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Resveratrol may be beneficial in treatment of diabetic foot syndrome

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ABSTRACT

Diabetic foot syndrome (DFS) is a late-stage complication of type 2 diabetes which originates from interplay among impaired tissue regeneration, vasculopathy, neuropathy and inflammation all on the background of insulin resistance. Despite astonishing mortality rate pharmacological approach in management of diabetic ulceration is almost non-existent. Foot pressure relief, wound debridement and infection control remain widely accepted options in the treatment of DFS. We hypothesize that resveratrol treatment and subsequent activation of SIRT1 pathway might be highly beneficial for patients with DFS. This prediction is based on multiple lines of evidence implicating resveratrol and sirtuins in restoration of insulin sensitivity, microcirculation, tissue regeneration, function of peripheral nerves and production of cytokines. Stabilized "nutraceutical" formulations of resveratrol with high absorption rate are essential to examine its potential medical benefits since dietary polyphenols are known to be rapidly metabolized by gut microflora and oxidized during absorption. Clinical trials with nutraceutical formulations and placebo are required to understand if resveratrol indeed holds the promise for treatment of DFS.

Background

Type 2 diabetes mellitus (T2DM) occurs when chronically increased levels of plasma glucose are not matched by sufficiently increased levels of insulin secretion [1]. There is astonishing tendency in T2DM growth in the world. About 7% of world population is diagnosed with T2DM whilst the number of cases is expected to increase to $\geqslant$300 million by 2030 [2]. This prognosis seems to be outdated since the number of diabetics in the world in 2010 has reached 230 million [3]. Even well managed T2DM eventually leads to a variety of complications – cardiovascular disease, neuropathy, retinopathy, nephropathy and diabetic food syndrome. Although primary diabetic foot lesions tend to heal under medical supervision, 70% of diabetic ulcers become chronic [4]. Up to 20% of DFS patients will require lower limb amputation during their lifetime [5]. Diabetic foot amputations take place every 30 s worldwide [6]. It has been shown that ~85% of all non-traumatic amputations in diabetics resulted from diabetic ulcers [7]. Patients with DFS are known to have highest 5 years mortality rate exceeding the corresponding values in breast, colon and prostate cancers [8,9].

Despite enormous medical significance of diabetic ulcer treatment, pharmacological approach in management of diabetic ulceration is almost non-existent. Foot pressure relief, wound debridement and infection control remain widely accepted options in the treatment of DFS [10]. The DFS treatment puzzle is complicated by the fact that pharmacological optimization of glycemic control has little or no effect on the course of disease at late stages of diabetic ulceration [11]. Therefore original etiopathogenic association between T2DM and DFS becomes less relevant at some later point of the disease development. This theoretical problem dictates the necessity of using a new approach focused on targeting the 'specific' pathogenetic modalities of diabetic ulceration.

Clinically diabetic ulcers are classified in three major types: ischemic, neuropathic and neuroischemic, a category which combines two former types [12]. Although pathogenesis of DFS remains obscure, neuropathy and vascular occlusion are considered to be two major factors in diabetic ulceration [13]. Local inflammatory response and overproduction of chemokines (IL-6, IL-8, MCP-1, MIP-1α and TNF-α) are also extensively discussed [14,15]. Those pathogenetic variables must be essential in conceptual consideration of DFS treatment strategy. Theoretically, very few substances fit the comprehensible rational for DFS pharmacological management. Here we hypothesize that resveratrol, a polyphenolic compound, might be used as an essential nutraceutical agent in treatment of DFS. This evidence-based prediction originates from unique properties of resveratrol to modulate tissue regeneration, microcirculation, function of peripheral nerves, production of cytokines and insulin sensitivity.

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Resveratrol and sirtuins

Resveratrol (3,4′,5-trihydroxystilbene) represents a group of polyphenolic compounds called stilbenes. Fat-soluble *cis*- and *trans*-isoforms of resveratrol bound to a glucose molecule are present in some plants (grapes, peanuts and berries) and red wine [16]. Tremendous attention to the potential health benefits of resveratrol surfaced in the nineties when reduction in the risk of cardiovascular disease was linked to the moderate red wine consumption [17]. Beside direct anti-oxidant activity *in vitro* systems [18] resveratrol has multiple biological effects mediated through sirtuins (SIRTs), a family of NAD^+ dependent Sir2 histone deacetylases. Resveratrol is reported to activate Sir2 both *in vivo* and *in vitro* systems prolonging lifespan of yeast, *Caenorhabditis elegans* and *Drosophila* whereas deletion of sirtuins eliminates resveratrol effect on longevity in these species [19]. In mammals SIRT family is represented by at least seven proteins. Among them SIRT1 is the closest homolog of yeast Sir2 protein implicated in aging, apoptosis and regulation of metabolism [20]. However, inhibitory effect of resveratrol on insulin signaling pathways (AKT, MAPK and PI3K) is claimed to be a SIRT1-independent phenomenon [21].

