Effect of Glycemic Control on Electrophysiologic Changes of Diabetic Neuropathy in Type 2 Diabetic Patients

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Diabetic neuropathy is a common complication of diabetes mellitus. Effective blood glucose control retards changes in nerve conduction velocity in type 1 diabetes. This study examined the relationship between glycemic control and electrophysiologic changes in diabetic neuropathy in 57 type 2 diabetic patients. Nerve conduction in the peroneal motor nerve, tibial motor nerve, and sural nerve were measured at study entry and at follow-up 24 ± 3.12 months later. Changes in individual nerves are expressed as a percentage change (PC) and overall electrophysiologic changes are expressed as the sum of individual PCs. The PCs for peroneal motor nerve velocity, tibial motor nerve velocity, and sural nerve velocity were all lower in patients with a mean HbA1c of 8.5% or less compared with those in patients with a mean HbA1c of more than 8.5%, and SPCV (sum of PC in velocity) was significantly inversely correlated with mean HbA1c. However, there was no significant difference in SPCV in subjects with or without hypertension, hypertriglyceridemia, or low high-density lipoprotein cholesterol concentration. In conclusion, hyperglycemia is the most important etiology for electrophysiologic progression in type 2 diabetic patients. Furthermore, a mean HbA1c of more than 8.5% will result in significant deterioration in electrophysiology.

Key Words: type 2 diabetes, diabetic neuropathy, nerve conduction velocity

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Diabetic neuropathy is a common complication of diabetes mellitus, affecting an estimated 50–60% of diabetic patients [1–3]. It may result in sensory, motor, autonomic, or combined deficits. Sensorimotor diabetic peripheral polyneuropathy is a major risk factor for foot trauma, ulceration, Charcot's arthropathy, and limb amputation. The pathogenesis of diabetic neuropathy has not been fully elucidated. However, chronic hyperglycemia with its metabolic consequences may be the most important factor [4,5]. Many studies have found a positive relationship between hyperglycemia and the progression of diabetic neuropathy in type 1 diabetic patients, and effective control of diabetes has beneficial effects on electrophysiology in these patients [6–8]. However, few studies focus on diabetic neuropathy in type 2 diabetic patients, who account for more than 90% of all cases of diabetes mellitus. There are several differences between the neuropathy associated with type 1 and type 2 diabetes. In neuropathy of type 2 diabetes, a broader range of fiber types is involved, and it is likely to have features of covert or overt multifocality [9].

Sima and co-workers examined sural nerve biopsies obtained from type 1 and type 2 diabetic patients with distal symmetrical polyneuropathy [10]. They demonstrated that degrees of nerve fiber loss, paranodal swelling and paranodal demyelination, and disintegration of the axons with

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breakdown of their myelin sheaths (Wallerian degeneration) were significantly more prevalent in type 2 diabetes, whereas in type 1 diabetes, axo-glial dysfunction was increased. The histopathologic differences between the neuropathy associated with type 1 and type 2 diabetes suggest that there may be differences in pathogenesis. Therefore, it is not inevitable that each type of neuropathy will respond in the same manner to strict control of blood glucose concentrations.

Many methods are used to assess and stage diabetic neuropathy. Standard electrophysiologic methods have been used extensively to diagnose and follow the progression of diabetic neuropathy [11] and correlate reliably with neuropathic complications (foot ulcers and amputation) and mortality [12]. The aim of this study was to investigate the relationship between glycemic control and electrophysiologic changes of diabetic neuropathy in type 2 diabetic patients.

Materials and Methods

Subjects

Fifty-seven type 2 diabetic patients with diabetic neuropathy were recruited. Diabetic neuropathy was diagnosed on the basis of abnormalities in two of the four following major categories: symptoms, signs, nerve conduction studies, and quantitative sensory testing [7]. All patients had electrophysiologic abnormalities at the beginning of follow-up. There was no evidence of alcohol abuse or toxin exposure in any patient. Patients with peripheral neuropathy principally from causes other than diabetes, such as liver, renal, or orthopedic disease or endocrine or metabolic disorders, were excluded. Patients were recruited and followed-up by the same two investigators in the outpatient clinic. Ten patients were treated with twice-daily injections of insulin and the others were treated with only oral anti-diabetic drugs at the beginning of follow-up.

