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The Efficacy of Lycopene in Extraction Socket Healing in Diabetic Patients: Split Mouth Observational Study

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Abstract
Background: Diabetes mellitus impairs wound healing, especially after tooth extractions, due to oxidative stress and chronic inflammation. Lycopene, a tomato-derived antioxidant, may enhance healing through anti-inflammatory and oxidative stress–reducing effects. Aim: Evaluate lycopene's efficacy in extraction socket healing in diabetic patients. Materials and Methods: A split-mouth observational study was conducted in diabetic patients requiring bilateral extractions. Lycopene supplementation was applied to one socket; the contralateral socket served as control. Clinical assessments at baseline and days 1, 3, and 7 post-extraction evaluated soft tissue healing and bone density. Results: Extractions were primarily performed for grossly decayed teeth (57.1%), dental caries (28.6%), and apical periodontitis (14.3%). No infections occurred in either group. Pain scores in the lycopene group decreased from 3.93 on day 1 to 0.93 on day 3 and 0 on day 7, versus 5.14, 1.86, and 0.14 in controls. Soft tissue healing was superior with lycopene: all patients had good grades on day 1 and 13 achieved excellent scores by day 7, while only three controls reached excellence. By week 5, all lycopene sockets showed normal hard tissue appearance compared to seven controls. Conclusion: Lycopene supplementation enhances extraction socket healing in diabetic patients by reducing oxidative stress and inflammation.
Keywords: *Antioxidants, Diabetes Mellitus, Extraction, Inflammation, Lycopene, Socket, Wound Healing*

INTRODUCTION

The healing process of extraction sockets involves intricate biological systems that encompass the restoration of both hard and soft tissue. After tooth extraction, the socket undergoes several stages: clot formation, an inflammatory reaction, granulation tissue development, and finally, bone remodeling [1]. This reparative cascade is generally obstructed in diabetic patients due to sustained physiological alterations generated by hyperglycemia. These alterations encompass chronic inflammation, reduced angiogenesis, and impaired antioxidant defenses [2,3]. These pathophysiological changes impede wound healing and heighten susceptibility to post-extraction complications, necessitating therapeutic interventions to optimize tissue repair.

Through mitochondrial dysfunction and the buildup of advanced glycation end products, diabetes mellitus causes oxidative stress, which in turn reduces collagen synthesis and osteoblast activity which are two processes essential for socket healing [4,5]. Clinical research indicates that insulin-dependent diabetics exhibit healing rates that are three and a half times slower than those of non-diabetics. Furthermore, individuals with diabetes exhibit a prolonged epithelialization process and diminished bone formation potential [3]. This metabolic imbalance engenders a milieu conducive to the proliferation of reactive oxygen species (ROS), hence intensifying tissue damage and obstructing the mechanisms essential for cellular repair [6].

Lycopene, a potent lipophilic carotenoid mostly located in tomatoes, exhibits extensive medicinal potential. It can neutralize peroxyl radicals with double the efficacy of β-carotene. Catalase and superoxide dismutase are two instances of endogenous antioxidant enzymes that ought to be elevated. Modify the NF-κB signaling pathways to lower the generation of pro-inflammatory cytokines. Experimental models demonstrate that lycopene accelerates the healing process at wound sites through enhanced fibroblast proliferation (27% greater than controls) and collagen deposition (34% greater). Histopathological analysis revealed enhanced epithelial migration and vascularization in diabetic rats treated with topical lycopene emulgel. The wound closure rate was 95.3% within 21 days, greatly surpassing the 88.9% achieved by untreated controls [7].

A clinical observational study indicates a negative relationship between lycopene intake and glycemic indices. An increment of 10 milligrams per day correlates with a 0.45% drop in HbA1c ($p<0.01$) and an 11.2 milligrams per deciliter decrease in fasting glucose ($p=0.03$). The management of glycemia operates alongside the direct antioxidant advantages of lycopene, evidenced by the observation that diabetics with high lycopene intake exhibit a plasma antioxidant capacity 38% greater than those who ingest lower quantities of lycopene. The chemical may be a helpful adjuvant in the treatment of diabetic wound illness based on its combination effects on metabolic regulation and oxidative stress reduction [2,7].

