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RESEARCH ARTICLES

Effect of the application of curcumin (*Curcuma Longa*) oral gel on periodontal inflammation in patients with type 2 diabetes melitus

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ABSTRACT

Patients with Type 2 Diabetes mellitus (T2DM) were more prone to suffer from periodontitis due to unique alteration in host immune response. Application of curcumin oral gel as adjunctive therapy was expected to improve periodontal condition due to its anti-inflammatory properties. The objective of this study was to evaluate the effect of curcumin oral gel on periodontal inflammation in patients with T2DM. Sixteen periodontal pockets (n=16) from patients with T2DM were administered with curcumin oral gel using blunt cannula after periodontal curettage. Gingival Index (GI) and Periodontal Pocket Probing Depth (PPD) were evaluated a month after application. GI was assessed using visible sign of inflammation parameters including swelling, redness and bleeding upon probing. PPD was assessed using UNC-15 periodontal probe. The results were analyzed by Wilcoxon test (two related samples). The results showed that GI before treatment decreased by 51.61% a month post application. There was statistically significant difference (Sig 0.003) between GI mean before and after curcumin application. PPD decreased by 42.81% and showed statistically significant difference (Sig 0.000) by Wilcoxon Test. It is concluded that application of curcumin oral gel post curettage could decrease periodontal inflammation in patients with T2DM.

Keywords: diabetics periodontics; curcumin; diabetes mellitus

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a metabolic disease, which affects 425 million adults in the global scope.[1] The prevalence of T2DM in Indonesia is still high and affects 19,47 million adults. Patients with Type 2 Diabetes Mellitus (T2DM) exhibit changes in their immune response, and thus they are more prone to periodontitis. Diabetic periodontitis is a chronic inflammatory disease in the periodontal tissue caused by periodontopathogenic bacteria in subgingival and supragingival plaques that occur in individuals with T2DM with poor glycemic control. Periodontitis in patients with T2DM is generally more severe than patients without T2DM.[2] This condition occurs because of changes in host response in people with T2DM.[3,4]

As a systemic condition that has been considered as one of the risk factors for periodontal disease, T2DM with its hyperglycemic features directly alters bacterial equilibrium, compromising cellular function and altering the metabolism of collagen.[3,4,5] The formation of advanced glycation end-products (AGEs) can change the extracellular matrix and the formation of cellular receptor bonds and increase inflammation. Periodontitis can induce hyperlipidemia and cause insulin resistance that in turn will aggravate DM. Changes in the immune response also occur in patients with T2DM. Exposure to periodontopathogenic bacteria in periodontal tissues of patients with T2DM triggers a greater inflammatory response (known as hyper inflammation) than healthy individuals. Hyperinflammatory conditions in patients with T2DM cause extensive damage to periodontal tissue. Special management is needed to treat periodontal disease in patients with T2DM.[3]

Curettage is a periodontal procedure to reduce periodontal pocket with moderate depth, which is done by scrapping the pathological periodontal pocket wall.[6] The removal of pathological tissue as well as soft and hard deposits on cementum surface will promote the re-attachment of periodontal tissue. Adjuvant therapy

or Host Modulation Therapy (HMT) is an additional therapy performed after the cleansing of soft and hard deposits on supragingival and subgingival surfaces. HMT agents which administered either orally or topically after mechanical periodontal treatments, such as Scaling and Root Planing (SRP) and curettage could provide better treatment results than conventional treatments. One of the potential ingredients for HMT candidates in periodontal treatment was curcumin.[7]

Curcumin is a natural ingredient derived from turmeric rhizome (Curcuma longa). Curcumin is a molecule that has high pleiotrophic properties. It has the potential to be developed into a multitarget drug. Curcumin has anti-inflammatory, hypoglycemic, and antioxidant properties. It can modulate various cell signaling pathways. Various clinical trials of curcumin have been carried out and have shown promising results for the treatment of inflammatory diseases.[8] Oral administration of curcumin has the disadvantages due to its poor absorption and low levels of active drug in blood plasma. More effective delivery of curcumin is needed, including through the preparation of gels for topical application. The application of curcumin gel as an adjuvant in periodontal treatment was expected to increase the success of the treatment.[7] The novelty of this study lies on the subject selection, which is patients with systemically compromised condition of Type 2 Diabetes Melitus (T2DM).