Electrophysiology study

Nerve conduction studies were performed using an electrodiagnostic machine (Keypoint version 2.11, Medtronic Dantec, Skovlunde, Denmark) by the same technician under isothermal conditions in order to maintain the skin temperature at 30°C. Action potentials were recorded using surface electrodes. Nerve conduction in the peroneal motor nerve, tibial motor nerve, and sural nerve was measured in the conventional manner [13]. The mean values of bilateral nerve conduction velocity and amplitude from each tested nerve were used. Nerve conduction was measured at the initial examination and at follow-up 24 ± 3.12 months later (mean ± standard deviation; range, 15–28 months). Patients were excluded if they had unobtainable nerve electric responses in two investigations.

Changes in electrophysiology

The changes in individual nerves were first expressed as the percentage change (PC, %) calculated using the formula: PC = (Conduction velocity at follow-up) – (Initial conduction velocity)/Initial conduction velocity × 100%

The overall electrophysiologic change was then expressed as the sum of the individual PCs (%).

Laboratory examination

Blood glucose was monitored by measuring stable glycosylated hemoglobin levels (HbA1c, %) at every 3-month visit. The mean of all measurements was used for statistical analysis.

Statistical analysis

All analysis was conducted using SPSS version 12.0 (SPSS Inc, Chicago, IL, USA). The Mann-Whitney U test was used for comparisons between groups. Linear regression was used for establishing the relationship between the mean HbA1c and electrophysiologic changes. The difference was significant when p was less than 0.05.

Results

Demographic data of the 57 patients are shown in Table 1. Ages ranged from 38 to 82 years and the duration of diabetes was between 2 and 38 years. The initial HbA1c varied from 4.87% to 16.89%. Nine patients had hypertriglyceridemia (> 200 mg/dL) and 32 patients had low high-density lipoprotein (HDL) cholesterol (< 40 mg/dL) at the beginning of the study.

We divided patients into four subgroups according to the mean HbA1c: Group I, mean HbA1c less than 7%; Group II, mean HbA1c 7.01–7.5%; Group III, mean HbA1c 7.51–8.5%; and Group IV, mean HbA1c more than 8.5%. The PC of peroneal motor nerve velocity was significantly worse in patients in Group IV (–16.87%) than those in Groups I (–6.09%), II (–1.73%), and III (–8%) (Table 2). Similarly, the PC of tibial motor nerve velocity and sural nerve velocity were both significantly lower in patients in Group IV (–10.28% vs –0.09%, 5.39%, and 1.37%; –14.28% vs 2.29%, 4.4%, and 1.17%, respectively). The PC of peroneal motor

Table 1. Demographic characteristics of 57 patients with diabetic neuropathy

Sex (male/female)	21/36
Mean age (yr)	61.41 ± 10.02
Mean duration of diabetes (yr)	9.85 ± 7.19
Mean interval between NCV study (mo)	24.33 ± 3.12
Mean HbA1c (%)	7.84 ± 1.21
Mean initial HbA1c (%)	7.86 ± 2.01
Hypertension	29
Hypertriglyceridemia	9
Low HDL level	32

Data are presented as mean ± standard deviation or *n*. NCV = nerve conduction velocity; HbA1c = serum glycosylated hemoglobin level; HDL = high-density lipoprotein.

nerve amplitude, tibial motor nerve amplitude, and sural nerve amplitude were not significantly different between subgroups (Table 3).

In Groups I–III, the sum of percentage change in velocity (SPCV) was significantly lower than in Group IV, but there was no significant difference in the sum of percentage change in amplitude (SPCA) (Table 4).

The correlation of SPCV with mean HbA1c is shown in the Figure. SPCV was significantly inversely correlated with mean HbA1c: SPCV = –14.41(mean HbA1c) + 101.71 ($R^2 = 0.72$, $p = 0.001$).

The comparison of SPCV in patients with other underlying diseases is shown in Table 5. There was no significant difference in subgroups with or without hypertension, hypertriglyceridemia, and low HDL cholesterol.

Discussion

The deterioration in nerve conduction velocity was marked in patients with a mean HbA1c of more than 8.5% during a 2-year period. This downward trend was also noted in nerve conduction amplitude with increases in mean HbA1c. These results support the theory that hyperglycemia represents an important factor in the pathogenesis of diabetic neuropathy in type 2 diabetes. The result is analogous to the findings in type 1 diabetes [8,14]. Amthor et al found a significant reduction in nerve conduction velocities during an 8-year period in type 1 diabetic patients with a mean HbA1c of more than 10% [8]. Tkac and Bril also showed that diabetic neuropathy is more severe in diabetic patients with an HbA1c of more than 9% [7]. This implies the progression of diabetic neuropathy in type 2 diabetes, as well as in type 1 diabetes.

