Editorial
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Screening of Autonomic Neuropathy in Patients with Type 2 Diabetes

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Diabetic autonomic neuropathy (DAN) causes morbidity and mortality in patients with diabetes mellitus [1-4]; and among DAN, cardiac autonomic neuropathy (CAN) is an independent risk factor for cardiovascular mortality [5,6]. Although there has been very limited epidemiologic data in Korea, more than 50 % of patients with type 2 diabetes mellitus (T2DM) were reported to have DAN in Korea [4,7]. Furthermore, 45.3% of patients with newly detected T2DM had DAN at the time of diagnosis [7]. Current guideline or expert opinions recommend that screening for DAN should be instituted at diagnosis of type 2 diabetes [8-10], even for those who don't have any symptom of DAN [10].

As CAN is the most studied and clinically important form of DAN, noninvasive tests for CAN are recommended for DAN screening: response to deep breathing, standing, and Valsalva maneuver, and postural blood pressure testing [8,10,11]. Early stages of CAN may be completely asymptomatic and detected only by cardiovascular reflex tests (heart rate variability [HRV] to deep breathing and standing and Valsalva maneuver). HRV can also be assessed by spectral analysis of a series of successive R-R intervals, which can be measured across a range of frequencies and needs less patient participation [12,13]. Quantitative scintigraphic assessment of sympathetic innervation of the human heart [13,14] or quantitative regional measurements of myocardial β-adrenoreceptor density [15] can also be used for the assessment of CAN, of which the results are associated with cardiovascular risks [16]. Other than CAN, DAN also involves gastrointestinal, genitourinary, sudomotor or ocular systems and can be assessed by specific tests associated with its symptoms [10,11].

After identifying individuals at risk of DAN, effective management should be provided. However, at present, the treatment for DAN is limited to glucose control and symptom-based management. The Diabetes Control and Complications Trial demonstrated that intensification of glycemic control can reduce the incidence of CAN by 53% compared with conventional therapy [17]; and Steno-2 study showed that an intensive multifactorial cardiovascular risk intervention targeting blood pressure, lipid, smoking, and lifestyle factors as well as glucose control reduced the progression and development of CAN among T2DM patients [18]. However, multifactorial cardiovascular risk intervention with appropriate glucose control is recommended even for T2DM patients without CAN [8].

Intervention targeting DAN pathogenesis is very limited. A 4-month, randomized controlled clinical trial demonstrated that an antioxidant, α-lipoic acid, significantly improves CAN in patients with T2DM [19]. ACE-I or ARB also improved DAN in asymptomatic patients with T2DM patients [20]; however, most T2DM use them to manage blood pressure [8]. In diabetic animal model, peroxynitrite decomposition catalysts [21,22] and a selective tyrosine nitration inhibitor [23] have been reported to show neuroprotective effects. However, there has been limited translational works in diabetic patients, and no effective long-term treatment exists to date.

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Considering the lack of intervention to alter the DAN pathogenic process, the need for DAN screening should be re-evaluated. It should be confirmed by a randomized controlled trial whether a screening of DAN improves the morbidity, mortality, or quality of life of T2DM patients, especially if they have no related symptom.

However, there are medications to improve symptoms related to DAN, such as orthostatic hypotension, exercise intolerance, constipation, gastroparesis, and erectile dysfunction (reviewed in a review article [10]). Especially in the case of DAN in genitourinary system, appropriate intervention associated with residual urine or voiding difficulty can prevent worsening of renal functions [24] as well as improving voiding [25,26]. Although the presence of autonomic symptoms does not permit the diagnosis of DAN due to its nonspecificity [9], it might be clinically sufficient to check the presence of symptoms related to DAN without HRV evaluation or imaging techniques to confirm the presence of CAN in point of improving the quality of life of T2DM patients. Although autonomic symptoms have been reported to be poorly related to cardiovascular test abnormalities [27] and are not reliable indicators of the presence of autonomic neuropathy [28], we have no effective long-term treatment regimen for DAN except for relief of symptom at present. Kim et al. [29] showed that a symptom-based screening tool; that is, the Survey of Autonomic Symptoms (SAS) scale, was useful in detecting DAN. Considering its simplicity and usefulness to assess symptoms related to DAN, it might help to improve the management of T2DM in real world clinical environment.

Along with the elucidation of long-term effects of screening of DAN on morbidity, mortality, or quality of life in asymptomatic T2DM patients, comparison of the cost-effectiveness, morbidity, or other clinical outcomes between symptom-based versus HRV-based approach in evaluating CAN is warranted at this point. In addition, I'm expecting clinical and translational works to develop medications which can alter the pathologic process of DAN.

CONFLICTS OF INTEREST

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

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