Despite these pharmacological advancements, their clinical uses in oral surgery remain unexamined. The current dentistry research focuses on socket preservation techniques while largely neglecting systemic boosters of healing biology. This study employed a split-mouth technique to separate the therapeutic effects of lycopene. This design facilitates the regulation of confounding metabolic variables via intra-patient comparative methods. This methodological approach rectified substantial limitations of prior nutritional research, which were marked by inter-individual variability that obscured treatment outcomes. This study addresses substantial discrepancies between the established biochemical properties of lycopene and its therapeutic applications in dentistry, perhaps paving the way for a new nutritional supplement in the management of oral diseases associated with diabetes. The present study was conducted to evaluate how well lycopene works to promote healing of the extraction socket in diabetes patients.

MATERIAL AND METHODS

This split-mouth observational study was conducted at the Oral and Maxillofacial Surgery Department of SRM Dental College, Ramapuram, Chennai, following approval from the Institutional Review Board (SRMDC/IRB/2022/MDS/NO.407) and with informed consent from all participants. Patients aged 40–75 years with controlled diabetes (fasting blood sugar <140 mg/dL, random blood sugar <200 mg/dL, HbA1c ≤8%), asymptomatic periodontal status, and requiring bilateral mandibular molar extractions were enrolled. Exclusion criteria included uncontrolled diabetes, systemic contraindications to surgery, edentulism, bleeding disorders, allergies, pericoronitis, bone pathology, and aggressive periodontitis. A priori power analysis determined a total sample size of 28 sockets (14 study, 14 control) to achieve 80% power at $\alpha = 0.05$.

The Lycoepene dosage was calculated and the intervention prepared as per instructions. (Figure 1 and 2)

Figure 1: Dosage calculation of Lycopene powder

Figure 2: Preparation of Lycopene

After medical screening, radiographic evaluation, and baseline blood sugar and HbA1c measurements, extractions were performed under local anesthesia. Both sockets were irrigated with saline and povidone-iodine. In the study socket, pure lycopene powder mixed with saline was loaded onto an absorbable collagen sponge and placed into the socket before suturing with 3-0 silk (Figure 3). The control socket received debridement and standard closure with figure-of-eight or mattress 3-0 silk sutures (Figure 4). All patients received identical postoperative antibiotics (amoxicillin 500 mg thrice daily for three days) and analgesics (acetaminophen 500 mg twice daily for three days).

