Journal of Medical Sciences

ISSN 1682-4474

science alert

ANSInet
an open access publisher
http://ansinet.com

Research Paper

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued six times per year on paper and in electronic format.

For further information about this article or if you need reprints, please contact:

Ali Moghtaderi
Department of Neurology,
Zahedan University of
Medical Sciences,
Iran

J. Med. Sci., 6 (5): 818-822
September-October, 2006

Diabetic Neuropathy: Determining the Sensitivity of Peripheral Nerves During a Short Course of Glycemic Control

[1]Ali Moghtaderi, [2]Roya Alavi-Naini,
[3]Mehdi Mohammadi and [2]Homayra Rashidi

The effect of controlling diabetes on peripheral neuropathy is a continuing debate since many years ago. This study tried to determine the correlation between a short course of glycemic control on the conduction velocity and electromyographic changes of the peripheral nerves of the lower limbs. The authors conducted a historical cohort study on 120 diabetic patients. This study assessed clinically and electrophysiologically the peripheral nervous system of two equal and adjusted groups of controlled and uncontrolled type 2 diabetic patients in which glycosylated hemoglobin (HbA_{1C}) were below or over 7.5% continuously at least during the last six months. Thirty-two men and 88 women enrolled in the study. Sixteen patients in controlled group and 24 patients in the uncontrolled group had peripheral neuropathy. Mean age and duration of diabetes (years±SD) in the first group was 50.8±10.8 years and 6.48±3.05 months; and in the second group was 48.9±11.4 years and 7.40±4.85 months respectively. Sixteen patients in controlled group and 24 patients in the other group had peripheral neuropathy. The uncontrolled diabetic patients had higher rate of peripheral neuropathy in the lower limbs in which the hyperglycemic state is an effective factor. The common peroneal nerves are more sensitive to glycemic changes and prone to involve faster. Nerve conduction studies and electromyographic findings were only statistically significant but there was not any significant clinical difference.

Key words: Diabetes, peripheral neuropathy, glycosylated hemoglobin

ANSInet
Asian Network for Scientific Information

[1]Department of Neurology, [2]Department of Infectious Diseases,
[3]Department of Biostatistics,
Zahedan University of Medical Sciences, Iran

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a frequent complication of diabetes. Electromyographic (EMG) evaluation of diabetic patients as a neuropathic marker is evident from the previous studies and is one of the mainstays of diagnosis of peripheral nervous system involvement (Dyck *et al*., 1992; Greene *et al*., 1990). About 15-25% of patients with diabetes mellitus have both symptoms and signs of neuropathy, but nearly 75-85% have either neuropathic symptoms or nerve conduction abnormalities (Dyck *et al*., 1993; Graf *et al*., 1979).

Although it is a chronic process, often unnoticed by the patient, polyneuropathy is most common in diabetics more than 50 years of age; it is uncommon in those under 30 years of age and rare in childhood. When the polyneuropathy becomes symptomatic, the main complaints are persistent and often distressing numbness and tingling, usually confined to the feet and lower legs, and worse at night and in severe cases the hands may be involved. Levels of glycosylated hemoglobin (HbA_{1C}), an index of long term euglycemia, are helpful to show glycemic control at least for three months. Allen *et al.* (1997) and Martin *et al.* (2006) indicates that sustained hyperglycemia is related to functional changes, at the minimum, in peripheral sensory and motor nerve conduction at a diabetes duration of 4 years. It was proposed that diabetic neuropathy is associated with reduced nerve conduction and increased blood glucose concentrations (Clark and Lee, 1995). The objective of this study is to determine the effect of a short course of glycemic control on the nerves conduction velocities (NCV), EMG changes of the lower limbs and determine the most sensitive nerve to hyperglycemia in the lower limbs.