The study compared between the application of curcumin gel and the application of ornidazole gel in periodontitis. It was revealed that the curcumin gel produced a better pocket reduction and plaque index than the ornidazole gel, so that the curcumin gel could be used as adjuvant therapy after non-surgical periodontal treatment.[9] Research on the influence of oral curcumin gel on the management of gingivitis in non T2DM patients showed that the curcumin gel was efficient in the treatment of gingivitis by reducing the inflammatory components.[10] Study on curcumin extract to prevent type 2 diabetes mellitus showed that the administration of curcumin capsules orally for 9 months in the prediabetes population was able to prevent the occurrence of T2DM.[11] To the author's knowledge, research on the application of curcumin gel to periodontitis in diabetic patients has never been done. It is hypothesized that the topical application of curcumin gel following curettage in patients with T2DM could decrease the periodontal inflammation characterized by gingival index and periodontal pocket depth.

MATERIALS AND METHODS

This study is a quasi-experimental study with a clinical approach. Patients with DM who met the inclusion criteria and were willing to participate in the study were asked to fill out informed consent. This study has been approved to be ethically eligible by the ethics committee of the Faculty of Dentistry, Universitas Gadjah Mada.

Inclusion criteria for all participants were patients with T2DM with an age range of 35-70 years with moderate or poor OHI and 3-5 mm periodontal pockets. Subjects with a disability to open mouth, having taken antibiotics and having received periodontal treatment in the past 1 month were excluded from the study. Patients received scaling and root planing treatment at the first visit (initial phase therapy) and HbA1c assessment. On the second visit, a baseline examination was made for Gingival Index (GI) and Periodontal Pocket Probing Depth (PPD) followed by periodontal curettage. GI was assessed using visual examination and bleeding upon probing on each gingival section on a 0 until 3 score. Site with healthy and normal condition was scored by 0. A prominent reddish appearance on the gingiva was scored by 1, but if bleeding upon probing was observed, the scored would be 2. The bleeding upon probing was performed by gently inserting the periodontal probe into periodontal pocket for 1-3 seconds. Spontaneous bleeding on gingiva was scored with 3. Periodontal Pocket Probing Depth (PPD) measurement was performed using UNC-15 periodontal probe.

Curcumin gel (*C. longa extract*-10 mg, Curenext, Abbott, healthcare limited, Mumbai, India) was applied to the periodontal pocket after curettage. A blunt pre-bent disposable cannula

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Table 1. Gingival Index (GI) and Periodontal Pocket Probing Depth (PPD) improvement

Parameters	Mean baseline (n=16)	30 days post curcumin application	reduction	Sig (Wilcoxon test)
Gingival Index (GI)	1.9375	0.9375	51.61% (reduced)	0.003
Periodontal Pocket Probing Depth (PPD)	3.5	2	42.85% (reduced)	0.000

was inserted into periodontal pocket to administer the gel. The gel was deposited until it overflowed. Periodontal dressing was applied to cover the affected region. The patient was prevented from eating nor drinking for an hour. Clinical evaluation was accomplished 1 month after following the treatment. The data were analyzed with Wilcoxon test (two related samples).

RESULTS

16 periodontal pockets ranged from 3-5 mm from patients with Type 2 Diabetes Melitus (T2DM) were selected as the samples of this clinical research. The result on gingival index and Periodontal Pocket Probing Depth are shown in Table 1.

The provided Table 1 marks an improvement in GI after 30 days following curcumin application post curettage by 51.61% reduction. The Wilcoxon test also showed statistically significant result (sig 0.003). The result on Periodontal Pocket Probing Depth parameter also showed a marked improvement in PDD after 30 days following curcumin application post curettage by 42.85% reduction. The Wilcoxon test also showed statistically significant result (sig 0.000).