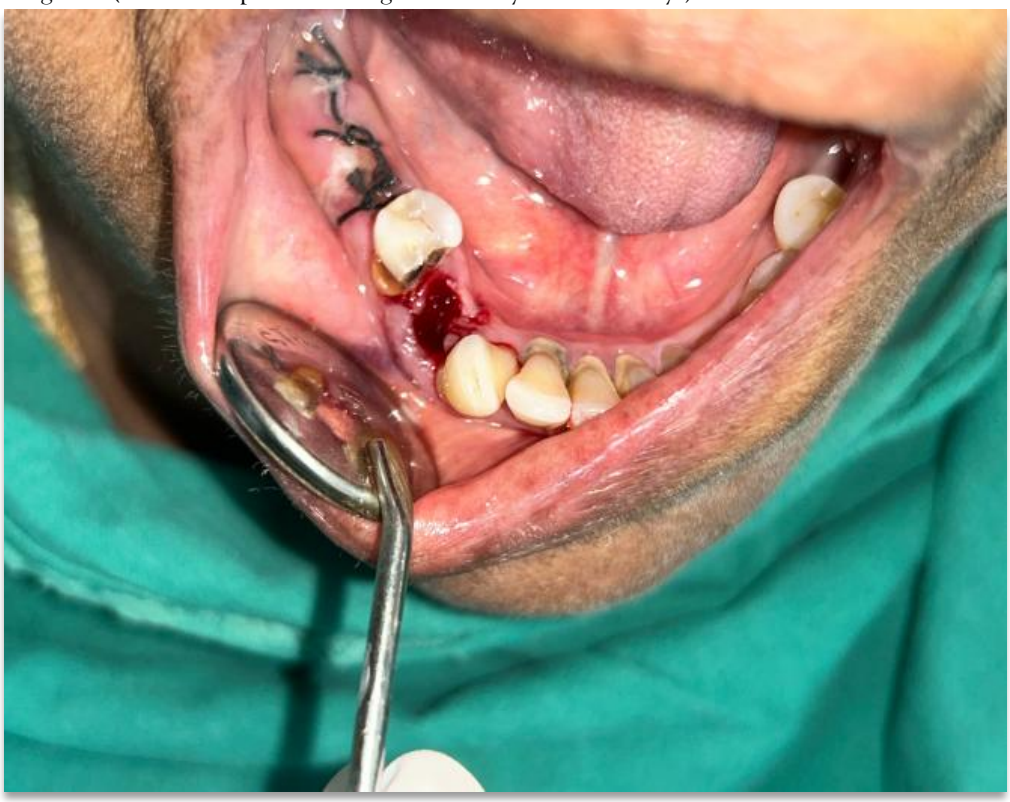


Figure 3: Study group underwent closure of extraction socket after Lycopene administration.

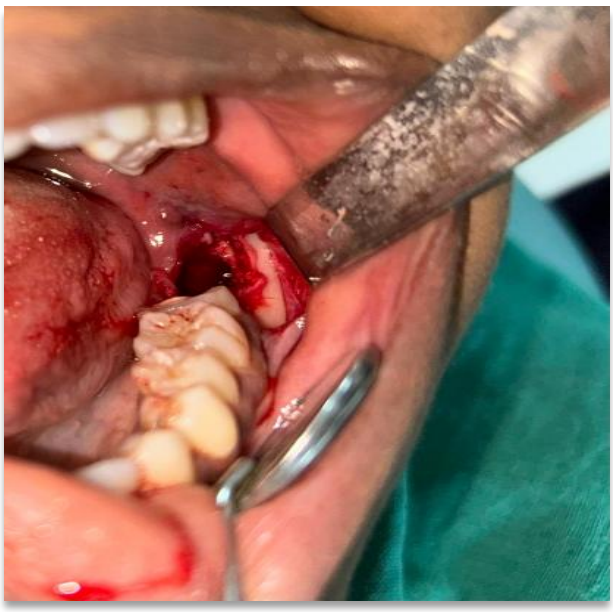


Figure 4: Control group participants underwent debridement and standard closure.

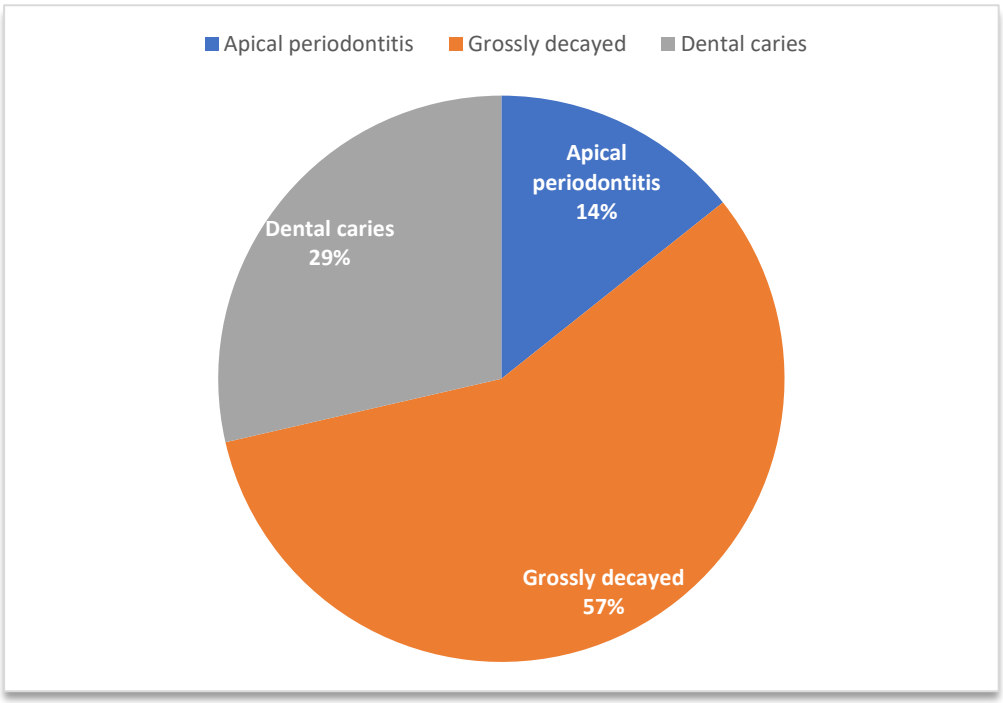
Soft tissue healing was assessed by Landry's Healing Index and pain by a visual analogue scale on days 1, 3, and 7. Hard tissue healing was evaluated by CBCT (HU measurements) at weeks 5 and 12. Infection was monitored clinically using established criteria.

