

Effects of High-Dose α -Lipoic Acid on Heart Rate Variability of Type 2 Diabetes Mellitus Patients with Cardiac Autonomic Neuropathy in Korea (*Diabetes Metab J* 2017;41:275-83)

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We appreciate Professor Lee's interest and agree with the comments on our article entitled "Effects of high-dose α -lipoic acid on heart rate variability of type 2 diabetes mellitus patients with cardiac autonomic neuropathy in Korea" which was published in *Diabetes and Metabolism Journal* [1].

Cardiac autonomic neuropathy (CAN) represents a significant cause of morbidity and mortality in diabetic patients and is associated with a high risk of cardiac arrhythmias and sudden death, which is possibly related to silent myocardial ischemia [2]. The most common symptoms of CAN are standing and include lightheadedness, weakness, palpitations, faintness, and syncope. In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability (HRV) with deep breathing [3]. In more advanced cases, patients may present with resting tachycardia (>100 beats/min) and exercise intolerance [4]. Advanced disease may also be associated with orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 or >10 mm Hg, respectively, upon standing without an appropriate increase in heart rate) [4]. The diagnosis includes documentation of symptoms and

signs of CAN, which include impaired HRV, higher resting heart rate, and presence of orthostatic hypotension. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin therapy for type 1 diabetes mellitus reduced the incidence of CAN by 53% compared with conventional therapy [5]. The Epidemiology of Diabetes Interventions and Complications (EDIC) study, the prospective observational study of the DCCT cohort, has shown persistent beneficial effects of past glucose control on microvascular complications despite the loss of glycemic separation [6].

In type 2 diabetes mellitus, the effects of glycemic control are less conclusive. The VA Cooperative Study demonstrated no differences in the prevalence of autonomic neuropathy in type 2 diabetic mellitus patients after 2 years of tight glycemic control compared with those without tight control [7]. On the other hand, the Steno-2 Trial reported that a targeted, intensive intervention involving glucose control and multiple cardiovascular risk factors reduced the prevalence of CAN in patients with type 2 diabetes mellitus and microalbuminuria [8]. Angiotensin-converting-enzyme inhibitors, angiotensin receptor

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blockers, or aldose reductase inhibitors appear to be promising but are yet to be validated [9].

We completely agree with the comments and questions. The Deutsche Kardiale Autonome-Neuropathie (DEKAN) study [10] and the Alpha Lipoic Acid in Diabetic Neuropathy (ALADIN) study [11] showed significant improvements in HRV indexes and CAN. Despite the high dosage (800 mg/day vs. 1,200 mg/day) and longer duration of treatment (4 months vs. 6 months), the results of our study did not show significant improvements in HRV indexes. However, we found a positive tendency in some of the HRV parameters of the high dosage α -lipoic acid (ALA) group. Our study described glycemic status (7.64% ALA vs. 7.65% placebo) but didn't check the status of other microvascular complications, stage of CAN, and evaluation of symptomatic improvements. We agree that further explanations and research are likely to be needed for the causes of different conclusions. We also agree that it is necessary to develop a HRV marker with a higher sensitivity such as 24 hours HRV monitoring tool. As suggested by Professor Lee, more studies are needed to clarify the efficacy and mechanisms of ALA on HRV in diabetic patients with CAN.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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