MATERIALS AND METHODS

The authors designed a retrospective cohort study. The study was reviewed and approved by the university ethics committee and written informed consent was obtained from all patients before entering into the study. One hundred and fifty type 2 diabetic patients (as classified according to the National Diabetes Data Group, 1979) of both sexes enrolled in the study. HbA_{1C} was measured after three and six months for all patients. We tried to omit other potential risk factors associated with diabetic neuropathy so the other causes of peripheral neuropathy (alcoholic, renal failure, liver disease, hypothyroidism, drug consumption, collagen vascular diseases and vasculitis) were excluded according to the history, physical examination and laboratory findings. We included only patients who had measurable sural, tibialis and peroneal responses. Thirty patients were omitted. During one and-a-half year 120 consecutive patients were selected and divided into two equal groups according to the HbA_{1C} level below or above 7.5%. None of them had previously carried out tests for DPN. They were treated with insulin and/or oral hypoglycemic agents. A questionnaire was completed for symptoms, signs, disease duration and demographic data for each patient. Neurologic examination includes evaluation of paresthesia, deep tendon reflexes, motor power, absence or presence of atrophy, trophic changes, pain and burning sensations. All EMG/NCV studies performed by only one neurologist who was blinded to the results of HbA_{1C}. Nerve conduction studies were performed with control of limb temperature, standard surface stimulation and recording techniques using Neuromatic 2000 C® instrument (Dantec, Denmark). Sural sensory and motor branches of posterior tibial and peroneal nerves of both feet were evaluated. Well-defined, artifact free responses were recorded. The mean values of conduction velocities and amplitudes were calculated. Normal reference values for age and sex were based on a previous local population study of healthy subjects without neuropathy divided into different age groups. Abnormal values defined as > 2 standard deviation (SD) of normal mean values. Based on nerve conduction velocity, amplitude, distal latency and EMG findings, peripheral neuropathy was confirmed or ruled out in each patient. Data were analyzed with SPSS software (11th version). Both Chi-square and T-test for independent samples were used to analyze quantitative variables.

RESULTS

The study group included 32 (26.7%) male and 88 female. The mean age was 47±7.5 years in men and 48±9.1 years in women (range: 38-72 years). The disease duration was 6.08±2.9 years in men and 5.42±3.0 years in women (range: 2.3-22.5 years). The mean HbA_{1C} (±SD) was 8.9±1.6%. The mean duration of diabetes was 6.48±3.05 years in controlled group and 7.40±4.85 in uncontrolled diabetic patients. Mean duration of disease (±SD) in forty patients (33.3%) with diabetic peripheral neuropathy was 9.03±5.1 and in the other two-thirds without DPN was 5.90±4.55 years. Table 1 summarizes clinical characteristics of patients.

Considering HbA_{1C}, we conducted a chi-square test to compare sex and presence of peripheral neuropathy; and a student T-test to compare mean age and duration of diabetes between two groups of patients. Statistical comparing of two groups of diabetic patients did not

Table 1: Clinical characteristics and significance analysis between morphological indexes of peripheral neuropathy and investigated risk factors of diabetic patients

Variables	HbA_{1C} ≤ 7.5%	HbA_{1C} >7.5%	Test	p-value
Sex				
Male	14 (23.3)	18 (30)	X^2 =0.682	0.409
Female	46 (76.7)	42(70)	df = 1	
Peripheral neuropathy				
Yes	16 (26.7)	24(40)	X^2 = 2.400	0.121
No	44 (73.3)	36 (60)	df =1	
Mean age (years±SD)	50.8±10.8	48.9±11.4	t = 0.966	0.336
			df = 118	
Duration of diabetes (years±SD)	6.48±3.05	7.40±4.85	t = -1.017	0.914
			df = 118	

Table 2: Duration of diabetes versus electromyographic findings in two groups

HbA_{1C}	Electromyography	No. of patients	Duration of the disease (years ±SD)	Independent-samples t-test
≤ 7.5%	Normal	44	5.48±4.6	t = -2.481
				df = 23.29
	Neuropathic	16	9.29±5.4	p = 0.021
> 7.5%	Normal	36	6.41±4.5	
				df = 45.45
	Neuropathic	24	8.91±5.1	p = 0.059

Table 3: Correlation coefficient between duration of the diabetes and sensory NCV (m sec^{-1}) according to nerve types and HbA1c

HbA_{1C}	Nerves (Sensory)	Mean±SD	R^2	p-value
≤ 7.5%	L. Sural	48.40±12.27	-0.237	0.069
	R. Sural	50.05±12.48	-0.149	0.257
> 7.5%	L. Sural	42.35±13.58	-0.067	0.611
	R. Sural	43.41±13.28	-0.144	0.274

Table 4: Correlation coefficient between duration of the diabetes and motor NCV (m sec^{-1}) according to nerve types and HbA1c

HbA_{1C}	Nerves (Motor)	Mean±SD	R^2	p-value
	L. Tibialis	39.45±7.33	0.161	0.219
≤ 7.5%	L. Peroneal	46.32±7.78	0.031	0.812
	R. Tibialis	39.36±6.79	0.046	0.729
	R. Peroneal	44.55±8.79	0.159	0.224
	L. Tibialis	36.42±9.88	-0.001	0.992
> 7.5%	L. Peroneal	40.74±17.16	-0.299	0.020
	R. Tibialis	35.17±10.13	-0.223	0.087
	R. Peroneal	39.10±18.42	-0.295	0.022

reveal any significant difference in terms of sex ratio, proportion of peripheral neuropathy, mean age of the patients. Despite high proportion of neuropathy in the uncontrolled group (40% versus 26.7%) there is not any significant difference between presence of peripheral neuropathy in controlled and uncontrolled diabetic patients (Table 1).

