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Diabetic Peripheral Neuropathy in Type 2 Diabetes Mellitus in Korea

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Diabetic peripheral neuropathy (DPN), a common and troublesome complication in patients with type 2 diabetes mellitus (T2DM), contributes to a higher risk of diabetic foot ulcer and lower limb amputation. These situations can negatively impact the quality of life of affected individuals. Despite its high prevalence and clinical importance, most diabetes mellitus patients not only do not recognize the presence of diabetic neuropathy, but also do not report their symptoms to physicians or other health care providers. Therefore, DPN is usually under diagnosed and undertreated. For early detection and appropriate intervention for DPN, a careful history, physical with neurologic examination, and prompt treatment are needed in T2DM patients.

Keywords: Diabetes mellitus, type 2; Diabetic neuropathies; Diabetic peripheral neuropathy; Pain

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) in Korea is estimated to be 7.3% (in those over 20 years of age), and it has increased about 5-fold over the past 30 years according to a report of the Korea National Health and Nutrition Examination Survey (KNHNES III, 2005) [1,2]. The number of patients with T2DM is expected to increase dramatically from about 3.2 million in 2011 (8.8% of the national population) to about 4.25 million (11.1%) by 2030 [3]. This enormous increase in the number of T2DM patients will inevitably be accompanied by chronic diabetic microvascular or macrovascular complications. Among the diabetic complications, diabetic peripheral neuropathy (DPN) is the most prevalent and troublesome complication in patients with diabetes mellitus (DM).

Diabetic neuropathy (DN), which may be focal or diffuse, is diagnosed when diabetic patients complain of symptoms and/or show signs of peripheral nerve dysfunction after the exclusion of other etiologies [4,5]. Chronic sensorimotor DPN is the most common form of DN [6,7]. Peripheral neuropathic pain in diabetic patients is defined as pain arising as a direct consequence of abnormalities in the peripheral somatosensory system in people with diabetes [8]. The symptoms can be present as severe numbness, paresthesia, or hyperesthesia, however, DPN may be asymptomatic in about 50% of patients [9]. As the DPN progresses, the painful symptoms usually disappear [10]. In addition, DPN is also associated with substantial morbidity, which includes not only a susceptibility to foot or ankle fractures and ischemic ulceration leading to lower-limb amputations, but also depression [11-13]. According to the Seattle Diabetic Foot Study, which included 749 diabetic patients, there were a number of findings that independently increase the risk for DM foot ulcer, including certain foot deformities, reduced foot arterial perfusion, and both sensory and autonomic neuropathy [14]. Diabetic patients with critical limb ischemia have high risks of lower limb amputation and

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death [15].

In addition to its influence on morbidity and mortality, painful symptoms in DPN have a significant detrimental impact on quality of life as the condition limits daily activities and interferes with sleep [16-18]. Considering the health-related economic viewpoint, diabetic foot disease significantly increases the health care costs in patients with DM. According to a retrospective study that analyzed insurance costs in the United States, the cost of care for patients with a foot ulcer is 5.4 times higher in the year after the first ulcer episode, but 2.8 times higher in the second year compared with that of diabetic patients without foot ulcers [19]. Therefore, early detection and prompt intervention for DPN must be performed for patients with T2DM.

PREVALENCE OF DPN IN KOREAN PATIENTS WITH T2DM

The prevalence of DPN is generally estimated to be 10% to 50% in patients with T2DM, and the incidence increases with age and duration of DM [17,18,20]. The reported prevalence of DN in Korea is variable, from 14.1% to 54.5% depending on the study population and the diagnostic method (Table 1) [21-24]. In the Diabcare-Asia 1998 study, which included 230 DM centers from 12 countries (n=24,317), the frequencies of retinopathy, microalbuminuria, and neuropathy were 21%, 39%, and 34%, respectively. The prevalence of those complications was significantly higher in those patients with higher hemoglobin A1c (HbA1c) levels [22]. A nationwide survey performed in 2006 by the Committee of the Korean Diabetes Association on the Epidemiology of Diabetes Mellitus (n=5,652) showed that the prevalence of DPN defined by neurologic symptoms or nerve conduction velocity abnormalities was 44.7%. This prevalence was higher than the prevalence of microalbuminuria or retinopathy [23]. In a prospective observational study among 508 Korean T2DM patients, diabetic foot disease occurred in 32 patients (6.3%), and the incidence of diabetic foot disease increased when peripheral neuropathy was present (odds ratio [OR], 2.949; 95% confidence interval [CI], 1.075 to 8.090) [24].

