Original Article

Nerve Conduction in Children Suffering Insulin Dependent Diabetes Mellitus

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Abstract. ***Objective :*** To determine the incidence of peripheral neuropathy in children suffering Insulin Dependent Diabetes Mellitus (IDDM) as well as to determine the relationship between other criteria of the disease and neuropathy. ***Methods :*** 40 children (17 males, mean age 11.9 years) suffering IDDM and receiving insulin therapy involving two injections a day and 30 healthy children (17 males, mean age 11.7 years) were included in the study. They were inquired about their demographical characteristics as well as the presence of neurological symptoms. Their detailed neurological examinations were conducted. Their glycemic control values (Hb A_1C) were recorded, and their nerve conduction studies were performed from right upper and lower extremities. ***Results :*** All nerve conduction values of children with IDDM were found to be significantly lower ($p<0.0001$) as compared to the control group. 60% of diabetic children (n=24) were found to suffer peripheral neuropathy. Statistically significant relationships were found between the glycemic control values and the peroneal, sural, tibial, ulnar and median nerve conduction velocities, and also between the duration of disease and the peroneal, sural, tibial and median nerve conduction velocities. ***Conclusion :*** The peripheral neuropathy is rather a frequently observed complication in diabetic children. The duration of disease and impaired glycemic control play an important role in the development of neuropathy. The introduction of new methods designed to ensure better glycemic control will reduce the incidence of the complication.
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Key words : *Insulin dependent diabetes mellitus; Neuropathy; Electrophysiological study; Nerve conduction study*

Diabetes Mellitus constitutes an important social health problem. About 10-15 % of cases of diabetes observed at all ages are represented by Insulin Dependent Diabetes Mellitus (IDDM). The insulin dependent diabetes mellitus is one of the most frequently observed chronic, metabolic endocrine diseases of childhood and early adult periods, and as a systemic disease, it exhibits significant levels of morbidity and mortality because of its complications observed during its acute and chronic periods.[1,2] In patients with impaired glycemic control, the chronic complications appear within 10 years, which have adverse effects on the quality and length of life.

The diabetic neuropathy is a frequently observed chronic complication of diabetes in children suffering IDDM, whose significance as a complication leading to undesirable results if not controlled effectively is being better recognized in recent years. Exercising a good follow-up program and application of proper therapy can help to reduce to a minimum the degree of metabolic disorders and micro-vascular complications which might arise.

The presnt study is aimed to determine the incidence of peripheral neuropathy (symptomatic or asymptomatic) in children suffering IDDM by means of an electrophysiological method, and to investigate the relationship between neuropathy and the duration of disease, the glycemic control and some other complications of the disease.

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MATERIALS AND METHODS

The present study was carried out on 40 children suffering IDDM and receiving therapy at the Endocrinology outpatient clinic of Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital, and on 30 healthy children who were paired with diseased children according to age and sex. The children suffering IDDM who were included in this study were 4-18 years old, were receiving insulin therapy involving two injections a day, did not have any familial or hereditary neurological disease history, had normal thyroid function tests, did not suffer any collagen tissue diseases and did not exhibit any nutritional deficiencies. The following evaluations were made on the patients included in the present study.

History : The patients were inquired about their demographical characteristics, whether or not they had an attack of ketoacidosis and the presence of neurological symptoms.

Physical Examination : The patients were subjected to a systemic examination, examination of eye (funduscopic evaluation) and examination of locomotor system with regard to other complications of diabetes. On neurological examination, the superficial somatic sensations (touch, superficial pain) and deep somatic sensations (vibration and joint-position sense) as well as the muscle strength and deep tendon reflexes were evaluated. The presence of any loss in sense of superficial pain was evaluated in 3 different points lying in the direction from distal toward proximal of each extremity. The sense of touch was evaluated by the aid of a piece of cotton while the sense of superficial pain by means of careful pinprick evaluation. The sense of vibration was examined by placing a 256 Hz diapason on the malleolar in the lower extremity, and on the projecting bone of radius in the upper extremity. The joint-position sense was also tested. The deep tendon reflexes were obtained from the biceps brachi, triceps brachi, brachioradialis, quadriceps (patellar reflex) and gastrocnemius (achilles reflex) muscles. The muscle strength was evaluated in each extremity in the direction from distal toward proximal.

