

Retrogression of Nervous Fibers According to the Age of Patients with Diabetes Mellitus (DM)

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Abstract. [Purpose] This study was performed to discover the possible onset time of diabetic neuropathy by age of diabetic patients, and to provide the knowledge necessary for preventing or managing diabetic neuropathy. [Subjects] The subjects of this study were outpatients who visited D Hospital Department of Neurology with complaints of significant neuropathic symptoms including dullness, numbness and paraesthesia. [Methods] Stimulations of 5 Hz, 250 Hz and 2,000 Hz were generated with a Neurometer CPT (Neurotron Inc., Baltimore, MD, USA) and delivered selectively to C fibers, A-delta fibers and A-beta fibers. The intensity of the stimulations of 5 Hz, 250 Hz and 2,000 Hz was incrementally increased as much as 0.01 mA. [Result] The results of this experiment show that the period of retrogression of nervous fibers was different significantly according to the age of patients with diabetes mellitus. Especially, in the case of individuals in their 50's, A β , A δ , and C fibers in both the right and left lower limbs significantly changed within a period of 2 months. In the case of individuals in their 60's, A β and C fibers of the right lower limb meaningfully changed 2 months after the onset of the disease, and A β , A δ , and C fibers of the left lower limb also significantly changed within a period of 2 months. [Conclusion] We discovered that patients suffering from DM especially in their 50's or 60's should be thoroughly followed for their condition, right from the onset of DM, in order to prevent the retrogression of nervous fibers.

Key words: Diabetes mellitus, Nervous fiber, Neuropathy

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease requiring medical treatment and a self-management program to prevent acute complications, and to reduce the risk of long-term complications¹⁾. Once DM occurs, a complete cure is impossible, and poor self-management will also cause various complications of DM²⁾. A common complication observed in diabetic patients is neuropathy³⁾. Neuropathy is observed in 8–15% of patients with DM at the time of their diagnosis⁴⁾, and is observed in 30–60% of the entire number of diagnosed diabetic patients^{5, 6)}. Since diabetic neuropathy can occur in all kinds of nerves, its symptoms are varied, however the symptoms can be classified into two groups: peripheral neuropathy, and autonomic neuropathy. Although diabetic neuropathy is not normally a direct cause of death, it can cause limitations of activity in daily living due to the disorder of the sensory and motor nervous systems and the autonomic nervous system^{2, 7)}.

Diabetic neuropathy usually begins with sensory disorder in the toes, and the sensory disorder gradually proceeds from the toes to the knees and later to the fingers or hands. The symptoms are accompanied by numbness and paresthesia in the affected parts, and the pains and symptoms hinder normal daily living⁸⁾. Hence, diabetic neuropathy, which is

common among diabetic patients and which greatly influences their lives, has become a prime concern for diabetic patients⁹⁾. Pittenger et al.¹⁰⁾ performed an experiment comparing 25 diabetic patients suffering from neuropathy with 20 individuals having no neuropathy. They showed the density of intra-epidermal nerve fibers (IENF) gradually decreases as measurements are taken farther away from a subject's trunk, and this phenomenon occurs only in patients with diabetic neuropathy. As the density of IENF decreases, thermal sense threshold, cold sense threshold, burning pain threshold, and pressure sense threshold all increase. Hence, they reported correlative relations between the density of IENF and diabetic neuropathy. Shun et al.¹¹⁾ also reported a close correlation between the decrease of the density of IENF and the increase in the thermal sense threshold during the disease period of DM. Also, Kennedy and Zochodne¹²⁾ reported that progressive diabetic neuropathy was irreversible. Although it is understood that the ultimate treatment for diabetic neuropathy is to control hyperglycemia, the symptoms of progressive diabetic neuropathy are not relieved by the control of blood glucose, since diabetic neuropathy has already caused organic changes in the areas being measured. Hence, once sensory defects occur in the limbs of a patient, a self-management program is essential to prevent complications such as foot ulcers⁸⁾. Ulcers can also occur in certain other parts of patients' bodies, when abnormal pressures are applied because of the sensory loss

Table 1. Threshold values of the right nerve fibers according to the duration of DM (Unit: μ A)