While chronic neuropathic pain is present in 13% to 26% of DM patients [25], it can be found not only in diabetic subjects, but also in impaired glucose tolerance (IGT) or impaired fasting glucose individuals [26]. According to a community-based cross-sectional study from the United Kingdom, chronic DPN is common and often severe but frequently unreported and therefore inadequately treated [18]. Interestingly, they showed that 12.5% of patients had never reported their symptoms to their doctors, and 39.3% never received treatment [18].

Table 1. Prevalence of diabetic neuropathy in patients with diabetes in Korea

	Study year	Diagnosis tool	Subjects No.	Prevalence, %
Kim et al.	1957-1977	NA	5,601	32.7
Han et al.	1963-1973	NA	1,332	22.9
Son et al.	1976	NA	3,076	28.9
Lee et al.	1976-1981	NA	779	14.1
Lee et al.	1981-1983	Symptoms, signs, NCV	300	54.5
Lee et al.	1982	Symptoms, signs, NCV	224	45.5
Hong et al.	1990	Symptoms, signs, NCV	837	48.9
Kim et al.	1993	Symptoms, signs, NCV	1,301	39.0
Park et al.	1994	Symptoms, signs, NCV	668	19.0
Kim et al.	1994	Symptoms, signs, NCV	235	37.5
Nam et al.	1999	Symptoms, signs, NCV	1,270	47.6
Park et al.	2003-2008	Symptoms, signs, NCV	508	13.9
Won et al.	2005	Symptoms, signs	875	53.9
Lim et al.	2006	Symptoms, signs, NCV	5,652	44.7
Won et al.	2010	Symptoms, signs	1,073	33.5

From Won JC, Ko KS. Korean Clin Diabetes 2010;11:177-83, with permission [21].
NA, not available; NCV, nerve conduction velocity.

There are some studies about the relationships between DPN and other diabetic complications in Korean T2DM patients. Chung et al. [27] reported that the prevalence of cardiovascular disease (CVD) was higher in patients with DPN. In their multivariate analysis, DPN was independently associated with CVD (OR, 1.801; 95% CI, 1.009 to 3.214) in T2DM patients (n=1,041), with a 52.8% prevalence determined by neurophysiologically diagnosing peripheral polyneuropathy based on electroneuromyographic findings. A close relationship between peripheral sensory neuropathy and peripheral vascular disease was also reported independent of glucose level and other microvascular complications, in particular, retinopathy in T2DM [20,28]. Other studies showed a relationship between DPN and arterial stiffness or insulin resistance [29,30]. The association between cardiovascular risk factors and development of large-fiber nerve dysfunction, which was measured by vibration perception threshold, was reported in type 1 DM patients (n=1,407) in the EURODIAB Prospective Complica-

tion Study [31]. These findings suggest the importance of DPN as a cardiovascular risk factor.

PATHOGENESIS AND MECHANISM OF DPN

Hyperglycemia not only activates the sorbitol accumulation with a subsequent increase in cellular osmolarity, but it also shunts to the hexose pathway, producing oxidative stress and the formation of advanced glycation end products (Table 2) [11]. Damage to peripheral nerves results in hyperexcitability in the primary afferent nociceptors. This damage leads to hyperexcitability in central neurons and the generation of spontaneous impulses within the axons as well as the dorsal root ganglion of these peripheral nerves [32,33]. This mechanism is suggestive of an abnormality contributing to the pain in DPN.

DIAGNOSIS OF DPN

The diagnosis of DPN usually depends on the subjective symptoms of neuropathy. Most of the clinical practice guidelines, including those from the Korean Diabetes Association, recommend that DPN screening should begin at the initial diagnosis of T2DM and should be performed at least annually thereafter [34-36]. The exclusion of non-diabetic causes of neuropathy, including alcoholism, vitamin B12 deficiency, endocrinopathies, vasculitides, heavy metal exposure, drug use, and malignancy, is important because these may account for 10% of the cases of neuropathy in people with DM [37].