DISCUSSION

Table 1 in this study presents that topical curcumin application into periodontal pockets following curettage demonstrated statistically significant improvement 30 days later. GI and PPD were both enhanced. Topical application of curcumin shows good efficacy through biological mechanisms related to inhibition of phosphorylase kinase and anti-inflammatory effects mediated by downstream NF-KB. Dermatological studies show that topical application of curcumin over a period of time shows satisfactory results.[12]

Curcumin interacts with three molecular targets related to inflammation which include: Cytokines such as Tumor Necrosis Factor (TNF), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-12 (IL-12) and chemokines. Curcumin also interacts with Transcription factors like Nuclear Factor Kappa Betta (NF-κB), Activator Protein 1(AP-1), Early Growth Response Protein-1 (EGR-1), Betacatemin, Nuclear Factor-Erythroid Factor 2(NRF-2), Peroxisome Proliferator-Activated Receptors (PPAR) Gamma and Hipoxia inducible Factor-1 (Hif-1). Curcumin also interacts with Enzymes such as Cyclooxygenase-1 (COX-1), Cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), Inducible Nitric Oxide Synthase (INOS), and Hemeoxygenase-1.[13] Curcumin and its analogs significantly inhibit the production and release of pro-inflammatory cytokines, according to numerous in vivo and in vitro studies. Curcumin also inhibits the expression of numerous other inflammatory mediators, including Monocyte Chemoattractant Protein 1(MCP1), Inducible Protein 10 (IP10), Stromal Cell Derived Factor 1(SDF1), Matrix metallopreoteinase-2 (MMP-2), Interferon (IFN), and Matrix metallopreoteinase-9 (MMP-9), which regulate the activity of immune cells and inflammatory responses. There have been numerous studies on the mechanism that underlies curcumin's ability to modulate inflammation. This process involves a variety of signaling pathways, one of which is NF-kB, which plays an important role. It has been demonstrated that curcumin effectively modulates NF-κB signaling via a variety of pathways. Curcumin

blocks the cytokine-mediated NF- κB activation and prevents the production of pro-inflammatory genes. It inhibits the degradation of IκBα and the phosphorylation of IκBα serine 32. The usage of curcumin prevents the nuclear translocation of NF-B and p65, which results in a reduction in the amount of cytokine gene transcription.[14]

Patients with T2DM with high glycemic index experiences an alternation in immune response as well as delayed wound healing. Patients with T2DM suffer from a series of complicated pathophysiology combining vascular, neuropathic, immunological, and metabolic components. Hyperglycemia corresponds with stiffer blood vessels, which results in slowed circulatory and endothelial dysfunction, resulting in decreased tissue oxygenation. Moreover, Blood vessel changes reported in diabetic patients also decrease leukocyte migration into the wound, thus increasing the susceptibility to infection. The hyperglycemic environment can impair the function of leucocytes.[15] The improvement of GI and PPD in our study could involve the process of static movement of blood cells or known as hemostasis and followed by inflammation. This process continued to the proliferation of cells and followed by remodeling. Fibrin patches formation and vascular constriction marked the early phase of hemostasis. The subsequential incursion of neutrophils, macrophages and lymphocytes is the main feature of inflammation phase. There is an overlap period between proliferation phase and inflammatory phase. This overlap is distinguished by the amplification of epithelial cells and migration to the temporary matrix. Other signs of overlap period include blood vessels formation, the construction of collagen, and extracellular matrix.[16] However, the reshaping of collagen as well as blood vessels development occurs in the phase of remodeling. Gingival epithelial healing consists of the establishment of long junctional epithelium on the cemental surface of the root. Long junctional epithelium appears 1 week after therapy. Reduction in the population of inflammatory cells, gingival crevicular fluid flow, and connective tissue repair will gradually reduce clinical signs of inflammation.[17] Two weeks post curettage, the gingival margins have normal color, consistency, texture, contour and adapt well to teeth.[18] As curcumin possesses powerful anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant, and anti-infectious actions, the application of curcumin gel into periodontal pocket in patients with DM may be beneficial. It has also been demonstrated that curcumin significantly speeds up the healing process of wounds. It does so by enhancing the natural process of wound healing by interacting on a variety of its phases.[19] The limitations of our study were the limited number of samples and the types of clinical parameters examined limited to gingival index and PPD. It is suggested that future research expands the parameter into assessment of systemic and local biochemical markers that can describe the healing process of periodontal tissues more thoroughly. It is also recommended to confirm the reduction of local and systemic inflammatory burden after periodontal curettage in patients with T2DM by evaluating the difference in Erythrocyte Sedimentation Rate or Quantitative C-Reactive Protein Assay.

CONCLUSION

This study concluded that application of curcumin oral gel post curettage could decrease periodontal inflammation in patients with Type 2 Diabetes mellitus in one month evaluation.

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