Biochemical Determinations : The microproteinuria values were determined quantitatively by means of a photometer using 3% trichloraacetic acid (TCA).[3] Normal values were taken to be 15-45 mg/dl. The HbA_1C values were determined by immunoturbinometric method, using Hitachi 911 autoanalyzer. The normal values for this method range between 4.3%–5.8% g/dl. [4]

Electrophysiological Study (electroneurography - 'ENG') : As a standard study, the sensory and motor branches of median and ulnar nerves of the right upper extremity were examined, while an electrophysiological study was conducted on the peroneal, tibialis posterior and sural nerves of the right lower extremity. The values of distal latency, conduction velocities, and amplitudes of compound muscle action potential (CMAP) and sensory compound nerve action potential (CNAP), from peak to peak, for these nerves were recorded. Amplitudes were measured by "From peak to peak" method. The measurements related to sensory branches of median and ulnar nerves were made by orthodromic method while the measurements related to sural nerve were made by antidromic method. The responses of motor and sensory nerves were measured by superficial electrodes. Care was taken to keep the room temperature constant during the measurements. The electrophysiological studies and neurological examinations of all patients and the control group were carried out and completed by the same physician (B.S.). The Nihon-Kohden Neuropeck II ENMG apparatus was used in the measurements.

Both the patient group and healthy children (control group) gave written consent to participate in the study.

The statistical analyses were performed using the Statistical Package for the Social Science Program (SPSS Version 9.05). The results were expressed as mean± 2 Standard Deviation. The comparisons between the two groups were made by means of t test, while the relationships between the parameters were evaluated by correlation analyses.

RESULTS

The mean age of patient group is 11.9 ± 3.6 years (17 males, 42.5%) while that of control group is 11.5±2.3 years (17 males, 56.7%), and there was no statistically significant difference between the two groups with regard to age and sex (p=0.55, p=0.30 respectively). In the patient group, the mean duration of disease was 4.9±3.2 years (ranging between 1-11 years).

The mean HbA_1C value obtained on the date of ENMG examination was 9.6±3.0, while the mean HbA_1C value of the last one year was 9.7±2.4. In two patients microproteinuria, while in 2 patients arthropathy were observed. During the last one year, only one patient was reported to have an attack of ketoacidosis once. The examination of eye revealed no presence of retinopathy in any one of our patients.

Ten children complained of neurological symptoms and eleven children showed one or more neurological deficits. The neurological examination of 11 patients revealed the presence of loss of reflex in 9 patients, impaired sense of vibration in 2 patients, loss in sense of superficial pain in 1 patient, loss of touch sense in 4 patients, paresthesia in 8 patients and weakness in muscle strength in 2 patients. (Table 1).

Table 1. Incidence of Neurological Symptoms and Findings in the Group of Patients

Neurological Symptoms/Findings	N	%
Decrease or loss in DTR	9	22.5
Weakness of muscle	2	5
Paresthesia/pain/cramp	8	20
Loss of touch sense	4	10
Loss of sense superficial pain	1	2.5
Impairment of sense of vibration	2	5
Impairment of sense of joint-position	-	-
Patients with one or several symptoms or findings	11	27.5

The results of electrophysiological studies showed the presence of peripheral neuropathy in 24 (60%) of 40 patients. Sixteen of these patients were found to suffer sensory and motor neuropathy, 6 of them motor neuropathy and 2 of them sensory neuropathy.