Findings compatible with neuropathic disorder in electromyographic survey of the patients with controlled diabetes revealed significant association with duration of the disease but in the uncontrolled group such an association was not shown (Table 2). Considering significant $p<0.05$, there is no meaningful correlation between sensory nerves conduction velocities and duration of the diabetes (Table 3). Significant correlation is present between motor branches of common peroneal NCV and duration of diabetes only in uncontrolled group (Table 4).

DISCUSSION

Alterations in nervous transmission might be an early feature of diabetic peripheral polyneuropathy, even in the subclinical stage. The most important factors in inducing peripheral neuropathy secondary to diabetes are age, duration of diabetes (Franklin *et al*., 1990; Maser *et al*., 1989) and vascular injury of the peripheral nerves (Matsutomo *et al*., 2005; Rodrigues Filho and Fazan, 2006; Valensi *et al*., 1997). It seems that the intensity and extent of the functional and anatomical abnormalities of diabetic neuropathy parallel the degree and duration of hyperglycemia (Clark and Lee, 1995) In this study the authors tried to show the correlation between controlling diabetes and alteration in conduction velocities and electromyographic changes in diabetic neuropathy. We assessed clinically and electrophysiologically the peripheral nervous system of two equal groups of controlled and uncontrolled type 2 diabetic patients in which glycosylated hemoglobin were below or over 7.5% continuously at least during the last six months.

We tried to reduce the effect of gender, age and presence or absence neuropathy. Statistical evaluation between glycosylated hemoglobin (HbA_{1C}) and the above factors revealed that there is no significant association between them. These findings are important in designing and interpreting clinical studies of diabetic neuropathy. Considering that in the two equal and adjusted groups in which the above factors didn't have any major influence on neuropathy, the authors think that the only effective factors are duration of disease and the amount of glycosylated hemoglobin. It seems that EMG findings in patients with uncontrolled diabetes don't have statistically meaningful correlation with disease duration but in controlled diabetics, it does (Table 2). We suggest that despite the influential effect of disease duration causing peripheral neuropathy, the uncontrolled patients suffer from some other factors especially metabolic one in which decrease the time latency for induction of neuropathy. The authors also suggest that poor glycemic control decreases the effect of disease duration in diabetic patients.

There is electrophysiological evidence to suggest that DPN is due to metabolic changes and nerve conduction abnormalities are at least partly dependent on the metabolic abnormalities (Porter *et al*., 1981) Graf *et al*. (1979) reported that fasting blood glucose in 20 diabetic patients were inversely related to the motor NCV of median, peroneal and posterior tibial nerves but not to the sensory NCV of sural and median nerves. Matsumoto *et al*. (1994) concluded that tight glycemic control from the onset of diabetes is essential for the prevention of DPN. Gregersen (1964, 1968) also reported

significant improvement in the NCV during treatment diabetes and controlling blood sugar in most cases during his studies but Ward and his colleagues did not find any relation between the motor NCV and postprandial blood glucose levels in their patients (Kasalova *et al*., 2006; Ward *et al*., 1971)

According to Gregersen (1968) that a reliable increase in motor NCV is first present after 2-3 days of treatment. Fraser *et al*. (1977) found significant improvement in peroneal motor NCV after six days of treatment in newly diagnosed patients. Campbell *et al*. (1976) observed decreased distal latency of the peroneal nerves in the same period of time in diabetic ketoacidosis. By three and six months after initiation of treatment a significant improvement was also seen in peroneal and ulnar nerves (Campbell *et al*., 1976; Graf *et al*., 1981) It is postulated that peripheral nerves may be more susceptible to acute metabolic damage than autonomic fibers (Campbell *et al*., 1976).

These findings support the hypothesis that some abnormalities in adult onset diabetes are related to the level of hyperglycemia. Many investigations showed that glycemic control is associated by improved nerve conduction velocity in diabetic patients (Campbell *et al*., 1976; Fraser *et al*., 1977; Graf *et al*., 1981; Gregersen, 1968). Franklin *et al*. (1990) reported that the prevalence odds ratio was 10.6 for the presence of neuropathy diabetic patients, compared with persons with normal glucose tolerance. The benefit of glycemic control on nerve conduction velocities has been shown in several clinic population (Ziegler *et al*., 1988). In the DCCT, intensive treatment decreased the occurrence of clinical neuropathy by 60% (Diabtes Control and Complications Trial Research Group, 1993) It was proposed that metabolic improvement is responsible for the early improvement of the NCV, but remyelination of the damaged nerve causes continuing late improvement (Oh, 2003). (Allen *et al*. (1997) anticipated that DPN consistent with a dying-back type neuropathy. Clark and Lee (1995) proposed that acute hyperglycemia decreases nerve function and chronic hyperglycemia is associated with the loss of myelinated and unmyelinated fibers, wallerian degeneration, and blunted nerve-fiber reproduction. The pathophysiologic mechanisms that underlie these changes are not clearly understood.

