A randomized, double-blind, split-mouth controlled clinical trial of systemically administered Lycopene on periodontal health

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ABSTRACT

Background/Purpose: This research aimed to compare the effects of systemically prescribed Lycopene as a monotherapy and as an alternative to scaling and root planing in patients with chronic gingivitis.

Materials and methods: The participants were randomly assigned to one of two treatment groups: the experimental group (n = 50), which received 10 mg of Lycopene a day for two weeks, or the control group (n = 50) received a placebo for two weeks. For each category, quadrant distribution was randomized, with two quadrants receiving oral prophylaxis (OP) and two quadrants receiving no care (non-OP). At baseline, 1st, and 2nd weeks, the sulcus bleeding index, plaque index, gingival index, and salivary uric acid level were measured.

Results: All clinical criteria, including SBI, PI, GI, and salivary uric acid levels, showed a statistically significant decline in all patient types. Both clinical parameters were significantly reduced ($p < 0.001$) in the OP-lycopene group relative to the non-OP-placebo group and non-OP lycopene group ($p < 0.05$). The PI value in the OP-lycopene group was statistically significantly lower ($p < 0.001$) than in the non-OP-placebo group; there was no statistically significant difference in the other groups. Salivary uric acid levels in the OP- and non-OP-lycopene groups were significantly lower ($p < 0.001$) than in the non-OP-placebo population.

Conclusion: Based on the findings of this study, Lycopene seems to have a bright future as a treatment option for plaque-induced generalized chronic marginal gingivitis. More research with a broad sample size and multicentre trials is required.

Clinical relevance: The article reveals the positive relationship between Lycopene and gingivitis. The analysis shows that a combination of systemically administered Lycopene with oral prophylaxis can be a valuable tool in treating chronic gingivitis and controlling respiratory oxidative stress.

1. Introduction

Periodontal condition comprises a heterogeneous group of disease which is presented as different clinical manifestations. It is an inflammatory, episodic and segmental illness with a broad spectrum of complex natural history. Due to complex interactions between the

pathogenic microorganism and the host's immune response, it leads to tissue damage.¹ Polymorphonuclear leukocytes (PMNs) (96%) are the most common inflammatory cells inside the connective tissues and epithelium of the gingiva. They play an innate role in the host's defense and contribute 90% of leukocytes isolated from the gingival crevicular fluid.^{2,3,4,12,13} PMNs lead to bacterial phagocytosis combined with a

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rapid rise in non-mitochondrial oxidation metabolism, which produces super oxidized radicals and an array of other reactive oxygen species (ROS). NADPH-oxidase complex 3 causes the secretion of proteolytic enzymes and immunomodulatory compounds that help to kill and digest bacteria.

Not only does ROS play an essential role in cells and metabolic processes⁴, but it is also believed to be involved as a consequent cause of elevated oxidative stress levels in the pathogenesis of several inflammatory disorders.^{5,6} A typical balance of ROS and antioxidant defense changes within the tissues in an adult patient's idle life period. Under oxidative stress, there is an imbalance of ROS or an abnormality of antioxidants status.⁷ A varied number of ROS are well known and can cause direct damage to proteins, DNA carbohydrates, and lipid substances, such as superoxide, hydroxyl radicals, hydrogen peroxide, hypochloric acid.^{7,8} Besides ROS development, tissue redox disruption modulates the expression by redox-sensitive transcription factors (e.g., NF-kB, AP-1) of several immune and inflammatory modules, causing indirect tissue damage and aggravating inflammation.^{9,10}

An established ROS function has been identified for the degradation of the tissue leading to periodontitis.¹¹ Studies have shown that the ROS leads to depolymerization and alteration of residual chain in all the glycosaminoglycan, glycosamines of the gingival-related connective tissue, particularly with highly reactive OH organisms. Hyaluronan, a non-sulfated glycosaminoglycan, was more sensitive than sulfated glycosaminoglycans to degradation by ROS. Similar conclusions^{12,13} have followed the application of gingival tissue proteoglycans and collagen to ROS.