When the patient group was compared with the control group, a statistically significant reduction was found in the levels of all nerve conduction velocities studied in the patient group (Table 2). The distal latency of tibial nerve was found to be longer in the patient group as compared to the control group, with a value of 3.73 ±

0.83 m/sec in the control group and 4.28±1.19 m/sec in the patient group (p= 0.026). Similarly, the distal latency of sural nerve was also found to be longer in the patient group, with values of 2.46±0.40 m/sec and 2.87±0.86 m/sec in the control and patient groups, respectively (p=0.01). No statistically significant difference was found between the distal latency values and amplitudes of CMAPs and CNAPs of other nerves (Table 3).

A statistically significant negative relationship was found between the HbA_1C concentration measured on the date of ENMG and the conduction velocity and the amplitude of CMAP of peroneal nerve.

Statistically significant negative correlations were found between the annually mean HbA_1C values and the conduction velocities of peroneal, sural, tibial, ulnar motor and sensory, median motor nerve and the amplitude of CMAP of tibial nerve motor branch. There were also significant positive correlations between the annually mean HbA_1C value and the distal latencies of ulnar sensory, tibial, peroneal motor branch.

A statistically significant negative relationship was found between the duration of disease and the peroneal, sural, tibial and median nerve motor branch conduction velocities, amplitudes of CNAP median and ulnar nerve and also a positive relationship was found distal latency of tibial and sural nerve. These relationships are shown in Tables 4-5 and Fig. 1-3.

Table 2. The Means of Nerve Conduction Velocities Measured in the Patient and Control Groups and their Comparison with Each Other.

	Patient Group mean ± SD (m/sec)	Control Group mean ± SD (m/sec)	p
MMvel	52.69 ± 9.73	57.06 ± 2.87	0.02
MSvel	53.18 ± 10.10	57.68 ± 5.11	0.029
UMvel	51.99 ± 4.55	57.80 ± 3.42	0.0001
USvel	53.90 ± 5.00	57.64 ± 4.91	0.0003
PMvel	47.9 ± 5.99	53.56 ± 2.99	0.0001
TMvel	45.99 ± 5.84	52.12 ± 3.92	0.0001
SSvel	48.13 ± 10.45	55.25 ± 4.43	0.0001

MMvel: Median motor conduction velocity, **MSvel:** Median sensory conduction velocity, **UMvel:** Ulnar motor conduction velocity, **USvel:** Ulnar sensory conduction velocity, **PMvel:** Peroneal motor conduction velocity, **TMvel:** Tibial motor conduction velocity, **SSvel:** Sural sensory conduction velocity

Table 3. The Means of Distal Latencies and Amplitudes CMAPs and CNAPs of Nerves Measured in the Patient and Control Groups and their Comparison with Each Other

	Patient Group mean ± SD (m/sec)	Control Group mean ± SD (m/sec)	p
MMdl	2.9 ± 0.7	3.1 ± 0.4	Non-significant
MMamp	11.2 ± 4.6	12.3 ± 3.3	Non-significant
MSdl	2.1 ± 0.5	2.2 ± 0.2	Non-significant
MSamp	20.7 ± 10.8	20.3 ± 7.1	Non-significant
UMdl	2.1 ± 0.3	2.2 ± 0.3	Non-significant
UMamp	9.8 ± 3.1	9.5 ± 3.5	Non-significant
USdl	1.9 ± 0.3	1.9 ± 0.2	Non-significant
USamp	15.9 ± 2.1	18.5 ± 6.1	Non-significant
PMdl	3.8 ± 0.9	3.8 ± 0.7	Non-significant
PMamp	4.7 ± 1.8	4.9 ± 1.8	Non-significant
TMdl	4.3 ± 1.2	3.7 ± 0.8	Non-significant
TMamp	10.8 ± 4.9	11.1 ± 3.5	Non-significant
SSdl	2.9 ± 0.0	2.5 ± 0.4	Non-significant
SSamp	16.2 ± 7.8	19.1 ± 5.7	Non-significant

MMdl: distal latency of median motor, **MMamp:** amplitude of median compound motor action potential (CMAP), **MSdl:** distal latency of median sensory, **MSamp:** amplitude of Median sensory compound nerve action potential (CNAP), **UMdl:** distal latency ulnar motor, **UMamp:** amplitude of Ulnar CMAP, **USdl:** distal latency of ulnar sensory, **USamp:** amplitude of ulnar CNAP, PMdl: distal latency of peroneal motor, **PMamp:** amplitude of peroneal CMAP, **TMdl:** distal latency of tibial motor, TMamp: amplitude of tibial CMAP, **SSdl:** distal latency of sural sensory, **SSamp:** amplitude of sural CNAP.