We conducted a bivariate correlations procedure to compute Pearson's correlation coefficient and analyze sensory and motor nerve conduction velocities. Only motor NCV of both common peroneal nerves of the uncontrolled group revealed correlation with duration of diabetes. It emphasizes that common peroneal nerve is more sensitive to glycemic changes of the human being. It is worth of mentioning that all the above findings are only statistically significant but clinically we couldn't detect a prominent difference.

The common peroneal nerve is the continuation of lateral trunk of sciatic nerve, formed from anterior division of the L4-S2 spinal nerves and separating from the sciatic nerve in the upper popliteal fossa. Axonal loss was the process commonly encountered in the diabetic patients but substantial axonal loss, as evidenced by a significant decrease in amplitude of nerve conduction studies, was present in a minority group. The predilection for axonal loss in many diabetic patients is due to metabolic problems induced neurotubular dysfunction. We suppose that ischemic changes and prolonged sitting especially on hard benches (Crisci *et al*., 1989) prone the common peroneal nerve to compression neuropathy especially in diabetic patients in whom vascular supply to the nerves diminished (Katirji and Wilbourn, 1988; Walker, 2005). Our findings that sustained hyperglycemia is an important factor in nerve conduction delay and presence of subclinical neuropathy confirms earlier reports (Diabtes Control and Complications Trial Research Group, 1993) Rota *et al*., 2005; Zieglerr*et al*., 1991)

CONCLUSIONS

The authors suggested that tight glycemic control from the onset of diabetes may be critical to primary prevention of diabetic distal polyneuropathy and common peroneal nerves are the most sensitive nerves in the lower limbs of diabetic patients. Performing earlier EMG/NCV studies in diabetic patients could reveal early subclinical polyneuropathy due to axonal injury secondary to metabolic changes.

REFERENCES

Allen, C., G. Shen, M. Palta, B. Lotz, R. Jacobson and D. D'Alessio, 1997. Long-term hyperglycemia is related to peripheral nerve changes at a diabetes duration of 4 years. The Wisconsin Diabetes Registry. Diabetes Care, 20: 1154-1158.

Campbell, I.W., D.M. Fraser, D.J. Ewing, V.S. Baldwa, A.B. Harrower, A. Murray, J.M. Neilson and B.F. Clarke, 1976. Peripheral and autonomic nerve function in diabetic ketoacidosis. Lancet, 2: 167-169.

Clark, C.M. and D.A. Lee, 1995. Prevention and treatment of the complications of diabetes mellitus. N. Engl. J. Med., 332: 1210-1217.

Crisci, C., M.K. Baker, M.B. Wood, W.J. Litchy and P.J. Dyck, 1989. Trochanteric sciatic neuropathy. Neurol., 39: 1539-1541.

Dyck, P.J., J.L. Karnes, P.C. O'Brien, W.J. Litchy, P.A. Low and L.J. Melton 3rd, 1992. The rochester diabetic neuropathy study: Reassessment of tests and criteria for diagnosis and staged severity. Neurology, 42: 1164-1170.

Dyck, P.J., K.M. Kratz and J.L. Karnes, 1993. The prevalance by staged severity of various types of diabetic neuropathy, and nephropathy, in population based cohort. Neurology, 43: 817.

Franklin, G.M., L.B. Kahn, J. Baxter, J.A. Marshall and R.F. Hamman, 1990. Sensory neuropathy in non-insulin-dependent diabetes mellitus. The San Luis valley diabetes study. Am. J. Epidemiol., 131: 633-643.

Fraser, D.M., I.W. Campbell, D.J. Ewing, A. Murray, J.M. Neilson and B.F. Clarke, 1977. Peripheral and autonomic nerve function in newly diagnosed diabetes mellitus. Diabetes, 26: 546-550.

Graf, R.J., J.B. Halter, E. Halar and D. Porte, 1979. Nerve conduction abnormalities in untreated maturity-onset diabetes: Relation to levels of fasting plasma glucose and glycosylated hemoglobin. Ann. Intl. Med., 90: 298-303.