Novel therapies explicitly aimed at mitigating oxidative stress at the tissue and cellular levels are being created, which helps in antioxidant synthesis, aggregation, control, and modification of reactive oxygen species (ROS) behavior.^{6,14,15} Chain-breaking or radical scavenging antioxidants including superoxide dismutase, catalase, tocopherol, carotenoids, metal-binding proteins, and compounds with oxidizable –SH (thiol) groups are likely to be important in periodontal disease.^{16,17} Antioxidant saliva structures are diverse and include various antioxidants, including uric acid, glutathione, and ascorbic acid. Periodontal infections seem to be linked to lower salivary antioxidant levels and elevated oxidative damage in the oral cavity.¹⁸

Lycopene is a carotenoid, and it is present mainly in tomatoes and tomato derivatives. It is a potent natural antioxidant and free radical scavenger.¹⁹ With singlet oxygen, it has the highest physical quenching rate.²⁰ It also reverses H₂O₂-induced DNA damage.²¹ Patients with inflammatory conditions have been shown to have lower serum lycopene (sLyco) levels.²² Many retrospective findings show that people who consume more dietary carotenoids have a lower incidence of many chronic diseases, including cardiovascular diseases.^{23,24}

The association between sLyco concentrations and the occurrence of periodontal disorder is not well understood. A recent study looked at the connection between monthly tomato intake, sLyco amounts, and self-reported history of congestive heart failure (CHF) in people with periodontitis. It was concluded that periodontitis and CHF risk were related and that high monthly tomato intake positively affects this association in periodontal patients.²⁵

Though studies have been done to explore the effect of Lycopene in the treatment of periodontal disease, no study has been carried out to examine the effect of full mouth disinfection and Lycopene in the treatment of gingivitis. Therefore, the purpose of the study was to evaluate the effect of systemically administered Lycopene (LycRed™) as a monotherapy and as an adjunct to full-mouth disinfection in chronic gingivitis patients over two weeks.

2. Materials and methods

To address the study's goal, the authors planned and conducted a randomized, double-blind, parallel, split-mouth controlled clinical trial in the Department of Periodontology and Oral Implantology. The

institutional review board and the local ethics committee approved the trial. The research was conducted following Helsinki's guidelines (October 2013) and CONSORT guidelines. The study involved all patients who did not have any systemic problems and followed the incorporating guidelines.

The study enrolled 100 people who were otherwise healthy but had plaque-induced generalized chronic marginal gingivitis. Pregnant women, Smokers, those with systemic diseases like diabetes or cardiovascular disease, and those who had taken antibiotics or antiseptics in the previous 6 weeks or antioxidants like Vitamin C, Vitamin E, or β -carotene in the previous 3 months were excluded. Before taking part in the study, all participants signed written informed consent.

Periodontal probing was performed for each patient at six sites in all of their teeth to rule out the risk of underlying periodontal disorder, and radiographs of suspicious sites were taken simultaneously.

LycRed™, Jagsonpal Pharmaceuticals Ltd, New Delhi, India, contains 100% pure Lycopene with added phytonutrients including phytoene and phytofluene-carotene, phytosterols, and vitamin E for synergistic action (Lyc-O-Mato™, LycRed Natural Product Industries, Beer-Sheva, Israel). In addition, Lyc-O-Mato™ has three times the antioxidant efficacy of pure Lycopene (Fuhrman et al., 1997).

2.1. Sample size

The estimated sample size was calculated to be 50.32 for each group. The participants were randomly assigned to one of two treatment groups by coin-flipping: experimental group (n = 50) 10 mg lycopene/day for two weeks; and control group (n = 50) placebo for two weeks. The placebo was administered to the controls (n = 50 subjects) similarly to the study sample. The patients were instructed to take two placebo capsules twice a day (4 capsules a day) for two weeks. A split-mouth design was used in each category. Oral prophylaxis was given to 25 patients in each group in the first and third quadrants, while the second and fourth quadrants received no care and vice versa. Coin flipping was used to assign subjects to quadrants; if one arm was complete, the remaining subjects were immediately assigned to the other. Thus, 100 quadrants of each category received oral prophylaxis (OP), while 100 quadrants received no local therapy. Thus, there were four treatment groups: OP-lycopene group, non-OP lycopene group, OP-placebo group, and non-OP-placebo group. OP-placebo was considered as a positive control, while non-OP-placebo was considered as a negative control.