Age	A-beta		A-delta		C	
	Duration	Threshold	Duration	Threshold	Duration	Threshold
under 39 year	From 97*	15.4 \pm 5.9	From 120	13.0 \pm 3.0	From 120	10.4 \pm 1.6
	Under 97	11.8 \pm 4.0	Under 120	12.0 \pm 2.4	Under 120	10.0 \pm 2.1
40–49 year	From 25*	13.9 \pm 5.2	From 49*	13.9 \pm 3.6	From 73*	11.9 \pm 3.7
	Under 25	12.4 \pm 3.9	Under 49	12.7 \pm 2.7	Under 73	10.8 \pm 2.9
50–59 year	From 2*	13.8 \pm 5.1	From 2*	13.2 \pm 3.6	From 2*	11.3 \pm 3.9
	Under 2	11.5 \pm 3.8	Under 2	12.1 \pm 2.7	Under 2	10.1 \pm 2.5
60–69 year	From 2*	14.1 \pm 4.7	From 120	13.4 \pm 3.1	From 2*	11.2 \pm 2.8
	Under 2	12.9 \pm 3.9	Under 120	12.9 \pm 2.3	Under 2	10.5 \pm 2.6
From 70 year	From 13*	16.7 \pm 5.4	From 13*	14.3 \pm 3.4	From 120	12.5 \pm 4.0
	Under 13	15.0 \pm 5.1	Under 13	13.2 \pm 3.1	Under 120	11.9 \pm 3.7

Mean \pm SD, Unit of duration: month, *: $p < 0.05$

caused by DM¹³). In severe cases the ulcers can cause infection and/or necrosis, necessitating amputation of affected extremities¹⁴).

Although it is fundamental to prevent diabetic neuropathy at the time of diagnosis, once complications of DM start to occur it is necessary to take measures to prevent secondary complications from occurring. However, preventative measures are often not taken on a timely basis due to a lack of accurate knowledge of diabetic neuropathy. Therefore, one of the important factors in preventing or managing diabetic neuropathy is to pinpoint the time of the onset of diabetic neuropathy. With regard to the time of onset of diabetic neuropathy, Pittenger et al.¹⁰) reported that there was a significant decrease in the density of IENF among patients who had suffered from DM for more than five years. However, Polydefkis et al.¹⁵) reported that the skin regenerative rate of DM patients decreased even without neuropathic symptoms. This phenomenon implies that the clinical manifestation of peripheral nerve malfunction can appear even in the early stage of DM.

Likewise, although there are various opinions regarding the time of onset of peripheral neuropathy, research into the onset time of diabetic neuropathy by age has seldom been performed. Therefore, this study was undertaken to discover the possible onset time of diabetic neuropathy by age of diabetic patient, and to provide the knowledge necessary for preventing and managing diabetic neuropathy.

SUBJECTS AND METHODS

The data were collected from 2008 to 2011. The total number of cases studied was 1,137. The subjects of this study were outpatients who visited D Hospital Department of Neurology with complaints of significant neuropathic symptoms including dullness, numbness and paraesthesia. Those who were chronic drinkers of alcoholic beverages, or those who had a history of taking medications such as antituberculosis or anticancer drugs, musculoskeletal diseases, entrapment neuropathy, myeloradiculopathy and peripheral vascular diseases were excluded from the study. Stimulations of 5 Hz, 250 Hz and 2,000 Hz were generated with a Neurometer CPT (Neurotron Inc., Baltimore, MD,

USA) and delivered selectively to C fibers, A-delta fibers and A-beta fibers. Measurements of the current perception threshold were performed manually. The intensity of the stimulation at 2,000 Hz was incrementally increased as much as 0.01 mA. Two electrodes coated with conductive gel were attached to each subject's bilateral DIP (distal interphalangeal) joint of the first toe to identify legs that had a peroneal nerve dysfunction. The current was increased until the patients began to feel the current at the skin where the electrodes were attached, and the perception threshold was measured to an accuracy within 20 μ A by actual stimulation or pseudostimulation, six to ten times at an intensity equal to or of higher than that determined in a single blind study. The perception thresholds at 250 Hz and 5 Hz were measured in the same manner. For the statistical analysis, the independent t-test was used to investigate differences in the threshold values according to the duration of DM. The statistical software used was SPSS (ver. 20.0) for Windows and significance was accepted for values of $\alpha < 0.05$.