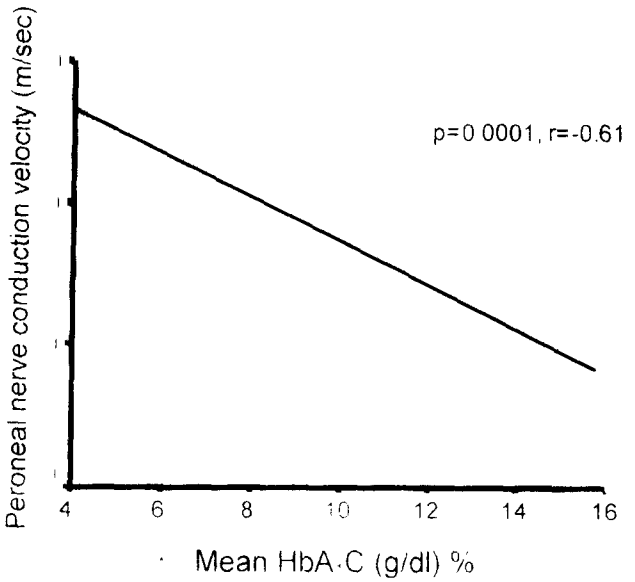

Fig. 1. Relationship between mean HbA_1C and peroneal nerve conduction velocity

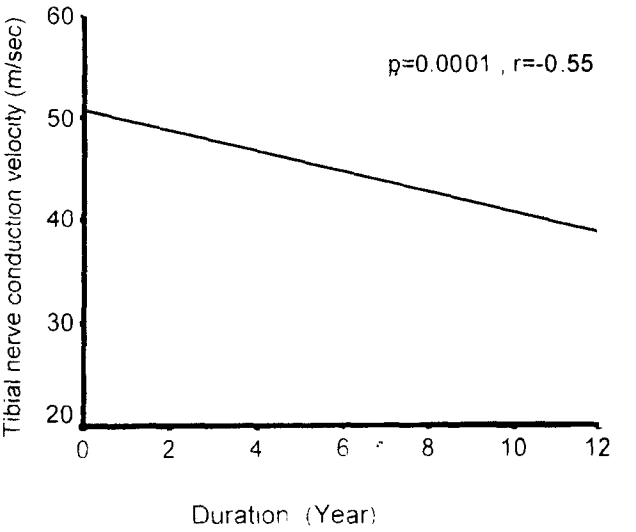

Fig. 2. Relationship between duration of disease and tibial nerve conduction velocity

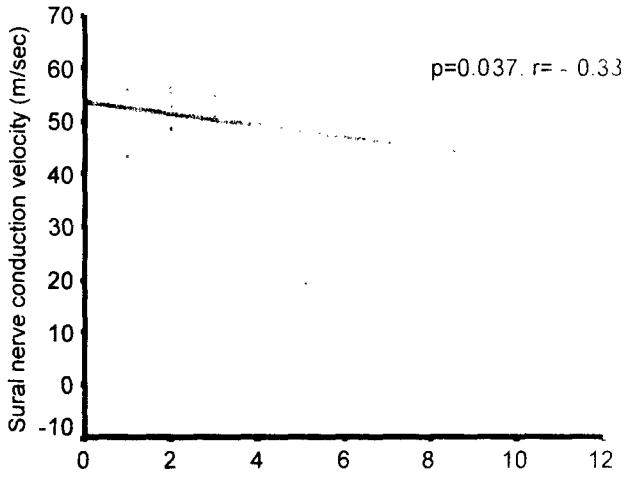

Fig. 3. Relationship between duration of disease and sural nerve conduction velocity

DISCUSSION

IDDM constitutes a universal health problem. Diabetes mellitus is reported to cause illness in more than 5 million people each year in USA, with an average increase of 5 % per year observed in its incidence.[5] The diabetic neuropathy is observed in 5–91 % of diabetic patients. [5-12] This wide range observed in its prevalence is due to the inadequacy of epidemiological researches based on actual population, the different methods used in the evaluation and the differences in defining the cases.

