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Perspective

Local drug delivery of folic acid promotes oral mucosal wound healing

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Folic acid (FA) is a B vitamin obtained from the diet as well as synthesized by gut microflora. It is an essential micronutrient in humans and is required in the range of 6–20 ng/ml. The recommended daily dietary intake of FA is 400 μg. However, the majority of FA in the diet are destroyed during processing, canning, and cooking, which is partially compensated by the gut microflora. It plays a critical role in erythropoiesis, pregnancy, cardiovascular system, and mucosal health. It is an essential micronutrient involved in the one-carbon transfer or methylation reactions, purine and pyrimidine biosynthesis, and conversion of homocysteine to methionine.[1–3]

Evidence shows that FA deficiency is associated with neural tube defects, heart disease, and poor wound healing outcomes. Its deficiency leads to DNA damage, impaired DNA repair, abnormal DNA methylation, and increased propensity to mutagenesis, which predisposes to increased cancer risk.[1–3] The same can be reversed by FA supplementation, which increases apoptosis of dysplastic epithelial cells with damaged DNA, by increasing the expression of the p53 gene and decreasing the expression of the Bcl-2 gene. This process plays a vital role in host defense and the suppression of mutagenesis.[3,4]

In the oral mucosa, FA deficiency is manifested as an end-organ deficiency with decreased epithelial integrity and barrier functions accompanied by increased nuclear staining in the basal cells with degeneration and widening of intercellular spaces in the spinous layer. These epithelial aberrations in the maturation and keratinization process predispose the oral mucosa to infection and ulceration. Moreover, there is diminished blood cell function with increased susceptibility to the development of stomatitis, gingivitis, periodontitis, and poor healing outcomes.[2,5]

Interestingly, FA supplementation in both systemic and local forms has been shown to augment the resistance of oral epithelial cells against local irritants and inflammation.[2,5] In a double-blind, randomized trial, Vogel et al. evaluated the effect of FA supplementation 2 mg twice daily for 30 days on gingivitis.[2] They observed no significant differences in plaque and gingivitis scores between the FA and control groups. However, a significant reduction in gingival exudates flow was found in the FA group as compared to the control group. They concluded that FA supplementation enhanced the gingival resistance to local irritants and also decreased gingival inflammation.[2] Further, Pack in a randomized, double-blind clinical trial evaluated the efficacy of a topical FA mouth rinse on established gingivitis.[6] The active drug group (5 ml of FA

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mouth rinse; one mg/1 ml, twice daily) was compared to a placebo mouth rinse (twice daily) in terms of color change, bleeding sites, and plaque scores. At four weeks, the FA group demonstrated a significant reduction in both color change and bleeding scores as compared to the control group. They observed that FA mouth rinse promotes gingival health through local rather than systemic influence.[6]

In an epidemiological study by Esaki et al. involving 497 non-smoking adults with 20 or more teeth, the relationship between dietary intake of FA and gingival bleeding was investigated using a multivariate analysis model.[7] They observed an inverse relationship between the FA level and gingival bleeding scores and concluded that FA might be used as a clinical target to promote gingival health. In a recent placebo-controlled clinical trial by Keceli et al., 60 periodontitis patients were randomized to scaling and root planing (SRP) with FA supplementation and SRP with placebo.[1] The clinical attachment levels were found to be significantly improved in SRP + FA as compared to SRP + placebo, demonstrating better healing and clinical outcomes in periodontitis patients with systemic FA supplementation.[1]

Due to the presence of end-organ deficiency of FA in the oral mucosa, the local drug delivery of FA directly to the diseased area is quite promising. It can be a game-changer for oral wound healing.[2,5,6] Several recent animal studies suggest the beneficial effects of local folic acid in wound healing outcomes. Duman et al., studied the effect of topical folinic acid, a 5-formyl tetra hydrofolic acid on wound healing in rats.[8] The wound healing was assessed by gross and histological analysis in control, 2.5% folinic acid, 1% folinic acid, and dexpanthenol treatment groups. Wound closure was evaluated using image analysis software and connective tissue characteristics post-treatment using the microscopic examination. They found that 2.5% of folinic acid can improve wound healing by increased epithelialization, angiogenesis, inflammatory cell migration, and collagen deposition.[8]

In another animal study, Xiao et al. tested whether the copper-based metal–organic framework nanoparticles HIKUST-1 combined with FA (F-HIKUST-1) can improve wound healing in diabetic mice.[9] They found that the conjugate F-HIKUST-1 can decrease the toxicity of HIKUST-1 by slow-releasing copper ions and enhance wound healing by increased angiogenesis, collagen deposition, re-epithelization, and wound closure rate. Similarly, Zhao et al. demonstrated that FA supplementation promotes wound healing by attenuating diabetes-induced protein nitrotyrosination and prevents glutathione (GSH) decrease in the skin tissue around the wound.[10] FA supplementation was found to increase fibroblast proliferation, collagen content, granulation tissue formation, and tissue regeneration. They concluded that FA has preventive and therapeutic benefits in diabetes-induced wound healing complications.[10]

For oral mucosal diseases, innovative local drug delivery systems in the form of mouth rinses, gels, and local delivery patches can be developed for better healing outcomes. We need to open new vistas in the development of local drug delivery devices for targeted FA delivery directly to the lesion site, circumventing the oral/systemic route.[3,6,8–10] Further, multicentric randomized controlled clinical trials are necessary to establish the adjunct use of systemic and local FA supplementation in the management of oral mucosal diseases. This will lead to the development of a novel and alternate strategy to mouthwashes and topical steroids, which are associated with various side effects like tooth discoloration, candidiasis, cytotoxicity, and poor wound healing outcomes.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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