RESULTS

The investigation of nervous retrogression according to age showed that A β fibers of individuals under age 39 had significantly changed 97 months after the onset of diabetic mellitus ($p < 0.05$), however, A β fibers of individuals in their 40's had significantly changed by 25 months ($p < 0.05$), and A δ fibers of individuals in their 40's had significantly changed by 49 months ($p < 0.05$), and C fibers had significantly changed by 73 months ($p < 0.05$). Among individuals in their 50's, A β , A δ , and C fibers had all changed significantly by 2 months after DM onset ($p < 0.05$). Among individuals in their 70's or above, although A β and C fibers had significantly changed 2 months after the onset of diabetic mellitus ($p < 0.05$), A δ fibers did not show any significant change even after 120 months. Among individuals in their 70's, although A β and A δ fibers had changed significantly 13 months after the onset of the disease ($p < 0.05$), C fibers did not significantly change even after 120 months (Table 1).

The investigation of nervous retrogression according to age showed that A β fibers of individuals under the age of 39 had significantly changed 25 months after DM onset

Table 2. Threshold values of the left nerve fibers according to the duration of DM (Unit: μ A)

Age	A-beta		A-delta		C	
	Duration	Threshold	Duration	Threshold	Duration	Threshold
under 39 year	From 25*	13.3 \pm 4.7	From 120	12.6 \pm 3.6	From 49*	10.9 \pm 1.8
	Under 25	11.0 \pm 4.0	Under 120	11.8 \pm 2.7	Under 49	9.6 \pm 2.4
40–49 year	From 61*	14.5 \pm 5.8	From 120	13.6 \pm 4.2	From 120	11.7 \pm 4.2
	Under 61	12.4 \pm 4.6	Under 120	12.8 \pm 3.8	Under 120	10.9 \pm 3.9
50–59 year	From 2*	13.8 \pm 5.2	From 2*	13.2 \pm 3.7	From 2*	11.2 \pm 3.9
	Under 2	11.3 \pm 3.4	Under 2	11.9 \pm 2.6	Under 2	10.0 \pm 2.5
60–69 year	From 2*	14.3 \pm 4.7	From 2*	13.1 \pm 2.7	From 2*	11.1 \pm 2.9
	Under 2	12.5 \pm 3.7	Under 2	12.4 \pm 2.4	Under 2	10.0 \pm 2.6
From 70 year	From 13*	16.8 \pm 5.5	From 25*	16.9 \pm 5.5	From 120	15.4 \pm 5.9
	Under 13	15.2 \pm 5.1	Under 25	15.2 \pm 5.2	Under 120	11.8 \pm 4.0

Mean \pm SD, Unit of duration: month, *: $p < 0.05$

($p < 0.05$), and C fibers changed after 49 months ($p < 0.05$); however, A δ fibers did not change even after 120 months. Among individuals in their 40's, although A β fibers had changed 61 months after DM onset ($p < 0.05$), A δ and C fibers did not change significantly even after 120 months. Among individuals in their 50's, A β , A δ , and C fibers had all significantly changed 2 months after DM onset ($p < 0.05$). In the case of the individuals in their 60's, A β , A δ , and C fibers had all changed significantly 2 months after DM onset ($p < 0.05$). In the case of individuals in their 70's or above, A β fibers had changed significantly by 13 months after DM onset ($p < 0.05$), and A δ fibers had changed significantly 25 months after DM onset ($p < 0.05$), but C fibers did not show any significant change even after 120 months (Table 2).

DISCUSSION

Neuropathy caused by diabetes mellitus (DM) can be a very serious disease from the viewpoint of physical therapy since it increases the risks of fracture and soft tissue injury in falls by reducing patients' sensory and motor control abilities, as well as accelerating the degeneration of joints and their surrounding tissues, thus causing various kinds of secondary disability¹⁶. It is known that symptoms and neurological examination, sensory loss, and electrophysiological studies should be included in the diagnosis criteria of neuropathy, and a quantitative sensory test is one of the most meaningful diagnosis methods¹⁷. Park⁹ suggested that cool thermal quantitative sensory testing (QST) would be useful for monitoring neuropathic changes even in the early stage of DM, because the reduction of nerve conduction velocity caused by DM occurs steadily at the rate of around 1 m/s/year, implying it takes at least 3 years to observe clinically significant changes in nerve conduction velocity. In addition, Krishnam et al.¹⁸ also reported that quantitative sensory nerve testing would be useful for monitoring changes in nerve function caused by DM. Thus, for this study, we employed a quantitative electrophysiological diagnosis method that evaluated selective peripheral nerve function by measuring the minimum current that is felt by the nerve fiber through the sensory nerve. Neurometer CPT is an instrument that is used in clinical practice to measure

the sensory threshold for the evaluation of peripheral neuropathy and diabetic neuropathy.