In the present study, we have found peripheral neuropathy in 24 (60 %) of our 40 IDDM patients, based on the results of electrophysiological studies. A similar study was conducted by RJ. Young *et al* on 79 IDDM patients whose ages ranged between 16-19 years. Their mean duration of disease was 5 years. A control group consisting of children of matched sex and age was chosen. The results of electrophysiological method used in that study showed peripheral neuropathy in 72 % of patients.[9] Fýcýcýoðlu *et al.* investigated the presence of peripheral neuropathy in 38 IDDM patients with average age of 10.5 ± 3.2 years and average duration of disease of 3.1 ± 2.8 years, and in a control group consisting of 31 children of matched age, sex and the results of ENG showed impaired peripheral nerve function in 13 (34.2 %) patients.[10]

The classical symptoms of diabetic neuropathy are not widespread in children suffering IDDM.[11-13] Electrophysiological studies help in early diagnosis of neuropathy before the appearance of clinical symptoms of the disease.[8] In the present study, we established the presence of diabetic neuropathy in 11 of our patients by means of subclinical ENG studies, without any neurological symptoms and findings. Furthermore, in 3 of the IDDM patients, included in the present study, we did not fiund any peripheral neuropathy based on ENG results, although they showed neurological symptoms. The standard classical measurement of peripheral nerve conduction velocities involves primarily the testing of functions of largest and fastest myelinated fibres. An early change in the largest myelinated fibres is not an expected characteristic in diabetes. This explains why the results of ENG did not show neuropathy in 3 of our patients although they had neuropathy clinically.[11]

In diabetic neuropathy, the lower extremities are affected more frequently than the upper extremities. [8] In general, neuropathy is a form of polyneuropathy starting from the lower extremities and progressing slowly. [13] In the present study, we found neuropathy in the lower extremity in 21 (52.5 %) of our patients.

In a study carried out by Kaar *et al* in Oulu University on 161 children suffering from IDDM, the median sensory and peroneal motor nerve conduction velocities were measured. Forty-nine (30%) of these children with an average age of 12.5 ± 3.6 years and average duration of disease of 5.3 ± 3.9 years showed impaired peroneal nerve functions. [13] In the present study too, we have most frequently found a reduction in the peroneal nerve conduction velocity in 17 (42.5 %) children. We also showed the presence of reduction in tibial nerve conduction velocity in 12 (30%), and in sural nerve conduction velocity in 11 (27.5 %) patients.

In many of the studies reported, the presence of a directly proportional correlation between the duration of diabetes disease and the frequency of peripheral neuropathy is stated.[10, 12-21] This correlation is more manifest in adult populations. Eng *et al.* followed up 190 diabetic children for a period of 8 years and showed that, while the electrodiagnostic anomalies represented a figure of 14 % at the beginning, this proportion increased to 48 % at the end of 8 years.[11] So, the findings of that study also supported the presence of a relationship between neuropathy and duration of disease in diabetic children. In a study reported in 1997, Solders *et al.* determined the nerve conduction values and autonomic nerve functions of IDDM patients by following them up for a period of 10 years.[20] 164 patients with an average age of 10.7 ± 3.7 years and having their disease diagnosed newly were included in the study. The condition of the patients was checked by ENG at the beginning of the study and then on the 2nd, 5th and 10th years. During the diagnosis stage, most patients were found to have impaired nerve conduction values. This impairment, which was more manifest particularly in the sensory nerves, showed some improvement within 2 years, but in the later follow-up studies, the impairment in nerve junctions was again observed. As also supported by the study carried out by Solders *et al.* the metabolic events occurring at the beginning of diabetic neuropathy may be reversible. The sorbitol produced during the acute hyperglycemic attacks accumulates in the Schwan cells, causing edema and degeneration-regeneration cycle develops in the nerves as a result of frequent hyperglycemic attacks, the axonal degeneration produced