Direct morphologic evaluation of nerves via whole nerve biopsy has been used as an important tool for diagnosis and evaluation of the progression of diabetic neuropathy [15]. However, full fascicular biopsy is associated with long-term sensory deficits and other adverse effects. Furthermore, there is a strong correlation between morphologic changes in sural nerve biopsies and nerve conduction velocity, and conventional electrophysiologic tests in lower limbs are a reliable surrogate measure for structural abnormalities [16]. We found that maintaining the mean HbA1c below 8.5% retards the deterioration of both motor and sensory nerve conduction velocity in the lower limbs of type 2 diabetic patients. Therefore, retarding changes in nerve conduction velocity in the present study may reflect retarding structural changes. Lower limb motor nerve conduction velocity can predict foot ulceration and death in diabetes [12]. We found that conduction velocity progression was inversely correlated with mean HbA1c. Therefore, a lower mean HbA1c that prevents the deterioration of motor nerve velocity may contribute to reducing foot ulceration and death in diabetes.

Some patients with a mean HbA1c of less than 8.5% in the present study showed improvement in conduction velocity due to a higher initial HbA1c than their mean HbA1c. Several studies have found improvement in nerve conduction velocity after treatment for diabetes [13]. Thomas concluded that patients with newly diagnosed or poorly controlled diabetes frequently have reduced nerve conduction velocity that improves rapidly with the establishment of euglycemia [17].

Some studies have observed other risk factors correlated to the severity of diabetic neuropathy [7,18,19], such as hypertension, hypertriglyceridemia, and low HDL cholesterol concentration. However, SPCV was not significantly different in subjects with or without hypertension, hypertriglyceridemia, and low HDL cholesterol concentration in the present study. This demonstrated that hyperglycemia, which is directly related to myo-inositol loss and sorbitol excess [20–22], is the major factor in electrophysiologic progression in type 2 diabetes.

There was no significant difference in amplitude changes between patients with mean HbA1c of 8.5% or less and those with a mean HbA1c of more than 8.5%. This may have resulted from the small difference in speed and amplitude deterioration. Differences in amplitude may take longer to become evident in type 2 diabetes. Velocity changes may be a more sensitive index than amplitude changes for the evaluation of diabetic neuropathy in type 2 diabetes.

Table 2. Percentage change (PC) in nerve conduction velocity according to mean glycosylated hemoglobin (HbA1c) group

	Mean HbA1c				*p*				
	Group I ≤ 7% (*n* = 14)	Group II 7.01–7.5% (*n* = 11)	Group III 7.51–8.5% (*n* = 19)	Group IV > 8.5% (*n* = 13)	Group I vs II	Group II vs III	Group III vs IV	Group I vs IV	Group II vs IV
Peroneal motor nerve (%)	–6.09 ± 2.64	–1.73 ± 1.92	–8.00 ± 1.11	–16.87 ± 1.49	0.327	0.009	< 0.001	< 0.001	< 0.001
Tibial motor nerve (%)	–0.09 ± 2.14	5.39 ± 1.61	1.37 ± 3.00	–10.28 ± 3.05	0.081	0.067	0.009	< 0.001	< 0.001
Sural nerve (%)	2.29 ± 4.54	4.4 ± 3.43	1.17 ± 1.89	–14.28 ± 2.09	0.951	0.505	< 0.001	< 0.001	< 0.001

Data are presented as mean ± standard deviation.

Table 3. Percentage change (PC) in nerve conduction amplitude according to mean glycosylated hemoglobin (HbA1c) group

	Mean HbA1c				*p*				
	Group I ≤ 7% (*n* = 14)	Group II 7.01–7.5% (*n* = 11)	Group III 7.51–8.5% (*n* = 19)	Group IV > 8.5% (*n* = 13)	Group I vs II	Group II vs III	Group III vs IV	Group I vs IV	Group II vs IV
Peroneal motor nerve (%)	–9.21 ± 7.18	–8.64 ± 6.49	–7.68 ± 6.73	–11.81 ± 5.49	0.510	0.887	0.336	0.830	0.541
Tibial motor nerve (%)	–9.79 ± 6.88	–9.75 ± 7.35	–8.26 ± 5.56	–11.46 ± 5.68	0.601	0.588	0.165	0.905	0.414
Sural nerve (%)	–9.29 ± 6.45	–9.49 ± 7.43	–8.17 ± 5.89	–9.92 ± 4.59	0.742	0.914	0.394	0.807	0.503

Data are presented as mean ± standard deviation.