In general, nervous retrogression is influenced by the cell injury caused by hyperglycemia. Chronic hyperglycemia stimulates the production of free radicals and increases oxidative stress; in turn these factors cause damage to the peripheral nerve system. The proteins damaged by oxidative stress causes energy loss and disorder in delivering substances to cells, and these conditions also lead to cell death¹⁹. Hyperglycemia damages cells through mechanism related to metabolic syndrome, and metabolic syndrome is known to be closely associated with type 2 DM²⁰. Park^{21, 22} reported that, the risk of having metabolic disorder increases in men living in Korea up to the age of 50 and then decreases slightly after this age, whereas it increases especially after the age of 50, the age of menopause, in women living in Korea. An experiment performed to check the rate of incidences of metabolic syndrome by age in Korea. Men: 9.4% in their 20's; 19.5% in their 30's; 27.5% in their 40's; 28.9% in their 50's; 24.3% in their 60's; and 23.1% in their 70's. Women: 6.8% in their 20's; 11.0% in their 30's; 24.1% in their 40's; 45.8% in their 50's; 54.3% in their 60's; and 54.5% in their 70's. These statistics show that although the rate of metabolic syndrome among females increases in proportion to their age, the rate among males peaks in their 40's and 50's and then decreases in their 60's and 70's. However, if the average of the sum of male and female rates by age in Korea is combined, the combined rate is as follows: 8.1% in their 20's, 12.3% in their 30's, 25.8% in their 40's, 37.3% in their 50's, 39.3% in their 60's, and 28.8% in their 70's. Hence, these statistics show that the prevalence rates of metabolic syndrome of people in their 50's and 60's are higher than those of other ages. As nervous retrogression is affected by metabolic disorder, nervous retrogression of individuals in their 50's and 60's may progress more rapidly than in individuals of other ages.

As the results of this experiment show, in the case of individuals under the age of 39, A β fibers in the right lower limb had significantly changed 97 months after the onset of DM, and A β and C fibers in the left lower limb had meaningfully changed after 25 months and 49 months, respectively. Therefore, the statistics indicate that DM patients

under the age of 39 should be checked for the occurrence of nervous retrogression and take care to prevent it before the 25th month after the onset of DM. In the case of the individuals in their 40's, A β , A δ , and C fibers in the right lower limb had meaningfully changed 25 months, 49 months, and 73 months after DM onset, respectively. However, in the left lower limb, only A β fibers showed a significant change after 61 months. This means that DM patients in their 40's also need to have their condition checked and taken care of before the 25th month from the onset of the disease. In the case of individuals in their 50's, A β , A δ , and C fibers in both the right and left lower limbs had significantly changed 2 months after DM onset. Hence, patients in their 50's also need to be monitored for the progression of nervous retrogression from the beginning of the onset of DM. In the case of individuals in their 60's, A β and C fibers of the right lower limb had meaningfully changed 2 months after the onset of the disease, and A β , A δ , and C fibers of the left lower limb had also significantly changed after 2 months. Therefore, patients in their 60's also need to have their condition checked and taken care of. In the case of individuals in their 70's, A β and A δ fibers in the right lower limb showed significant changes 13 months after the onset of the disease, and A β and A δ fibers in the left lower limb showed significant changes 13 months and 25 months after DM onset, respectively. This shows that patients in their 70's or above need to have their condition monitored in the 13 months from the onset of the disease.

We discovered that patients suffering from DM especially those in their 50's or 60's should have their condition thoroughly followed from the onset of DM in order to prevent the retrogression of nervous fibers, as nervous retrogression of A β fibers inevitably occurs in DM.