Oral prophylaxis was done on the selected quadrants (OP-lycopene group and OP-placebo group) as a variation of the Full Mouth Disinfection protocol of Quirynen (1995), modified for the present study, and it was done to avoid the possibility of cross-contamination between treated and untreated quadrants. Scaling was performed with a piezoelectric ultrasonic scaler (Woodpecker UDS P Led ultrasonic scaler, Woodpecker) with additional use of manual instruments where necessary, taking approximately 1 h in each quadrant. After instrumentation, optimal disinfection was sought by first brushing the back of the tongue for 60 s with a 1% chlorhexidine gel (Hexigel™, ICPA Health Products Ltd). Afterward, two rinses are made with a 0.2% chlorhexidine (Rexidine™, Indoco Remedies Ltd) solution for 1 min (gargling during the last 10 s to reach the tonsils). Subsequently, subgingival irrigation of the gingival sulcular area was performed for 10 min in 3 intervals with a 1% chlorhexidine gel (Hexigel™, ICPA Health Products Ltd). The subjects were also instructed to use 0.2% chlorhexidine mouthwash (Rexidine™, Indoco Remedies Ltd) twice daily for two weeks.

The following primary outcome variables were evaluated.

- 1 Sulcus Bleeding Index (Muhlemann and Son 1971),
- 2 Plaque Index (Turesky – Gilmore – Glickman modification of the Quigley – Hein Plaque Index 1970),
- 3 Gingival Index (Löe and Silness Index 1963) was assessed at baseline, 1 and 2 weeks. Erythrosine dye was used to disclose plaque after taking gingival index and bleeding index.

4 Uric Acid Index was determined by using a commercially available reagent kit and the method suggested by Fossati et al. (1980). (AutopakR, Bayer Diagnostics, India). In this assay, uric acid was converted to allantoin and hydrogen peroxide, which oxidized the chromogen (4-amino antipyrine) under the catalytic control of peroxidase to produce a red compound whose strength of color was proportional to the amount of uric acid present in the sample; it was read at a wavelength of 510 nm (492–550 nm). The reaction's last color remains unchanged for 15 min. In saliva, uric acid is a significant antioxidant (>70%). Its proportions fall because of periodontal disorder, but there is no difference across demographic groups¹⁸. The current research also aims to see whether extraneous antioxidant treatment (in this case, Lycopene) improved gingival protection in cases where normal antioxidants like uric acid are depleted because of different pathological conditions. No dietary limitations were imposed during the treatment. The subjects were asked to follow standard oral hygiene procedures, i.e., brushing twice a day with a fluoridated dentifrice, without using any other chemotherapeutic agent.

2.2. Statistical analysis

Paired *t*-test and the independent *t*-test were used to analyze the inter-group and intra-group differences. Correlations between salivary uric acid levels and percentage reduction in gingivitis and gingival bleeding in both groups were evaluated using the Pearson test. The level of significance was weighed against the *p*-value. If *p* < 0.05, a significant difference exists in both groups. The data were subjected to computer program statistics (SPSS Version 20.0; SPS Inc., Chicago, IL).

3. Results

The mean ages of the patients were 29.58 years $\pm$ 9.42.56% of the patients were males. At the onset of the study, both groups showed comparable findings to all the measured parameters. Differences within the two groups were analyzed employing paired *t*-test.

Dental examination at the onset of the study showed comparable findings of the oral status of both groups' patients. At 1- and 2-week examinations, it was found that the bleeding was reduced significantly (*p* < 0.05) as compared to baseline values in all the patients. When inter-group differences in SBI values were assessed, it was found that there was a statistically significant decrease (*p* < 0.001) in the OP-lycopene group as compared to the non-OP-placebo group. A statistically significant decrease (*p* < 0.05) was observed in the OP-lycopene group compared to the non-OP-lycopene group (Table 1).

On GI examination, a statistically significant difference (*p* < 0.05) was found at both 1- and 2-week examinations within the groups compared to baseline. The GI in OP-lycopene was reduced significantly (*p* < 0.001) in comparison to non-OP-placebo. This group also showed a statistically significant difference (*p* < 0.05) compared to the OP-placebo group (Table 2).

