Folic acid may be a potential addition to diabetic foot ulcer treatment – a hypothesis

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ABSTRACT

Delayed wound healing in diabetes is a challenging medical and societal problem for which there is currently no efficacious treatment. One of the major contributors of this problem is nitric oxide (NO) deficiency. NO is a critical signalling molecule essential for normal wound repair. Sustained hyperglycaemia in diabetes leads to increased vascular superoxide production, which inactivates NO and causes vascular dysfunction. New therapeutic regiments and strategies to enhance endothelial NO production are a new hope to improve impaired diabetic wound healing. One of the agents that have the ability to improve endothelial NO generation in diabetic patients is folic acid. Folic acid ability to conserve NO bioactivity may be due to homocysteine-lowering effects of folates, antioxidant actions and effects on cofactor availability. Considering these data, we hypothesised that folic acid supplementation may ameliorate delayed diabetic wound healing by increasing NO bioavailability. The potential of exogenous folic acid as an inexpensive and safe oral therapy stimulates ongoing investigations.

Key words: Diabetes • Folic acid • Nitric oxide • Wound healing

Chronic wounds in diabetic patients represent a challenging medical and societal problem leading to a substantial reduction in quality of life. Various factors are known to contribute to impaired wound healing in diabetes, including inflammatory response, decreased quantity of granulation tissue, peripheral neuropathy, reduced wound angiogenesis and abnormal vascular endothelial function (1,2). Endothelial dysfunction, which is estimated to occur in 30% of diabetic patients, is mainly because of reduced nitric oxide (NO) bioactivity (1,3). Increased intravascular superoxide (O$_2^-$) formation accounts for a significant proportion of the NO deficiency in diabetic vessels (3). NO is a critical signalling molecule essential for normal wound repair by inducing angiogenesis, migration and proliferation of fibroblasts, epithelial cells, endothelial cells and keratinocytes (4). Normal function of endothelial nitric oxide synthase (eNOS), the predominant NO synthase isof orm in the vasculature (5), requires the presence of the substrate L-arginine and the essential cofactor (6R)-5,6,7,8-tetrahydro-L-biopterin (BH4) (6).

Folates belong to the vitamin B group and are involved in a large number of biochemical processes, particularly in lowering plasma homocysteine (7,8). Homocysteine, a sulhydryl-containing amino acid, decreases the bioavailability of NO, either by an accelerated oxidative inactivation of NO and/or by an increase in serum asymmetric dimethylarginine, an endogenous inhibitor of eNOS (9–12). Furthermore, it has previously been shown that each micromole increase in plasma homocysteine levels leads to a 10% increase in the risk of diabetic foot ulceration (13). Regarding
these data, it seems that homocysteine-lowering effect of folates may help to increase NO bioavailability and so decrease the risk of diabetic foot ulcer. Recent researches have also shown that the administration of folic acid improves endothelial function in patients with both diabetes or hyperhomocysteinemia (14–16).

Ameliorating endothelial dysfunction and conserving NO bioactivity by folic acid may not be only because of homocysteine-lowering effects of folates but also because of other potential benefits of folates such as direct interactions with the eNOS, antioxidant actions and effects on cofactor availability (17,18). The active metabolite of folic acid, 3-methyltetrahydrofolate, protects against eNOS uncoupling to favour the generation of NO rather than oxygen-free radicals (6,17,19). Nilisha Shukla and his colleagues have shown that folic acid and/or its active metabolite elicits direct antioxidative effects, including the suppression of nicotinamide adenine dinucleotide phosphate oxidase expression (20), principal source of $O_2^-$ in diabetes (4).

Folic acid can also conserve BH$_4$ bioactivity by stimulating the endogenous regeneration of quinoid BH$_2$ to BH$_4$ (6). NO and L-citrulline production by eNOS in endothelial cells correlates closely with the intracellular concentration of BH$_4$ (21). Recent researches have shown that BH$_4$ restores endothelial function in animal models of diabetes (22) and insulin resistance (23), as well as in patients with hypercholesterolemia (24), diabetes mellitus (25) and essential hypertension (26).

Folic acid supplementation is also shown to exert positive effects on wound healing process, including activation of anabolic processes by intensifying the gluconeogenesis in the wound tissues and stimulating wound DNA synthesis (27,28). Considering all these data, we hypothesised that folic acid ability to lowering plasma homocysteine and increasing NO bioavailability may be efficacious to ameliorate delayed diabetic wound healing. This hypothesis can be examined by the administration of 2 weeks of folic acid supplementation, which has been shown to improve endothelial dysfunction independent of homocysteine-lowering effect (8). Doses of folic acid would be based on what is considered to be high and low dose in man, that is, 0.5 mg/3 kg per day and 0.1 mg/3 kg per day. The potential of exogenous folic acid as an inexpensive and safe oral therapy stimulates ongoing investigations.

REFERENCES