Resveratrol and tissue regeneration

Wound closure is a primary goal in DFS treatment. Diabetic ulcers are most persistent and severe case of ulceration in human body. In worst case scenario they spread from papillary/reticular dermis to subcutaneous adipose tissue, muscles and bones [15]. Therefore search for ulcer-alleviating substances with a potential use in DFS treatment must be narrowed to the compounds with a broad range of regenerative power. Resveratrol seems to meet such a requirement. Besides its significant positive effect on skin fibroblast proliferation and anti-collagenase activity [22] resveratrol promotes dose-dependently maturation of pluripotent mesenchymal stem cells in adipose tissue [23]. Although subcutaneous adipose tissue contains fewer number of pluripotent mesenchymal progenitor cells as compared to visceral fat [24] those cells are capable of differentiation into preadipocytes, osteoprogenitor cells, vascular smooth muscle cells and vascular endothelial cells [25,26]. Another valuable pharmacological characteristic of resveratrol applicable to DFS treatment is related to its inhibitory activity on matrix metalloproteinases (MMPs). It has been shown that agonists of SIRT1, including resveratrol, have negative effect on MMPs transcription in the skin [27]. MMPs in particular MMP-8 and MMP-9 play a key role in diabetic wound healing. Those enzymes cause degradation of collagen and other structural constituents of extracellular matrix of the skin [28]. High level of MMP-8, -9 in secretion fluid from diabetic ulcers appeared to be a negative predictor of wound healing [29]. Therefore stimulation of pluripotent cell differentiation and inhibition of MMPs might be considered as a logical rationale motivating resveratrol use for diabetic wound healing.

Resveratrol and circulatory disorder

Chronic limb ischemia represents most common feature of DFS. Atherosclerotic peripheral arterial disease secondary to T2DM is believed to be most common cause of circulatory abnormalities in DFS [30]. Although surgical revascularization has a positive short-term impact on diabetic ulcer healing and amputation rate, the frequency of restenosis in DFS remains extremely high [31]. Recurrence of circulatory disorder is much higher in diabetic patients with limp ulceration as compared to non-diabetics with ischemic ulcers [32]. This clinical fact suggests that besides atherosclerosis diabetic microvasculopathy plays an enormous role in pathogenesis of DFS. However up-to-date there is no efficient palliative strategy targeting microvasculopathy in DFS patients. A new strategic perspective in wound management is now emerging from recent advances of molecular medicine. Wound repair and revascularization are known to be controlled by expression of vascular endothelial growth factor (VEGF) in granulating tissues. VEGF has broad spectrum of activity in ulcer healing ranging from capillary network growth to enhanced cell migration, collagen deposition and wound epithelialization [33]. This knowledge creates theoretical basis for development VEGF gene delivery-based protocols for wound treatment [34]. Resveratrol is among few substances known to affect significantly expression of VEGF. Despite its inhibitory effect on blood vessel formations in tumors [35] resveratrol is shown to upregulate conditional expression of VEGF in human skin cells [36,37]. Therefore while innovative DNA-based strategies for DFS management are under development, resveratrol treatment might be used as reasonable alternative targeting VEGF-mediated angiogenesis in diabetic wounds.