Though the symptoms can exist without signs, the severity of painful symptoms can be reliably assessed by the visual analogue scale or the numerical rating scale (0, no pain; 10, worst possible pain). This latter assessment is most widely used in neuropathic pain assessment [5]. In addition, validated scales and questionnaires such as the Neuropathic Pain Symptoms Inventory, the Brief Pain Inventory, and the Neuropathic Pain Questionnaires are widely used (Table 3) [5]. However, the nerve conduction study remains the most reliable, accurate, and sensitive method to evaluate peripheral nerve function, and it has been adopted as the gold standard. This approach is not only time-consuming, expensive, and insensitive for the detection of small-fiber neuropathy, but also it is impractical to perform in an outpatient clinic setting. However, the Semmes-Weinstein monofilament (SWMF) test is simple to use as a screening tool to identify patients at risk for diabetic foot complication in the primary care setting [38,39]. The inability to sense the 10 g force pressure is considered as insensate and an independent predictor for higher risk of foot ulceration [40]. Lee et al. [38] considered the SWMF test as a useful screening tool for DPN. The nerve conduction study (NCS) was used as a gold standard to compare the sensitivity and the specificity of the SWMF test. The results were considered as abnormal if the patient could not perceive the 5.07/10 g SWMF at more than four of ten sites (37 T2DM outpatients). The sensitivity and the specificity at two sites (the third and fifth metatarsal head sites) were 93.1% and 100%, the same as at the ten sites. It is likely that the two-site SWMF test is a useful screening test for DPN as is the ten-site test. In a study of 126 diabetic patients, 41% complained of DPN symptoms, and SWMF and vibration perception were more impaired in patients with subjective sensory symptoms [39]. In 82 diabetic patients, the medial plantar sensory NCS provided a more sensitive diagnosis of DPN, even in patients with normal range measurements in the sural nerve [41]. The medial plantar sensory nerve action potential was abnormal in 46.7% of the symptomatic and 14.3% of the asymptomatic diabetic patients with normal routine NCS in this study [41]. The medial plantar sensory NCS may be helpful in the diagnosis of subclinical DPN in the asymptomatic diabetic patient. Compared to the

Table 2. Pathogenesis of diabetic peripheral neuropathy

Hyperglycemia
Increased ROS generation
Sorbitol accumulation
Osmolarity-related nerve damage
Hexosamine pathway
Modify specific transcription factors
Formation of AGEs
Decreased biologic function of proteins
Inhibit neuronal activity
Initiate Inflammatory signaling cascade
Dyslipidemia
FFA-induced lipotoxicity
ROS and mitochondria-activated injury
Inflammatory cytokine
Oxidized and glycated LDLs
Insulin resistance
Inflammation and ER stress in neuron

ROS, reactive oxidative stress; AGE, advanced glycation end product; FFA, free fatty acid; LDL, low density lipoprotein; ER stress, endoplasmic reticulum stress.

Table 3. Diagnosis of diabetic peripheral neuropathy

	Diagnostic method
Visual examination	Skin changes, ulceration or ulcer
Neuropathic pain assessment	Michigan Neuropathy Screening Instrument (MNSI)
	Neuropathy Disability Score (NDS)
	Brief Pain Inventory (BPI)
	Neuropathic Pain Questionnaire (NPQ)
	Neuropathic Pain Symptom Inventory (NPSI)
Peripheral motor neuropathy	Callus formation, muscle atrophy, planus feet or deformity
	Muscle strength
	Deep tendon reflex at Achilles tendon
Sensory function	Pinprick test (Apply proximal to great toenail)
	Temperature perception (Tiptherm rod on dorsum of foot)
	Vibration perception (128 Hz Tuning fork at great toe apex)
	Neurothesiometer or Biothesiometer at tip of hallux, measured in volts
	Touch sensation 10 g monofilament (SW monofilament)
Electrophysiologic study	Nerve conduction study
Skin biopsy	Quantification of intra-epidermal nerve fiber
Skin blood flow measurement	Measurement microvascular perfusion
QOL questionnaire	
Norfolk QOL questionnaire	Specific symptoms and impact of large, small and autonomic nerve-fiber functions
Neuro QOL	Patients' perceptions of the impact of neuropathy and foot ulcers
PN-QOL-97	Health-related quality of life measure for Peripheral neuropathy
New tests	
Large fiber function test	Steel ball-bearing
	Tactile circumferential discriminator
	Autonomic nerve conduction study
Small fiber function test	NeuroQuick
	Neuropad

SW monofilament, Semmes-Weinstein monofilament (SWMF); QOL, quality of life.

single test, the combinations of tests have a greater than 87% sensitivity in detecting DPN [4].

TREATMENT OF DPN

The aims of DPN treatment are to decrease the painful symptoms, to treat the specific pathogenic mechanism, and to prevent progression or subsequent complications. Treatment of the pain of DPN is mainly symptomatic management [42]. Most of all, strict diabetic control and correction of metabolic risk factors should be initiated. The lifestyle intervention that improves glycemic control and decreases blood pressure with lipid profiles improves both the painful neuropathic symptoms and the intra-epidermal nerve fiber density. These findings suggest that early diagnosis and prompt intervention may be of significant clinical benefit [32].