becomes permanent over time. As a result of chronic hyperglycemia, structural impairment of peripheral nerve occurs due to abnormal glycolosis of axonal and cell proteins, in addition to glycolysis of hemoglobin, and the endo-neural hypoxia caused by hyperglycemia inhibits axonal transport by means of the microvascular mechanisms, thereby causing axonal atrophy and the start of irreversible period of the disease.[22]

Gallai *et al* investigated the median, tibialis posterior, radial and sural nerve conduction velocities in 50 IDDM patients with an average age of 13 ± 1.3 years and average diabetes duration of 2.3 ± 1.4 years, and found no

Table 4. Relationship Between Duration of Disease, Annual Mean HbA_1C and HbA_1C on the Date of ENG, and Nerve Conduction Velocities and Neuropathy

	HbA_1C on the date of ENMG	Annual Mean HbA_1C	Duration of Disease
Neuropathy		p=0.01	p=0.0001
	Non-significant	0=0.38	r=0.56
MMvel		p=0.01	p=0.037
	Non-significant	r=–0.40	r=–0.33
MSvel			
	Non-significant	Non-significant	Non-significant
UMvel		p=0.07	
	Non-significant	r=–0.41	Non-significant
USvel		p=0.03	
	Non-significant	r=–0.34	Non-significant
PMvel	p=0.002	p=0.0001	p=0.003
	r=0.47	r=–0.61	r=–0.45
TMvel		p=0.002	p=0.0001
	Non-significant	r=–0.47	r=–0.55
SSvel		p=0.002	p=0.037
	Non-significant	r=–0.47	r=–0.33

MMvel: Median motor conduction velocity, **MSvel:** Median sensory conduction velocity, **UMvel:** Ulnar motor conduction velocity, **USvel:** Ulnar sensory conduction velocity, **PMvel:** Peroneal motor conduction velocity, **TMvel:** Tibial motor conduction velocity, **SSvel**: Sural sensory conduction velocity

Table 5. Relationship Between Duration of Disease, Annual Average HbA_1C and HbA_1C on the Date of ENG, and Distal Latency and Amplitudes of Compound Muscle Action Potential (CMAP) or Sensory Nerve Action Potential (CNAP) of nerves

	HbA_1C on the date of ENMG	Annual Average HbA_1C	Duration of Disease
MMdl	Non-significant	Non-significant	Non-significant
MMamp	Non-significant	Non-significant	Non-significant
MSdl	Non-significant	Non-significant	Non-significant
MSamp	Non-significant	Non-significant	p=0.003
			r= –0.45
UMdl	Non-significant	Non-significant	Non-significant
UMamp	Non-significant	Non-significant	Non-significant
USdl	Non-significant	p= 0.036	
		r= 0.32	Non-significant
USamp	Non-significant	Non-significant	p= 0.001
			r= –0.52
PMdl	Non-significant	p= 0.016	
		r= 0.38	Non-significant
PMamp	p= 0.044		
	r= –0.32	Non-significant	Non-significant
TMdl		p=0.045	p=0.014
	Non-significant	r= 0.32	r= –0.39
		p=0.05	
TMamp	Non-significant	p=0.31	Non-significant
SSdl	Non-significant	Non-significant	p= 0.011
			r= 0.40
SSamp	Non-significant	Non-significant	Non-significant

MMdl: distal latency of median motor, **MMamp:** amplitude of median compound motor action potential (CMAP), **MSdl:**distal latency of median sensory, **MSamp:** amplitude of Median sensory compound nerve action potential (CNAP), **MDdl:** distal latency ulnar motor, **UMamp:** amplitue of Ulnar CMAP, **PMdl:** distal latency of peroneal motor, **PMamp:** amplitude of peroneal CMAP, **TMdl :** distal latency of tibial motor, **TMamp :** amplitude of tibial CMAP, **SSdl :** distal latency of sural sensory, **SSamp:** amplitude of sural CNAP.

relationship between the duration of diabetes and nerve conduction velocities.[8] This discrepancy was explained by the short diabetes duration of the IDDM patient population selected for the study, which did not allow the verification of expected correlation.