Table 1

Design	T/t group	Baseline	1 week	% reduction	2 weeks	% reduction
Lycopene	OP	1.20 $\pm$ 0.84	0.80 $\pm$ 0.45*	33.3 $\pm$ 7.74	0.40 $\pm$ 0.55*	66.67 $\pm$ 5.75 [#]
	Non-OP	1.40 $\pm$ 0.89	1.20 $\pm$ 0.84*	14.26 $\pm$ 5.62	0.80 $\pm$ 0.45*	42.86 $\pm$ 8.24
Placebo	OP	1.40 $\pm$ 0.55	1.00 $\pm$ 0.71*	28.57 $\pm$ 3.56	0.60 $\pm$ 0.55*	57.14 $\pm$ 2.94
	Non-OP	1.00 $\pm$ 0.71	0.80 $\pm$ 0.45*	20.0 $\pm$ 6.10	0.70 $\pm$ 0.55*	30.0 $\pm$ 3.76

* Statistically significant (*p* < 0.05) within the group.

Statistically significant relative to NOP-placebo (*p* < 0.001) and NOP-lycopene (*p* < 0.05).

Table 2

Design	T/t group	Baseline	1 week	% reduction	2 weeks	% reduction
Lycopene	OP	1.60 $\pm$ 1.41	0.80 $\pm$ 0.45*	50.0 $\pm$ 17.02	0.40 $\pm$ 0.55*	75.0 $\pm$ 15.25 [#]
	Non-OP	1.40 $\pm$ 1.14	0.80 $\pm$ 0.84*	42.86 $\pm$ 6.56	0.50 $\pm$ 0.55*	56.43 $\pm$ 12.94
Placebo	OP	1.60 $\pm$ 0.89	1.20 $\pm$ 0.45*	25.0 $\pm$ 12.36	0.60 $\pm$ 0.55*	62.5 $\pm$ 9.55
	Non-OP	1.20 $\pm$ 0.45	1.00 $\pm$ 0.71*	16.67 $\pm$ 9.16	0.89 $\pm$ 0.55*	26.0 $\pm$ 18.18

* Statistically significant (*p* < 0.05) within the group.

Statistically significant relative to NOP-placebo (*p* < 0.001) and NOP-lycopene (*p* < 0.05).

The PI scores showed a statistically significant (*p* < 0.05) reduction in the OP-lycopene, OP-placebo, and NOP-lycopene groups from baseline at 1- and 2-week intervals. When inter-group differences were assessed, it was found that there was a statistically significant reduction (*p* < 0.001) in the OP-lycopene group as compared to NOP-placebo, while there was no statistical difference observed in the other groups. However, the reduction in the OP-placebo was found to be greater than the NOP-lycopene group (Table 3).

When the salivary uric acid level was measured, it was observed at both 1 and 2 weeks that the intra-group reduction was significant (*p* < 0.001) in the OP-lycopene and NOP-lycopene groups when compared to baseline values. The OP-placebo group also showed a significant reduction (*p* < 0.05) compared to the baseline value at 1 and 2 weeks. However, the OP-lycopene group showed statistically significant results on inter-group evaluation compared to NOP-placebo (*p* < 0.001). (Table 4).

Fig. 1 presents the flow diagram for patient recruitment and selection.

4. Discussion

The primary goal of this study was to see how systemically administered Lycopene affects the SBI, PI, GI, and salivary uric acid levels in patients with gingivitis when used with scaling and root planing. The results confirm a significant difference among the OP-Lycopene and Placebo groups in terms of GI, SBI, PI, and salivary uric acid level (*p* < 0.05). OP- lycopene group significantly reduces the sulcular bleeding index, plaque index, gingival index, and salivary uric acid level compared placebo group.

During inflammatory periodontal disorders, the clinical activities contributing to periodontal degradation are likely to be complex interactions involving an imbalance of enzymatic and non-enzymatic degenerative pathways. Since microorganisms play such a significant role in the pathogenesis of periodontal disease, treatment focuses on reducing the number of pathogenic microorganisms in contact with periodontal tissues. As a result, most periodontal treatment plans start with mechanical plaque removal. Nonsurgical mechanical therapy is usually done quadrant-wise or sextant.