Resveratrol and neuropathy

Neuropathy and microvascular disorder are closely related phenomena in diabetic patients. Insufficient oxygen supply to limb tissues leads to abnormal nerve-axon reflexes, thereby ameliorating local physiological vasodilatory response to trauma and/or infection [38]. Accumulation of inflammatory cells and fluid as well as activation of coagulation system in the limb tissues contributes to the reduced endoneuronal blood flow [39]. Furthermore, advanced glycation products and substances released from biochemical pathways activated by advanced glycation (TNF-α, interleukin-1 and -6) promote degeneration of all fiber types in peripheral nerves [40]. Since oxidative stress is a primary pathogenetic mechanism in mediating the effect of hypoxia and advanced glycation in biological systems [41] it is reasonable to expect that resveratrol, a highly potent antioxidant, may have significant effect on diabetic neuropathy. In fact, grape-seed extracts are shown to reduce demyelination and improve motor nerve conductive velocity as well as Schwann cell morphology in diabetic rats [42]. Resveratrol-induced activation of SIRT1 and subsequent increase in glutathione and glutamine in neurons confer neuroprotection as reported in many *in vitro* and *in vivo* systems [43,44]. Therefore neuroprotective effect constitutes another valuable therapeutic modality of resveratrol action with prospective significance for DFS treatment.

Resveratrol and inflammation

Inflammation and wound repair are irreversibly linked. Mitigated inflammatory response with deficient migration of macrophages and abolished cytokine production leads to insufficient collagen production, weak proliferative response and poor wound closure. On the other hand excessive inflammation often predetermines the severity of the symptoms and survival rate of DFS patients. From a gnoseologic point of view it is very important to distinguish between inflammatory mediators triggering tissue repair and cytokines aggravating diabetic ulceration. A newly developed agent-based model of diabetic wound healing has proposed [45] that excessive production of TNF-α and reduced synthesis of TGF-β1 is a key feature reflecting mediator disbalance in diabetic wound. If true, therapeutic manipulations targeting any of these variables might be highly effective in DFS treatment.

There is growing body of evidence that resveratrol treatment affects multiple pathways related to inflammation. Among key features of its anti-inflammatory activity is upregulation of TGF-β1 transcription in the skin [46]. On the other hand resveratrol-induced SIRT1 activation is known to be in an inverse relationship

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with TNF-α production by fibroblasts [47]. Taken together these data allow suggesting that resveratrol may selectively target and disrupt a major "vicious cycle" in cytokine disbalance in diabetic ulcers thereby alleviating intensity of inflammatory response.

Conclusion

Many lines of evidence suggest that dietary polyphenols, including resveratrol may have noticeable effects on glucose homeostasis. It has been shown *in vitro* and *in vivo* studies that pure resveratrol can considerably improve glycemic profiles, normalize insulin secretion rate and insulin sensitivity. Complementary evidence from epidemiological studies is less convincing [48]. As a matter of fact majority of dietary polyphenols are metabolized by gut microflora or become oxidized during absorption [49]. Therefore it would be unreasonable to expect that dietary intake of polyphenols will mirror *in vitro* data by showing significant and reproducible impact on glucose homeostasis parameters in patients. Stabilized "nutraceutical" formulations of resveratrol with high absorption rate are required to examine its potential medical benefits.

In this paper we hypothesize that resveratrol treatment and subsequent activation of SIRT1 pathway might be highly beneficial for patients with DFS. This assumption is based on mechanism-based considerations and multiple lines of evidence discussed above. DFS originates from interplay among impaired tissue regeneration, circulatory abnormalities, neuropathy and inflammation. Although scaling the developmental momenta in each patient is nearly impossible, it is obvious that omitted targeting of pathogenetic variables of DFS will compromise success in therapy. Remarkably resveratrol seem to posses all desirable characteristics of the drug capable of restoring wide array of abnormalities in DFS. It is also important that the anticipated therapeutic action of resveratrol seems likely to employ preexisting physiological pathways within the framework of homeostatic regulation suggesting lower risk of toxicity and side effects. Our analysis would be incomplete without acknowledging resveratrol effects on mechanisms of insulin resistance and insulin sensitivity. Disbalance between insulin secretion and insulin sensitivity is a major developmental mechanism of all diabetes-related complications. Although adjustments in glycemic control have no immediate impact on ulcer size and progression, DFS patients with poor glycemic control have higher amputation rate [50]. Systematic interventions in glycemic control might be more effective at earlier stages T2DM when a confluence of abnormalities leading to development of DFS (vasculopathy, neuropathy and inflammation) occurs [51]. Therefore resveratrol effect may include some preventive benefits in high-risk patients at pre-clinical stage of DFS. Clinical trials with nutraceutical formulations are necessary to understand if resveratrol indeed holds the promise for treatment of DFS.

Conflict of interest

None declared.

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