Editorial Article

The Role of Alpha-Lipoic Acid in The Treatment of Diabetic Peripheral Neuropathy

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Diabetic neuropathy (DN) is one of the major complications of diabetes mellitus (DM), affecting approximately one third of DM patients, while recent evidence indicates that it could be diagnosed even in the stage of prediabetes [1-3]. A variety of factors have been implicated, including DM duration, poor glycaemic control, vascular risk factors and others [1, 2, 4, 5].

The commonest form of DN is distal symmetrical polyneuropathy, also called diabetic peripheral neuropathy (DPN) [4, 5]. DPN affects both small and large nerve fibres, with a stocking-and-glove distribution. It represents a cardinal risk factor for diabetic foot ulcerations [1, 4, 5]. Additionally, some patients complain of neuropathic pain, described as burning, pins and needles, sharp, cramping, tingling, cold, or allodynia [1, 4, 5].

Diagnosis of DPN and alleviation of pain have greatly improved [1, 4, 5]. However, improvement is still needed in pathogenesis-oriented treatment [2, 4, 5]. Alpha-lipoic acid (ALA) is very useful in this context [4, 6]. It is an anti-oxidant, which is of particular relevance, given that oxidative stress is implicated in the pathogenesis of DPN [7-9]. ALA plays an important role in mitochondrial bioenergetic reactions. It contains two thiol groups capable of being oxidised or reduced. Its reduced form is dihydrolipoic acid and its oxidised form as ALA [6-9]. It crosses the blood-brain barrier and regenerates other antioxidants, such as vitamin C, vitamin E, and glutathione [7-9]. Acute ALA infusion appears to improve nitric oxide-mediated endothelium-dependent vasodilation, thus improving microcirculation in patients with DN [7-9]. Moreover, there is evidence that ALA reduces lipid peroxidation of nerve membranes, further protecting from the development of DPN [9].

ALA was recognised as an anti-oxidant in the 80s [10]. Normally, it is produced by both animals and human and can be detected in liver and skeletal muscles [7-10]. Today, except for natural sources, such as spinach, broccoli, tomatoes, garden peas and Brussels sprouts, there are also nutritional supplements of ALA, which are typically comprised either of R-alpha-lipoic acid alone or a racemic mixture of R-alpha-lipoic acid and S-alpha-lipoic acid [7-10].

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In DPN, the usual oral daily therapeutic dose is 600 mg [6-13]. It has also been used intravenously [13]. A meta-analysis by Ziegler et al. [14] has shown significant improvements in pain, burning, and numbness, as well as pin-prick and touch-pressure sensation and ankle reflexes after 3 weeks. Adverse events were not increased [13] .

The 4-year NATHAN (Neurological Assessment of Thioctic Acid in Diabetic Neuropathy) 1 trial [15] is the largest and longest trial with ALA. Overall, 460 DM patients were randomised to ALA or placebo. ALA achieved significant improvements in some clinical signs, especially muscular weakness of lower limbs [15]. Among ALA-treated subjects, improvement was more frequent and deterioration was rarer in comparison with placebo. However, no improvements were seen with ALA in nerve conduction attributes and quantitative sensory testing [15]. Of note, male gender, normal body-mass index and blood pressure, history of cardiovascular disease along with DM and DPN duration and DPN severity were identified as predictors of more favourable response to ALA treatment [16].

In the recent years, favourable experience with ALA has accumulated further through studies and pooled analyses [4, 6, 17]. Impressively, a more recent trial has demonstrated reduced neuropathic symptoms and triglycerides, as well as improved quality of life after 40 treatment days [18].

Furthermore, ALA may exert some beneficial metabolic effects, notably reductions of serum glucose and body weight, as well as improvements in insulin action and sensitivity [6] These actions represent added benefits for DM patients. Generally, ALA is very well tolerated [6] .

In conclusion, ALA has repeatedly demonstrated meaningful efficacy and acceptable safety in the treatment of DPN [4, 6] . It represents a useful pathogenesis-oriented treatment that deserves to be considered by the everyday clinician.

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