Table 3

Design	T/t group	Baseline	1 week	% reduction	2 weeks	% reduction
Lycopene	OP	1.80 $\pm$ 0.84	0.80 $\pm$ 0.45*	55.56 $\pm$ 7.74	0.60 $\pm$ 0.55*	66.67 $\pm$ 5.75 [#]
	Non-OP	1.60 $\pm$ 0.55	1.20 $\pm$ 0.45*	25.0 $\pm$ 3.03	0.80 $\pm$ 0.45*	50.0 $\pm$ 3.03
Placebo	OP	1.60 $\pm$ 0.55	0.80 $\pm$ 0.45*	50.0 $\pm$ 3.03	0.60 $\pm$ 0.55*	62.5 $\pm$ 2.94
	Non-OP	2.00 $\pm$ 0.71	1.60 $\pm$ 0.55	2.00 $\pm$ 1.76	1.80 $\pm$ 0.71	10.0 $\pm$ 5.76

* Statistically significant (*p* < 0.05) within the group.

Statistically significant relative to NOP-placebo (*p* < 0.001).

Table 4

Design	T/t group	Baseline	1 week	% reduction	2 weeks	% reduction
Lycopene	OP	3.52 ± 0.46	0.80 ± 0.45*	49.48 ± 6.65	0.60 ± 0.55*	71.24 ± 6.78 [†]
	Non-OP	3.64 ± 0.69	1.20 ± 0.45*	38.20 ± 5.37	0.80 ± 0.45*	66.38 ± 5.23
Placebo	OP	3.68 ± 0.57	2.51 ± 0.45#	31.67 ± 4.59	0.60 ± 0.55#	51.48 ± 2.94
	Non-OP	3.57 ± 0.52	1.60 ± 0.55	21.28 ± 5.64	1.80 ± 0.71	25.12 ± 4.61

* Statistically significant ($p < 0.001$) within the group.

Statistically significant ($p < 0.05$) within the group.

[†] Statistically significant relative to NOP-placebo ($p < 0.001$).

Recent research suggests that periodontal infections may be found in intraoral areas other than periodontal pockets, such as the lips, mucosa, spit, and tonsils, and translocation within these ecological niches and between persons.²⁶ The intra-oral translocation of periodontal pathogens jeopardizes the result of periodontal treatment. If such a translocation happens, it seems logical that a periodontal pathogen colonizing other untreated pockets or extra dental domains during traditional mechanical therapy might reinfect an already treated pocket. It will have a negative impact on the treatment's results. If we were to increase the feasibility of nonsurgical mechanical treatment, such a discovery would cause a shift in our strategy. Recently, a full-mouth approach to nonsurgical treatment was proposed,²⁷ and it was used in a modified form in the present study. There are specific patients like those that do not respond well to traditional mechanical therapy alone, patients who have poor oral hygiene measures, and those patients where conventional mechanical debridement procedures do not remove all periodontopathic bacteria from the subgingival environment, especially

those in inaccessible areas such as furcations, grooves, concavities, and deep pockets. This subset of patients would benefit from the use of an adjunctive antimicrobial. The best medium for delivering chemical plaque control agents from a cost-benefit standpoint is toothpaste, but the simplicity of formulation and consumer tastes have preferred the use of mouth rinses, and many other newer types are now being produced.

Because of a lack of sufficient antioxidant defense, tissue damage caused by free radical development, such as ROS, is increased in people with periodontal disease.²⁸ However, owing to the scarcity of unique oxidative stress biomarkers, investigating disease-related oxidant-antioxidant mismatch remains difficult. Furthermore, since antioxidants function in concert by chain-breaking reactions, measuring individual antioxidants can give a misleading impression. In the world of periodontics, several antioxidants have been tested. For example, a clinical study found that using perfortan locally in patients with periodontal disease reduced lipid peroxidation and increased antioxidant production in saliva significantly.²⁹

