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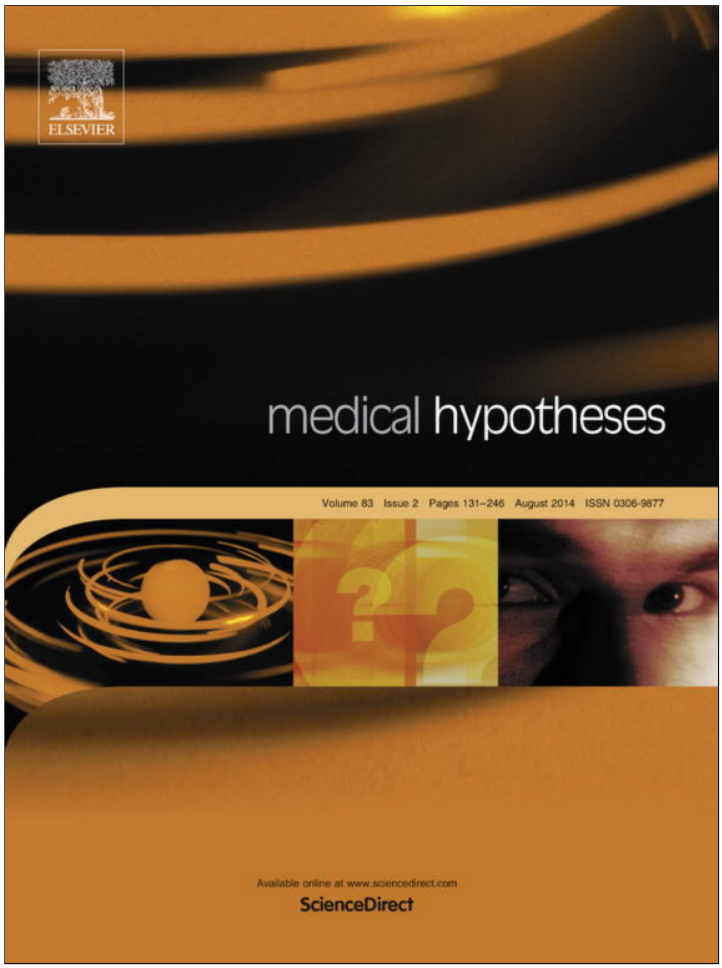

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Treatment with topical nitroglycerine may promote the healing process of diabetic foot ulcers ☆

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ABSTRACT

Diabetes mellitus is one of the main problems of the health care systems of all societies. A vast number of diabetic patients suffer from diabetic foot ulcers (DFUs) some of which may lead to the amputation of the organ(s). Nitric oxide (NO) is an indigenous gas that is produced at various sites in the body and has been shown to possess important roles in wound healing. Previous studies have shown that not only is the production of NO decreased in diabetic patients but also the sensitivity of the cells of such patients to NO is dramatically reduced. Nitroglycerine (isosorbide dinitrate) can be employed as an effective donor of NO to diabetic wounds. On such a basis, we suggest a novel hypothesis that delivery of compensatory amounts of NO to the ulcers by the administration of topical nitroglycerine enhances blood flow and biochemical activity of the ulcers and thus promotes wound healing.

Introduction

Diabetes mellitus is one of the main problems of health care systems of all societies. The number of people with diabetes worldwide was estimated at 131 million in 2000; it is projected to increase to 366 million by 2030 [1]. One of the most important problems that people with diabetes mellitus face, are the ulcerations that appear in their lower extremities which in some cases may lead to amputation with a prevalence of 4–10% if proper care is not taken [2]. More than 80,000 amputations are performed each year on diabetic patients in the United States [1]. Routine ulcer care, treatment of infections, amputations, and hospitalizations cost billions of dollars every year and place a tremendous burden on the health care systems. Diabetic foot ulcers (DFUs) result from simultaneous action of multiple contributing causes. The major underlying causes are peripheral ischemia resulting from peripheral vascular disease and neuropathy [1,3]. These vascular modifications are the key points in pathogenesis of diabetes and are the main issue of relevant research. NO is an indigenous gas that is made at various sites in the body and performs important functions in the process of wound healing [4].

Background

There are multiple factors that contribute to the initiation of DFUs. Peripheral vascular complications such as ischemic conditions are the main causes responsible for the development of the ulcers [1,2]. Endothelial cell dysfunction may occur as a result of persistent hyperglycemia that finally leads to the resultant decrease in endothelium-derived nitric oxide. This decrease in the production of nitric oxide is mainly due to a deficiency in nitric oxide synthase in diabetic patients. On the other hand, sensitivity of the vessels of patients with diabetic type 1 to indigenous NO is significantly lesser than that of normal humans [5,6]. Nitric oxide as a mediator of tissue repair promotes angiogenesis, increases inflammatory cells migration to the site of wounds, and enhances blood flow to the capillary beds adjacent to the sites of ulcers. Decreased production of nitric oxide in DFUs results in impaired cutaneous vasodilation, decreased neurogenic vascular response, diabetic neuropathy and endothelial cell dysfunction which leads to impaired formation of granulation tissue. Nitroglycerine (isosorbide dinitrate) is widely used as a medication in cardiovascular conditions [7]. It could be employed as a good source of NO to compensate the reduced NO production in DFUs when applied topically.