For pharmacological treatment, first line therapy consists of tricyclic antidepressants (TCA), duloxetine, pregabalin or oxycodone (Table 4) [36]. If the pain is not controlled with first-line therapy, second-line therapy or combination therapy can be used, for which the potential side effects and possible drug interactions must be considered. Topical treatment with a 5% lidocaine plaster or capsaicin is also considered.

Randomized controlled trials have been performed for the treatment of DPN in Korean patients with T2DM using alpha-lipoic acid, pregabalin, or tramadol/acetaminophen combination treatment. The neuropathic symptom score, assessed by the Total Symptom Score, was improved after intravenous alpha-lipoic acid treatment at a dose of 600 mg/day for 14 days in 19 T2DM patients compared to 13 control subjects ($P<0.05$) [43]. Open-label study with oral thioctic acid 600 mg once daily for 8 weeks ($n=61$) also improved DPN symptoms without serious adverse effects in Korean diabetic patients [44]. In an open, randomized, comparative study conducted in 163 T2DM subjects with DPN, tramadol/acetaminophen (Ultracet®) treatment ($n=79$) for 6 weeks was as effective as gabapentin ($n=84$) for the decrease of pain intensity, an increase in the quality of life, an increase in mood, and a decrease in sleep disturbance in the treatment of painful DN [45]. Ten weeks of pregabalin treatment for patients with neuropathic pain (DPN [type 1 or 2 diabetes, $n=18$], postherpetic neuralgia [$n=146$], or posttraumatic neuropathic pain [$n=76$]; $n=162$ pregabalin, $n=78$ placebo) showed a significant reduction in the Daily Pain Rating Scale score with improvement in anxiety and a decrease in sleep disturbance [46]. Despite the improvement in treatment modalities for chronic pain in recent years, patients with DPN still continue to be inadequately treated [47].

Table 4. Pharmacologic treatment of diabetic peripheral neuropathy

	Action mechanism	Drug	Daily dosage	Side effect	Caution
Pathogenetical treatment	Glucose & metabolic control				
	Free radical scavenger	Alpha-lipoic acid	600 mg IV	Nausea, vomiting	
		(Thioctic acid)	600-1,800 mg		
Symptomatic treatment					
Tricyclic antidepressant (TCA)	Inhibition of NE/Serotonin reuptake at synapses of central descending pain control system	Amitriptyline	10-150 mg	Tiredness, dry mouth, blurred vision, urinary retension, constipation, dizziness	Glaucoma, orthostatic hypotension, recent coronary artery disease, BPH arrhythmia
		Imipramine	25-150 mg		
		Nortriptyline	25-150 mg		
Selective serotonin/NE reuptake inhibitor	Inhibition of presynaptic reuptake of serotonin/NE	Duloxetine[a]	30-120 mg	Nausea, reduced appetite somnolence, dry mouth dizziness, constipation	Aggravation of depression
		Venlafaxine	150-225 mg	Nausea, vomiting	
Anticonvulsant α2-δ ligands	Calcium channel antagonist	Pregabalin[a]	150-600 mg	Drowsiness, edema	Congestive heart failure
		Gabapentin	300-3,600 mg	Somnolence, dizziness, fatigue, ataxia	Renal dysfunction
		Carbamazepine	200-600 mg	Dizziness, leucopenia hyponatremia	Steven-Johnson syndrome
		Lamotrigine	200-400 mg		
Opioid	μ-opioid receptor agonist	Tramadol	50-400 mg	Incontinence, nausea, constipation, vomiting, sedation	Dependence
		Ultracet (tramadol+acetaminophen)	3-8 T		
		Oxycodone CR	10-100 mg		
Local treatment	Substance P release C-fiber nerve ending	Capsaicin cream	Qid topically	Skin irritation	
Other	Non-pharmacologic	Percutaneous electrical nerve stimulation			

NE, norepinephrine; BPH, benign prostatic hyperplasia.
[a]Duloxetine and pregabalin are only two Food and Drug Administration (FDA)-approved treatments of diabetic peripheral neuropathy.

CONCLUSION

The dramatic increase in the prevalence of T2DM with its acute or chronic complications are a major health concern in Korea. Screening of high risk individuals, early detection, and proper management of DPN in patients with T2DM is urgently needed. Careful foot examination, active application of outpatient screening tools including the assessment of pedal pulses, and an organized diabetic foot-care program are needed.

Despite the improvement in treatment modalities for chronic pain in recent years, patients with DPN continue to be inadequately treated. Therefore, active pharmacologic treatment should be considered to relieve neuropathic pain and improve the quality of life in patients with T2DM.

CONFLICTS OF INTEREST

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

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