A good control of glycemia reduces the risk of occurrence of diabetic neuropathy.[9,10,12,13,15,17,19,23,24] In the present study too, a statistically significant relationship was found between the mean HbA_1C concentration, an indicator of glycemic control, and incidence of neuropathy (p=0.01, r=0.38).

In several studies conducted,[19,25] improvement was shown to be achieved during the metabolic impairment period of neuropathy as a result of glycemic control by intensive insulin therapy, injection of multidose insulin or subcutaneous insulin infusion (insulin pump). In a follow-up study carried out by application of frequent injections according to the results of blood glucose tests performed at home, Holman showed that the condition of sensory nerve functions was better maintained after a period of 2 years, as compared to the other group. In a DCCT (Diabetes Control and Complications Trial) group study, it was shown that 1441 patients, subjected to an intensive therapy exhibited better nerve conduction, autonomic test and clinical findings after 5 years, as compared to the conventional group.[25]

Amthor *et al* published, in 1994, the results of their study in which they investigated the effect of strict glycemic control for a period of 8 years on peripheral nerve functions.[19] 45 IDDM patients ranging between 18-42 years in age were included in the study. The duration of diabetes ranged between 7-23 years. The patients were divided into groups of conventional therapy (2 times injection a day), multiple injections (4-6 times a day) and continuous insulin infusion. As compared to the conventional therapy, the therapy involving continuous subcutaneous insulin infusion was found to cause statistically significant improvement on the nerve conduction velocity of all nerves (ulnar, peroneal and tibial) studied. In the same study, the reduction in the nerve conduction velocities was shown to be more in the patients with an average HbA_1C value over 10% as compared to those with an HbA_1C value less than 10%.

In many other studies, statistically significant correlations were obtained between nerve conduction velocities and HbA_1C concentrations. A statistically significant correlation was shown to exist between sural nerve conduction velocity and HbA_1C,[8-10] between peroneal nerve conduction velocity and HbA_1C,[9,11,13] between median motor nerve conduction velocity and HbA_1C[9] and between median sensory nerve conduction velocity and HbA_1C.[11]

The findings of our study support the statistically significant negative correlations between peroneal motor, tibial motor, ulnar motor and sensory nerve conduction velocities and the mean HbA_1C value.

The statistically significant relationship (p=0.01, r=0.38) found between the annual mean HbA_1C value and neuropathy points out to the important role played by glycemic control in the development of diabetic neuropathy in children suffering DM.

We have diagnosed microproteinuria in two of our patients. These patients suffering from microproteinuria, an indicator of nephropathy, also exhibited neuropathy, and one of them arthropathy in addition. The combined presence of these 3 late complications supported the hypothesis related to the microvascular system discussed in the pathogenesis section.[26] The statistically significant relationship (p=0.002, r= 0.47) found between arthropathy and microproteinuria confirms the above argument.

In conclusion, in the present study the incidence of peripheral neuropathy in children suffering IDDM was found to be 60 %. Sixteen of the total number of 24 children suffering peripheral neuropathy had sensory and motor, 6 had motor and 2 had sensorial peripheral neuropathy. In patients with poor glycemic control, the incidence of neuropathy increases with increase in the duration of disease. Eleven of 24 (45.8 %) patients, found to exhibit neuropathy, were at the sub-clinical stage as determined by electrophysiological studies. This proportion suggests the importance of electrophysiological studies in investigating the presence of neuropathy in children with IDDM.

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