Graf, R.J., J.B. Halter, M.A. Pfeifer, E. Halar, F. Brozovich, and D. Porte, 1981 Glycemic control and nerve conduction abnormalities in non-insulin-dependent diabetic subjects. Ann. Intl. Med., 94: 307-311.

Greene, D.A., A.F. Sima, M.A. Pfeifer and J.W. Albers, 1990. Diabetic neuropathy. Annu. Rev. Med., 41: 303-317.

Gregersen, G., 1964. Motor-nerve function and duration of diabetes. Lancet., 171: 733.

Gregersen, G., 1968. Variations in motor conduction velocity produced by acute changes of the metabolic state in diabetic patients. Diabetologia, 4: 273-277.

Kasalova, Z., M. Prazny and J. Skrha, 2006. Relationship between peripheral diabetic neuropathy and microvascular reactivity in patients with type 1 and type 2 diabetes mellitus-neuropathy and microcirculation in diabetes. Exp. Clin. Endocrinol. Diabetes, 114: 52-57.

Katirji, M.B. and A.J. Wilbourn, 1988. Common peroneal mononeuropathy: A clinical and electrophysiologic study of 116 lesions. Neurology, 38: 1723-1728.

Martin, C.L., J. Albers, W.H. Herman, P. Cleary, B. Waberski, D.A. Greene, M.J. Stevens and E.L. Feldman, 2006. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. Diabetes Care, 29: 340-344.

Maser, R.E., A.R. Steenkiste, J.S. Dorman, V.K. Nielsen, E.B. Bass *et al*., 1989. Epidemiological correlates of diabetic neuropathy. Report from Pittsburgh epidemiology of diabetes complications study. Diabetes, 38: 1456-1461.

Matsumoto, T., Y. Ohashi, N. Yamada and M. Kikuchi, 1994. Hyperglycemia as a major determinant of distal polyneuropathy independent of age and diabetes duration in patients with recently diagnosed diabetes. Diabetes Res. Clin. Pract., 26: 109-113.

Matsutomo, R., K. Takebayashi and Y. Aso, 2005. Assessment of peripheral neuropathy using measurement of the current perception threshold with the neurometer in patients with type 2 diabetes mellitus. J. Intl. Med. Res., 33: 442-453.

National Diabetes Data Group, 1979. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group Diabetes, 28: 1039-1057.

Oh, S.J., 2003. Nerve conduction in peripheral neuropathies. In Clinical Electromyography: Nerve Conduction Studies. Baltimore: Lippincott Williams and Wilkins, pp: 703-704.

Porter, D., R.J. Garf, J.B. Halter, M.A. Pfeifer and E. Halar, 1981. Diabetic neuropathy and plasma glucose control. Am. J. Med., 70: 195-200.

Rodrigues Filho., O.A. and V.P. Fazan, 2006. Streptozotocin induced diabetes as a model of phrenic nerve neuropathy in rats. J. Neurosci. Meth., 151: 131-138.

Rota, E., R. Quadri, E. Fanti, G. Isoardo, F. Poglio, A. Tavella, I. Paolasso, P. Ciaramitaro, B. Bergamasco and D. Cocito, 2005. Electrophysiological findings of peripheral neuropathy in newly diagnosed type II diabetes mellitus. J. Peripher. Nerv. Syst., 10: 348-353.

The Diabetes Control and Complications Trial Research Group, 1993. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N. Engl. J. Med., 329: 977-986.

Valensi, P., C. Giroux, B. Seeboth-Ghalayini and J.R. Attali, 1997. Diabetic peripheral neuropathy: effects of age, duration of diabetes, glycemic control, and vascular factors. J. Diabetes Complications, 11: 27-34.

Walker, R., 2005. Diabetes and peripheral neuropathy: keeping people on their own two feet. Br. J. Community Nurs., 10: 33-36.

Ward, J.D., C.G. Barnes, D.J. Fisher, J.D. Jessop and R.W. Baker, 1971. Improvement in nerve conduction following treatment in newly diagnosed diabetics. Lancet, 1: 428-430.

Ziegler, D., K. Wiefels, K. Dannehl and F.A. Gries, 1988. Effects of one year of near-normoglycemia on peripheral nerve function in type 1 (insulin-dependent) diabetic patients. Klin Wochenschr, 66: 388-396.

Ziegler, D., P. Mayer, H. Muhlen and F.A. Gries, 1991. The natural history of somatosensory and autonomic nerve dysfunction in relation to glycaemic control during the first 5 years after diagnosis of type 1 (insulin-dependent) diabetes mellitus. Diabetology, 34: 822-829.