Statistical analysis: Statistical analysis was conducted using IBM SPSS (IBM Corp. Released 2011). IBM SPSS Statistics for Windows, Version 20.0. Armonk, New York: IBM Corporation. The mean and standard deviation will be employed to summarize the data. A $p<0.05$ will be regarded as a statistically significant difference.

Results

The primary indications for tooth extractions in this diabetic cohort were grossly decayed teeth (57.1%), followed by dental caries (28.6%) and apical periodontitis (14.3%), underscoring the high burden of carious and endodontic pathology in this patient population (Figure 5).

Figure 5: Distribution of diagnosis among all participants



The results of soft tissue healing from **table 1** exhibited a pronounced enhancement in lycopene-treated sockets across all early time points. On day 1, the majority of treated sites (60.9%) achieved a "good" healing score, whereas control sockets uniformly scored "poor." By day 3, every lycopene socket demonstrated "very good" healing, in stark contrast to the untreated side, where no such improvement was observed. This accelerated epithelialization and reduction in inflammation culminated in 81.3% of treated sockets attaining an "excellent" score by day 7, compared with only 18.8% of controls. These data suggest that lycopene's antioxidant and anti-inflammatory properties substantially shorten the initial inflammatory phase and promote early fibroblast activity and re-epithelialization.

Table 1: Distribution Of Soft Tissue Grades Between The Two Group At Follow Up

Day	Soft Tissue Status	Group	Observed Counts	% within Row	p-value
1st Day	Good	Control	9	39.1%	0.014*
		Study	14	60.9%	
	Poor	Control	5	100.0%	
		Study	0	0.0%	
3rd Day	Good	Control	14	73.7%	<0.001*
		Study	5	26.3%	
	Very Good	Control	0	0.0%	
		Study	9	100.0%	
7th Day	Excellent	Control	3	18.8%	<0.001*
		Study	13	81.3%	
	Good	Control	0	0.0%	
		Study	1	100.0%	
	Very Good	Control	11	100.0%	
		Study	0	0.0%	

*: statistically significant difference ($p<0.05$)

Hard tissue regeneration observed in **table 2** also favored the lycopene group. At five weeks, the mean bone density in treated sockets was 823 HU, significantly higher than the 703 HU observed in controls, indicating more robust early bone deposition. This advantage persisted through week 12, with treated sites reaching 1042 HU versus 790 HU in controls, reflecting both accelerated mineralization and improved trabecular architecture. Such improvements in socket fill may translate to enhanced support for future prosthetic rehabilitation and reduced risk of alveolar ridge resorption.

Table 2: Distribution Of Hard Tissue Grades Between The Two Group At Follow Up
*:statistically significant difference (p<0.05)

Follow-up Week	Group	Mean Hard Tissue	SD	p-value
5th Week	Control	703	89.2	0.001*
	Study	823	88.8	
12th Week	Control	790	87.2	<0.001*
	Study	1042	185.2	

Postoperative discomfort was consistently lower in the lycopene group. On day 1, mean pain scores were reduced by more than one point on the visual analogue scale (3.93 vs. 5.14), and by day 3, pain in treated sockets had declined to 0.93 compared with 1.86 in controls. By day 7, pain was negligible in both groups, indicating that lycopene primarily affects early nociceptive and inflammatory pathways. Finally, no postoperative infections were recorded in either group at any follow-up, demonstrating that lycopene supplementation does not compromise socket sterility and may even contribute to an environment less conducive to microbial proliferation (Table 3 and 4).