Table 4. Sum of percentage change in velocity (SPCV) and amplitude (SPCA) according to mean glycosylated hemoglobin (HbA1c)

	HbA1c ≤ 8.5% (n = 44)	HbA1c > 8.5% (n = 13)	p
SPCV (%)	0.19 ± 15.84	–41.43 ± 12.47	< 0.001
SPCA (%)	–26.89 ± 18.93	–31.38 ± 14.37	0.493

Data are presented as mean ± standard deviation.

In conclusion, there is a tendency toward deterioration of diabetic neuropathy with poor blood glucose control in type 2 diabetes. Furthermore, a serum HbA1c of more than 8.5% will result in significant deterioration in electrophysiology.

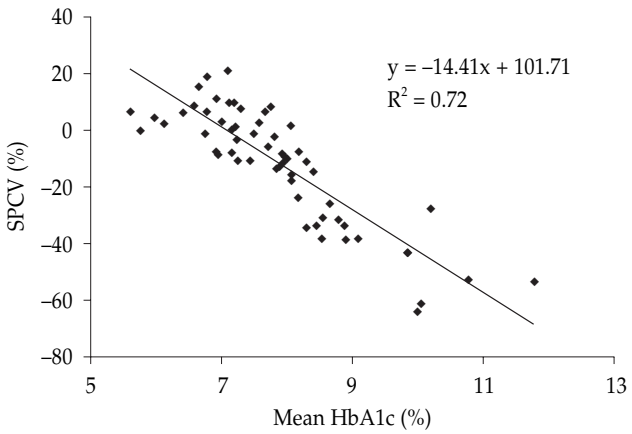

Figure. *Relationship between sum of percentage change in velocity (SPCV) and mean serum glycosylated hemoglobin level (HbA1c).*

Table 5. Sum of percentage change in velocity (SPCV) in subjects with and without hypertension, hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol concentration

	Hypertension		Hypertriglyceridemia		Low HDL cholesterol	
	With (n = 29)	Without (n = 28)	With (n = 9)	Without (n = 48)	With (n = 32)	Without (n = 25)
SPCV (%)	–9.60 ± 23.45	–8.98 ± 23.29	–6.93 ± 15.22	–9.74 ± 24.47	–8.67 ± 23.25	–10.10 ± 23.51
p	0.949		0.948		0.701	

Data are presented as mean ± standard deviation.

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血糖控制對第二型病糖尿病病人神經病變在神經生理學變化之影響

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糖尿病神經病變是糖尿病常見的併發症之一。許多研究已發現在第一型糖尿病人上有效地控制血糖，對於減緩神經傳導速度的變化是有益處的。但很少研究針對第二型糖尿病的糖尿病神經病變。此次研究的目的在探討第二型糖尿病血糖控制與糖尿病神經病變之電氣生理學變化的關係。共收集57位有神經病變的第二型糖尿病病人。腓骨運動神經、脛骨運動神經及腓腸神經之神經傳導測試分別在研究開始時及 24 ± 3.12 個月後追蹤時量測。個別神經變化以變化百分比 (PC) 表示，而變化百分比是由〔(追蹤時的傳導數值－開始時的傳導數值)／開始的傳導數值 × 100%〕計算而得。而整體的神經生理變化則以個別變化百分比加成之總和表示。平均 HbA1c 為每三個月測得的 HbA1c 平均而得。研究結果顯示腓骨運動神經、脛骨運動神經及腓腸神經之神經傳導速度變化百分比在平均HbA1c ≤ 8.5% 的病人皆小於平均 HbA1c > 8.5% 的病人，而且神經傳導速度的變化百分比總合 (SPCV) 與平均HbA1c呈現顯著負相關。而神經傳導速度的變化百分比總合 (SPCV) 在有或無高血壓、高三酸甘油脂血症和低高密度膽固醇的病人間並無顯著差異。結論，高血糖是第二型糖尿病病人的神經生理學變化的重要病因。此外，當平均 HbA1c 高於 8.5 時，將會造成神經生理學上顯著的惡化。

關鍵詞：第二型糖尿病，糖尿病神經病變，神經傳導速度

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