Gingival bleeding was enhanced dramatically after a period of Vitamin C deficiency and then returned to baseline after a period of Vitamin C replenishment in another clinical trial.³⁰ Antioxidants can also be used in carotenoids. According to in vitro experimental systems, Lycopene is the most potent antioxidant among the common carotenoids.³¹ Lycopene exhibits the highest physical quenching rate with singlet oxygen and is at least three-fold more effective than β -carotene in preventing cell death by quenching NOO radicals. Lycopene minimizes cell damage by limiting free-radical formation, destroying the free radicals or their precursors, stimulating antioxidant enzyme activity, repairing oxidative damage, stimulating repair enzyme activity, and reversing DNA damage induced by H_2O_2 . It has the unique feature of becoming bound to chemical species that react to oxygen, thus being the most efficient biological antioxidantizing agent.

Carotenoids in mixtures are more potent than single compounds.³²

Fig. 1. Flow diagram for patient recruitment and follow-up.

When Lycopene or lutein is present, the synergistic impact is more substantial. The precise positioning of various carotenoids in the cell membrane can be linked to the superior defense of mixtures.³² Since the influence of antioxidant medications can be better observed as they are given to participants over this length of time, this study sought to test gingival improvements when the medication was taken for two weeks.²¹ Compared to the positive (OP-placebo) and negative (non-OP-placebo) controls, the OP-lycopene group showed a substantial decrease in gingivitis. The findings show that Lycopene should be used with scaling to treat mild chronic marginal gingivitis. In the Sulcus Bleeding Index parameter, there was a statistically significant decrease in bleeding between the OP Lycopene and Non-OP Placebo groups. The difference was also statistically significant, but less so, between the OP Lycopene and Non-OP lycopene groups. It suggests that oral prophylaxis was the deciding factor in the reduction of bleeding between these two groups.

Although the OP-lycopene group had a more considerable mean reduction in GI than the non-OP-lycopene group, there were no statistically significant variations between the two groups. However, the statistically significant difference in GI between the OP Lycopene group and OP Placebo group suggests that Lycopene is crucial in reducing GI scores. Therefore, further research is needed to see whether Lycopene can be used as a “stop-gap” monotherapy for plaque-induced chronic marginal gingivitis control, exceptionally when oral prophylaxis may be postponed. The significant decrease in PI scores between the OP Lycopene and Non-OP Placebo groups suggests the importance of oral prophylaxis and Lycopene in improving periodontal health. However, there was no significant difference between the OP Placebo group and Non-OP Lycopene group, the fact that more significant reduction of PI scores in the former suggests that oral prophylaxis is more critical than Lycopene in terms of PI scores.

In this analysis, uric acid levels were also linked to antioxidant therapy reactions. Uric acid inhibits transition metal ion-dependent OH-generation in vitro, and it is a firm singlet O₂ quencher/scavenger and can capture peroxy radicals in an aqueous process.³³ Salivary uric acid levels are lower in periodontal disorders since they are the main (>70%) of saliva.³⁴ The uric acid levels in the oral prophylaxis groups were slightly lower than in the non-oral prophylaxis groups in the current sample. The results suggest that both oral prophylaxis and the administration of Lycopene are essential in reducing salivary uric acid levels. Chandra et al.,³⁵ published similar findings, concluding that salivary uric acid levels and gingival parameters in gingivitis patients treated with Lycopene as an alternative to mechanical therapy had a favorable association. While the mean reduction in GI (gingival index) was higher in the OP-lycopene group than in the NOP lycopene group, no statistically relevant differences were seen between the two groups in this analysis. Antioxidant status in unstimulated whole saliva was considered in this study.

Antioxidant concentrations in absolute terms are meaningless since they reflect the concentration in a pool of saliva collected over a few minutes, which does not happen in a regular person because of swallowing. When it comes to antioxidant species exposure in the gums and teeth, the rate of transmission of antioxidants is more significant. It requires further investigation.

Lycopene has much potential as an antioxidant drug for chronic gingivitis. Combining routine oral prophylaxis with Lycopene to achieve an additional effect is also intriguing and warrants further investigation. The present study was done on hundred subjects for a period of two weeks. A further long-term study with larger sample size is suggested to evaluate the effect of Lycopene on periodontal health conclusively.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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