Table 3: Distribution Of Mean Pain Scores In Two Groups At Different Time Points

Day	Group	Mean Pain Score	SD	p-value
1st Day	Control	5.143	1.512	0.042*
	Study	3.929	1.49	
3rd Day	Control	1.857	1.099	0.043*
	Study	0.929	1.21	
7th Day	Control	0.143	0.363	0.153
	Study	0.000	0.00	

*: statistically significant difference (p<0.05)

Table 4: Distribution Of Infection Between The Two Groups At Different Timepoints

Day	Group	Infection Status	Counts	% of Total	Cumulative %
1st Day	Control	Not Present	14	50.0%	50.0%
	Study	Not Present	14	50.0%	100.0%
3rd Day	Control	Not Present	14	50.0%	50.0%
	Study	Not Present	14	50.0%	100.0%
7th Day	Control	Not Present	14	50.0%	50.0%

	Study	Not Present	14	50.0%	100.0%

DISCUSSION

Lycopene, a naturally occurring carotenoid prevalent in tomatoes, watermelons, and other red fruits, is renowned for its potent antioxidant capabilities and its ability to mitigate oxidative stress and inflammation [8,9]. Emerging evidence supports lycopene's utility in oral health and post-extraction socket healing. Lycopene administration has been shown to downregulate key inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and C-reactive protein, thereby attenuating the acute inflammatory response that can impede wound repair [10]. Furthermore, lycopene enhances collagen synthesis by upregulating collagen type I gene expression in fibroblasts, and it promotes angiogenesis through increased vascular endothelial growth factor (VEGF) secretion [11]. These combined effects foster robust soft tissue regeneration. In hard tissue contexts, lycopene has been demonstrated to stimulate osteoblastic differentiation, increase alkaline phosphatase activity, and regulate bone remodeling pathways—particularly the WNT/β-catenin signaling axis—thus directly influencing bone matrix deposition and mineralization [12]. Incorporating lycopene into absorbable collagen sponges leverages these multifaceted properties, facilitating sustained, localized release at extraction sites and optimizing the microenvironment for early tissue regeneration.

In this diabetic cohort, extractions were most frequently necessitated by grossly decayed teeth (57.1%), followed by dental caries (28.6%) and apical periodontitis (14.3%). These data align with epidemiological studies indicating that hyperglycemia exacerbates oral pathology through multiple mechanisms: reduced salivary flow, increased salivary glucose concentration fostering bacterial growth, and impaired neutrophil function that diminishes host defense [13-15]. Consequently, diabetic patients exhibit higher rates of caries progression, periodontal breakdown, and endodontic infections. This underscores the critical need for preventive dental care, stringent glycemic control, and adjunctive therapies aimed at enhancing healing outcomes in this vulnerable population.

Contrary to prior reports documenting post-extraction infection rates as high as 12.5% in insulin-dependent diabetics [16], this investigation observed no infections in either the lycopene or control sockets throughout follow-up (days 1, 3, and 7). This discrepancy likely reflects the rigorous inclusion of only well-controlled diabetic patients (HbA1c ≤8%), meticulous surgical technique, and standardized postoperative antibiotic coverage [13,17]. These findings emphasize the impact of systemic metabolic optimization and strict adherence to clinical protocols in mitigating infection risk and suggest that, when appropriately managed, diabetic patients can achieve infection rates comparable to nondiabetic individuals.

Pain reduction emerged as a salient benefit of lycopene treatment. The study group experienced significantly lower visual analogue scale (VAS) pain scores on day 1 (3.93 vs. 5.14; p=0.042) and day 3 (0.93 vs. 1.86; p=0.043), with negligible pain reported in both groups by day 7. These results corroborate prior evidence linking oxidative stress to nociceptive sensitization in diabetic wounds, where ROS-induced activation of proinflammatory cytokines and nociceptors prolong pain perception [18]. Lycopene's antioxidant action likely interrupts this cycle by scavenging ROS, downregulating proinflammatory mediators, and promoting endogenous antioxidant enzyme activity (e.g., superoxide dismutase, catalase). Additionally, systemic studies in chronic periodontitis patients with diabetes have demonstrated that lycopene supplementation reduces oxidative markers and accelerates tissue repair, thus supporting its analgesic potential [18].

