Short Communication

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Vascular Factors in Diabetic Peripheral Neuropathy: From Pathogenesis to Assessment and Management

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Abstract

This short communication was aimed at re-establishing the evidence for vascular changes and risk factors in pathogenesis, assessment and treatment of diabetic peripheral neuropathy (DPN), through a brief literature update from an evidence-informed perspective. Diabetes mellitus is known for its hyperglycemia and altered metabolic control leading to microvascular (neuropathy, nephropathy and retinopathy) and macrovascular (cerebrovascular disease, peripheral vascular disease and cardiovascular disease) complications which cause significant morbidity and mortality. Vascular risk factors such as higher levels of total and low-density lipoprotein cholesterol and triglycerides, a higher body-mass index, higher von Willebrand factor levels and urinary albumin excretion rate, hypertension, and smoking were associated with the incidence of neuropathy. Vascular assessment is now recommended as part of a comprehensive screening examination for diabetic neuropathic foot. Vascular dysfunction predisposed development of autonomic neuropathy in DPN. Treatment using vascular endothelial growth factor (VEGF), a potent growth factor for angiogenesis was also shown to facilitate nerve regeneration and subsequently Ropper et al studied intramuscular gene transfer using plasmid VEGF in their randomized clinical trial Treatments such as transcutaneous frequency modulated neural stimulation produced release of VEGF.

Keywords: Vascular factors; Blood vessels; Arteries/veins; Hematology; Diabetic neuropathy.

Diabetes mellitus is known for its hyperglycemia and altered metabolic control leading to microvascular (neuropathy, nephropathy and retinopathy) and macrovascular (cerebrovascular disease, peripheral vascular disease and cardiovascular disease) complications which cause significant morbidity and mortality.[1]

There was impaired blood flow, epineurial arterio-venous shunting and a reduction in sural nerve oxygen tension in human DPN which improved following oxygen supplementation or vasodilator treatment suggesting that microvascular hypoxia was a primary pathogenetic mechanism in DPN.[2] Ischemic-hypoxic mechanisms caused reduced nerve blood flow and increased nerve vascular resistance thus playing a major part in pathogenesis of DPN.[3]

Stevens *et al*[4] described: "the potential factors contributing to nerve ischaemia include structural defects in the endoneurial microvasculature together with rheological abnormalities, abnormalities in vasoactive agents which regulate nerve blood flow including nitric oxide and the eicosanoids, and alterations in tone of the autonomic innervation of the nerve vasculature. The principle metabolic defects which have been implicated include disruption of the polyol pathway, altered lipid metabolism, advanced glycosylated end-product formation, increased oxidative stress, and diabetes-

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induced defects in growth factors."

Metabolic changes include high polyol pathway flux, increased advanced glycosylation, elevated oxidative stress, and impaired omega-6 essential fatty acid metabolism.[5] Early vasa nervorum functional changes were caused by the metabolic insults of diabetes, when there is alteration of the balance between vasodilation and vasoconstriction. Vascular endothelium is particularly vulnerable, with deficits in the major endothelial vasodilators, nitric oxide, endothelium-derived hyperpolarising factor and prostacyclin.[6]

Both metabolic and vascular factors play an inter-dependent role through nitric oxide which is best understood from the description by Stevens:[7] "metabolic defects may lead to a decrease in synthesis of nitric oxide in either the vascular endothelium or the sympathetic ganglia leading to decreased nerve blood flow. In addition, nitric oxide may be involved in more distal defects of somatic nerve metabolism which impair the activity of the nerve Na/K-ATPase by a mechanism involving phosphoinositide signaling and diacyl glycerol and may therefore affect nerve conduction velocity independently of ischaemia."

The evidence-informed paradigm shift warrants extension of knowledge beyond aldose reductase-microvascular hypothesis into glycation of nerve proteins, the involvement of fatty acid metabolism within the vasculature, and the undoubted role of growth factors[8] in the pathogenesis of DPN. Vascular risk factors such as higher levels of total and low-density lipoprotein cholesterol and triglycerides, a higher body-mass index, higher von Willebrand factor levels and urinary albumin excretion rate, hypertension, and smoking were associated with the incidence of neuropathy.[9] Vascular assessment is now recommended as part of a comprehensive screening examination for diabetic neuropathic foot.[10]

Vascular dysfunction predisposed development of autonomic neuropathy in DPN.[11] Treatment using vascular endothelial growth factor (VEGF), a potent growth factor for angiogenesis was also shown to facilitate nerve regeneration[12] and subsequently Ropper *et al*[13] studied intramuscular gene transfer using plasmid VEGF in their randomized clinical trial Treatments such as transcutaneous frequency modulated neural stimulation produced release of VEGF.[14]

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