REFERENCES

- 1) American Diabetes Association: Standards of medical care in diabetes – 2010. *Diabetes Care*, 2010, 33: S11–S61. [[Medline](#)] [[CrossRef](#)]
- 2) Poncelet AN: Diabetic polyneuropathy. Risk factors, patterns of presentation, diagnosis, and treatment. *Geriatrics*, 2003, 58: 16–18. [[Medline](#)]
- 3) van Schie CH: Neuropathy: mobility and quality of life. *Diabetes Metab Res Rev*, 2008, 24: S45–S51. [[Medline](#)] [[CrossRef](#)]
- 4) Lehtinen JM, Uusitupa M, Siitonen O, et al.: Prevalence of neuropathy in newly diagnosed NIDDM and nondiabetic control subjects. *Diabetes*, 1989, 38: 1307–1313. [[Medline](#)] [[CrossRef](#)]
- 5) Dyck PJ, Kratz KM, Karnes JL, et al.: The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: the Rochester Diabetic Neuropathy Study. *Neurology*, 1993, 43: 817–824. [[Medline](#)] [[CrossRef](#)]
- 6) Young MJ, Boulton AJ, MacLeod AF, et al.: A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia*, 1993, 36: 150–154. [[Medline](#)] [[CrossRef](#)]
- 7) Boulton AJ, Malik RA, Arezzo JC, et al.: Diabetic somatic neuropathies. *Diabetes Care*, 2004, 27: 1458–1486. [[Medline](#)] [[CrossRef](#)]
- 8) Kim YS: Complications of diabetes. *Kinesiology*, 2000, 3: 96–102.
- 9) Park TS: Management of painful diabetic neuropathies. *Korean J Med*, 2003, 66: 263–266.
- 10) Pittenger GL, Ray M, Burcus NI, et al.: Intraepidermal nerve fibers are indicators of small-fiber neuropathy in both diabetic and nondiabetic patients. *Diabetes Care*, 2004, 27: 1974–1979. [[Medline](#)] [[CrossRef](#)]
- 11) Shun CT, Chang YC, Wu HP, et al.: Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. *Brain*, 2004, 127: 1593–1605. [[Medline](#)] [[CrossRef](#)]
- 12) Kennedy JM, Zochodne DW: Experimental diabetic neuropathy with spontaneous recovery: is there irreparable damage? *Diabetes*, 2005, 54: 830–837. [[Medline](#)] [[CrossRef](#)]
- 13) Lee SJ: Diabetic foot ulcer. *Korean J Dermatol*, 2009, 61: 68–70.
- 14) Goh YJ: Foot care in diabetic patients. *Diabetes Metab J*, 2005, 25: 113–120.
- 15) Polydefkis M, Hauer P, Sheth S, et al.: The time course of epidermal nerve fibre regeneration: studies in normal controls and in people with diabetes, with and without neuropathy. *Brain*, 2004, 127: 1606–1615. [[Medline](#)] [[CrossRef](#)]
- 16) Aring AM, Jones DE, Falko JM: Evaluation and prevention of diabetic neuropathy. *Am Fam Physician*, 2005, 71: 2123–2128. [[Medline](#)]
- 17) Donaghue VM, Giurini JM, Rosenblum BI, et al.: Variability in function measurements of three sensory foot nerves in neuropathic diabetic patients. *Diabetes Res Clin Pract*, 1995, 29: 37–42. [[Medline](#)] [[CrossRef](#)]
- 18) Krishnan ST, Baker NR, Carrington AL, et al.: Comparative roles of microvascular and nerve function in foot ulceration in type 2 diabetes. *Diabetes Care*, 2004, 27: 1343–1348. [[Medline](#)] [[CrossRef](#)]
- 19) Ziegler D, Sohr CG, Nourooz-Zadeh J: Oxidative stress and antioxidant defense in relation to the severity of diabetic polyneuropathy and cardiovascular autonomic neuropathy. *Diabetes Care*, 2004, 27: 2178–2183. [[Medline](#)] [[CrossRef](#)]
- 20) Pouliot MC, Després JP, Nadeau A, et al.: Visceral obesity in men. Associations with glucose tolerance, plasma insulin, and lipoprotein levels. *Diabetes*, 1992, 41: 826–834. [[Medline](#)] [[CrossRef](#)]
- 21) Park HS: Epidemiology of metabolic syndrome in Korean population. *J Korean Soc Study Obes*, 2002, 11: 203–211.
- 22) Park HS, Oh SW, Kang JH, et al.: Prevalence and associated factors with metabolic syndrome in South Korea—From the Korean National Health and Nutrition Examination Survey. *J Korean Soc Study Obes*, 2003, 12: 1–14.