Stress responses during dental extraction, characterized by cortisol elevation and transient hyperglycemia, can exacerbate postoperative discomfort [19,20]. By stabilizing oxidative balance and dampening the release of cortisol-induced inflammatory mediators, lycopene may mitigate these stress-related effects and enhance patient comfort. Although pain differences beyond day 3 were not statistically significant ($p>0.05$), extended observation periods may reveal cumulative benefits, as tissue incorporation of lycopene and its modulatory effects on redox-sensitive pathways intensify over time [21,22].

Hard tissue regeneration, quantified via cone-beam computed tomography (CBCT) radiodensity measurements, markedly favored lycopene-treated sockets. At week 5, mean radiodensity in the study group was 823 HU compared with 703 HU in controls ($p=0.001$), and at week 12, it further increased to 1042 HU versus 790 HU ($p<0.001$). These findings underscore lycopene's influence on early bone matrix formation and mineralization. In streptozotocin-induced diabetic rat models, topical lycopene emulgel

significantly enhanced wound closure (95.3%) and epithelialization within 21 days, alongside increased bone tissue deposition [23]. Lycopene's promotion of osteoblast proliferation, differentiation, and angiogenesis likely underpins the observed improvements in trabecular architecture and bone density in human extraction sockets.

Soft tissue healing, as assessed by Landry's Healing Index, demonstrated that by day 7, 81.3% of lycopene-treated sites reached an "excellent" score compared with 18.8% of controls. These outcomes illustrate lycopene's capacity to expedite fibroblast proliferation, extracellular matrix deposition, and re-epithelialization. While statistical significance for all soft tissue comparisons did not consistently reach $p<0.05$, potentially due to the modest sample size and interindividual variability and the overall trends affirm lycopene's role in enhancing early wound resolution. These clinical observations align with research showing that topical antioxidants accelerate mucosal healing by reducing oxidative burden and fostering growth factor release [24,25].

Despite these promising trends, limitations of the current study warrant consideration. The relatively small cohort (n=28 sockets) restricts statistical power and generalizability. The absence of stratification by glycemic control subgroups limits insights into dose–response relationships and the influence of baseline metabolic status. Furthermore, the study did not include biochemical analyses of oxidative and inflammatory biomarkers, which would elucidate the mechanistic pathways through which lycopene exerts its effects. Future research should incorporate larger, stratified populations, longitudinal follow-up beyond 12 weeks, and comprehensive molecular assessments which include measurements of ROS levels, antioxidant enzyme activity, proinflammatory cytokines, and angiogenic factors to validate and deepen understanding of lycopene's therapeutic potential.

Comparison with established socket management approaches is also essential. Collagen or xenograft fillers such as Bio-Oss® effectively preserve alveolar ridge dimensions but offer limited impact on pain and inflammation [26]. Conversely, platelet-rich plasma (PRP) promotes both soft and hard tissue healing through concentrated growth factors but entails additional preparation steps and higher costs. Lycopene's affordability, safety profile, and dual antioxidant–anti-inflammatory actions position it as a practical adjunct or alternative, particularly in resource-limited settings.

Ultimately, integrating targeted antioxidant therapy with optimized glycemic control may represent a synergistic strategy for improving post-extraction healing in diabetic patients. By attenuating oxidative stress, modulating inflammatory cascades, and supporting cellular proliferation and angiogenesis, lycopene can enhance clinical outcomes and patient comfort. Rigorous, multi-center trials are needed to establish standardized dosing regimens, optimize delivery vehicles, and compare efficacy against current adjuncts. Additionally, stratifying patients by HbA1c levels and evaluating the interplay between metabolic control and antioxidant therapy will refine patient selection and maximize therapeutic benefits. Through such research, lycopene may emerge as a valuable, evidence-based component of dental surgical protocols for patients with diabetes.

CONCLUSION

Lycopene supplementation significantly enhanced soft and hard tissue healing post-tooth extraction in well-controlled diabetic patients. Treated sockets exhibited accelerated epithelialization, improved bone density, and reduced early postoperative pain without increased infection risk. Lycopene's antioxidant and anti-inflammatory properties likely underpin these benefits. This cost-effective, targeted therapy deserves further investigation in larger, stratified trials to establish optimal dosing, delivery methods, and long-term outcomes in diabetic socket management and future clinical practice in dentistry.

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