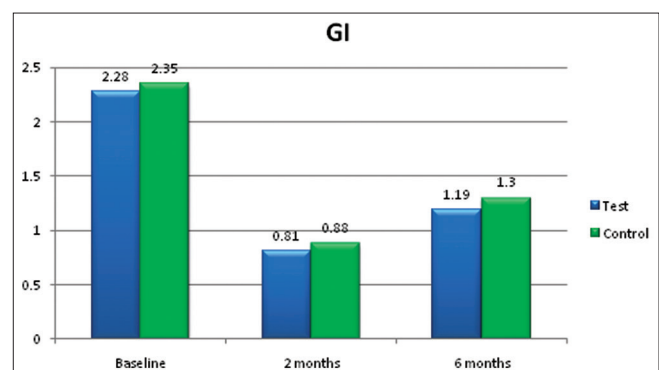


Figure 5: Gingival index (GI)

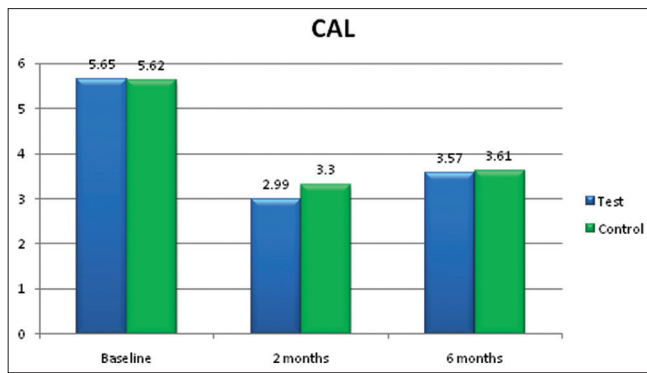
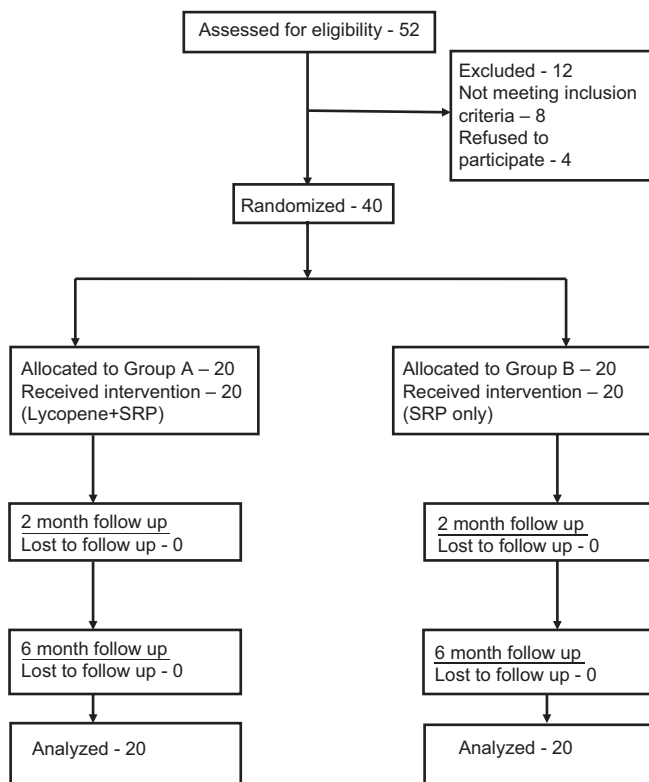


Figure 6: Clinical attachment level (CAL) in mm



CONSORT 2010 Flow Diagram

supplemented beyond 2–3 months. So, in this study also, lycopene was supplemented for 2 months only.

As lycopene is available in natural food items like tomatoes and watermelon, lycopene diet washout period was not considered.

### CONCLUSION

Oxidative stress has been observed to be a major pathological link between reactive oxygen species induced tissue destruction in patients with chronic periodontitis and altered glycemic control in diabetics. Lycopene has the strongest signet oxygen quenching

activity among the antioxidants of  $\beta$ -carotene family. This short-term study shows that it has a beneficial role both in combating oxidative stress induced tissue destruction and restoring glycemic control in patients with chronic periodontitis and type 2 diabetes mellitus. The benefits of lycopene administration can be fully appreciated if it could be used on a long-term basis or as a stop gap monotherapy, for which studies evaluating the consequences of its prolonged administration should be conducted.

Inter-group comparison showed the following:

- Lycopene along with nonsurgical periodontal therapy was effective in combating oxidative stress by significantly reducing serum MDA levels both at 2 months and 6 months
- Lycopene along with nonsurgical periodontal therapy was effective in restoring altered glycemic control due to oxidative stress in diabetic patients
- Lycopene along with nonsurgical periodontal therapy was also efficacious in reducing the PPD.

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