Hypothesis

Based on the previous studies stated above, we present a novel hypothesis which can be considered as an effective therapeutic approach in the treatment of DFUs. NO has a prominent role in

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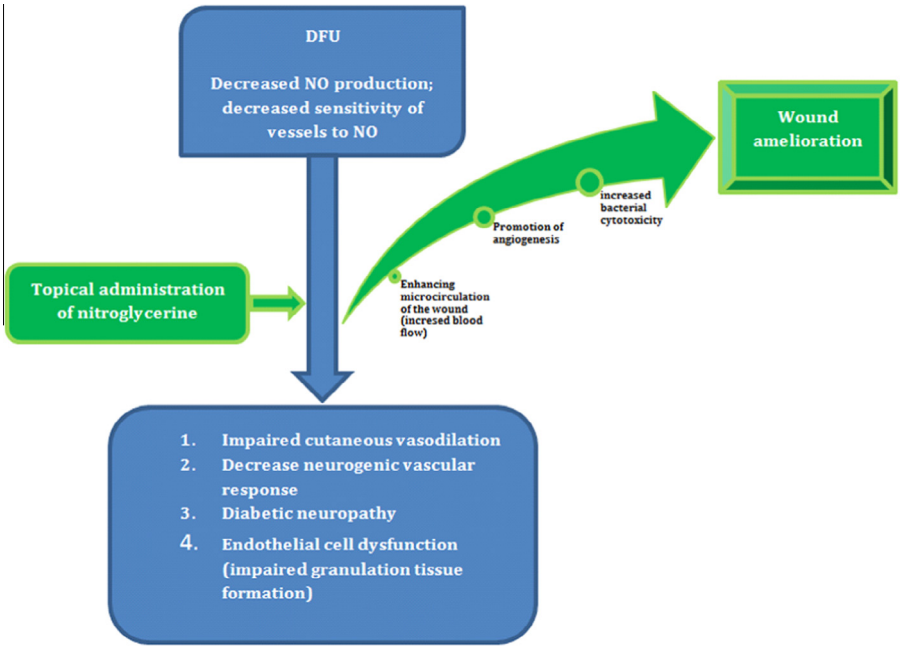

Fig. 1. Blood supply to diabetic foot ulcers (DFUs) is impaired due to a decrease in nitric oxide (NO) production by the vascular endothelial cells and reduced sensitivity of these cells to NO. Topical nitroglycerine applied on DFU delivers significant amounts of NO to the wound site. Increasing concentration of NO causes the vessels to dilate which consequently increases blood supply to the area. Enhancement of blood supply finally promotes mobilization of growth factors and inflammatory molecules involved in wound healing.

the inflammatory phase of wound healing. On the other hand, NO release from endothelial cells is dramatically decreased in diabetic patients. During the wound healing process, topical application of nitroglycerine as a synthetic and safe NO releasing agent onto the site of ulcers could be recruited to deliver compensatory amounts of NO and thus ameliorate the healing process of the ulcers (Fig. 1).

Discussion

The effect of NO on the healing process of ulcers consists of two main compartments. First of all is the effect of NO on the vasculature of the wounds. It causes vasodilation in both arteries and veins. On the other hand, the inhibition of NO synthesis leads to vasoconstriction and an increase in blood pressure as a result [8]. The hyperglycemic condition present in diabetic patients damages the endothelial cells. There is evidence regarding the decrease of NO production in diabetic mice models [9]. It has also been proven in clinical studies that production of NO is decreased in diabetic patients with peripheral neuropathy [10]. Another important point that should be taken into consideration is that sensitivity of the vessels of patients with diabetic type 1 to indigenous NO is significantly lesser than that of normal cases [5,6].

Second compartment of the effects of NO on the wounds is its inflammatory function. Studies show that NO has its highest amounts in the regions next to the ulcers [11]. Cytokines stimulate release of NO from macrophages and fibroblasts [12,13]. It is also shown that NO possesses cytotoxic and consequently antimicrobial properties [14]. Recently the use of NO has become so common in the health care systems to treat wounds of motor organs especially because of its positive effects on both vascular system and neuropathy of diabetic patients. Other studies indicate that the use of NO can reduce painful peripheral neuropathy [15,16]. More importantly, it was shown in a recent study that supplying topical NO is only effective in the healing of wounds in which contraction does not play an important role in the amelioration of the wound. DFUs are among such wounds [17].

Although there are reports that show the analgesic efficiency of isosorbide dinitrate spray in diabetic peripheral neuropathy [18]; however the ischemic nature of DFUs must be considered as the main target of nitroglycerine administration due to the vasodilation effects exerted by NO. It has been shown that passive diffusion of nitroglycerine through the skin produces therapeutic plasma levels in patients with angina pectoris [19]. Topical nitroglycerin (glyceryl trinitrate) has also been successfully used for the treatment of anal fissures which are thought to be of ischemic origin [19]. Therefore, ischemic DFUs are thought to be effectively ameliorated with this method. Brisinda et al., used paraffin to prepare diluted ointment of nitroglycerine in the treatment of anal fissures [20]. Eucerin, a commonly used ointment base [21], can be also recruited for the preparation of nitroglycerine topical ointment at different concentrations due to its desirable pharmacological properties including good drug releasing capacity [22].

Conclusion

These data all together suggest that administration of topical nitroglycerine can foster the amelioration of DFUs via donating compensatory amounts of NO to the site of ulcers. This may target the ischemia caused by peripheral vascular disease which is among the multiple causes for the development of DFUs. However, proper *in vitro* studies and clinical trials are required herein to precisely define the feasibility of this hypothesis as applicable for therapeutic purposes.

Conflict of interest statement

None declared.

Acknowledgment

None.

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