Optimal Blood Glucose Control During 18 Years Preserves Peripheral Nerve Function in Patients With 30 Years' Duration of Type 1 Diabetes

JAKOB R. LARSEN, MD[1,2]
HANS SJOHOLM, MD, PHD[3]
KRISTIAN F. HANSSEN, MD, PHD[1,4]
LEIV SANDVIK, PHD[5]
TORE J. BERG, MD, PHD[1,4]
KNUT DAHL-JORGENSEN[1,2]

OBJECTIVE — To assess the association between 18 years of mean HbA_{1c} and nerve conduction parameters of the lower limb in patients with type 1 diabetes of 30 years' duration.

RESEARCH DESIGN AND METHODS — HbA_{1c} has been examined prospectively since 1982 in a group of 39 patients with type 1 diabetes. Mean age at baseline was 25 years (range 18–40) with 12 years' disease duration. The mean age at diagnosis of diabetes was 12.5 years. Nerve function of lower limbs was assessed at baseline, after 8 years, and after 18 years.

RESULTS — A total of 23 men and 16 women were studied. Mean age was 43 years. Mean HbA_{1c} was 8.2% (range 6.6–11.3) during 18-year follow-up. Nerve conduction velocity (NCV) and nerve action potential amplitude (NAPA) at the last examination were significantly associated with mean HbA_{1c} ($P < 0.05$). From 1982 to 1999, there was a significant reduction in nerve function in patients with mean HbA_{1c} ≥8.4% (highest tertile). For example, the mean NCV in the tibial nerve was reduced from 47 to 31 m/s ($P < 0.01$). The number of nerves with NCV ($P < 0.01$) and NAPA ($P = 0.01$) reduced to below the reference level in each patient was also significantly associated to mean HbA_{1c}. No significant associations were found between nerve function parameters, sex, disease duration, blood pressure, serum cholesterol, microalbuminuria, or smoking.

CONCLUSIONS — The present study shows that mean HbA_{1c} is a strong predictor of nerve function. Mean HbA_{1c} <8.4% over 18 years was associated with near-normal nerve function.

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Diabetic polyneuropathy (DPN) is among the most common long-term complications of diabetes (1). Pathological electrophysiological nerve investigations in the lower limbs are a hallmark of DPN (2). Evaluating nerve conduction parameters in the lower limbs has been shown to be a reliable method of assessing the severity of DPN (3). The most common type of DPN is both a motor and sensory polyneuropathy but is primarily sensory. The natural history of DPN is still not well understood (4). Hyperglycemia is an important causal factor (5–9). Long-term studies of more than 10 years on the effect of chronic hyperglycemia on DPN are rare, especially in patients with intensive insulin therapy.

In this prospective study of type 1 diabetic patients undergoing intensive insulin treatment, we examined nerve conduction velocity (NCV) and nerve action potential amplitude (NAPA) in the lower limbs in 1982, 1990, and 1999. The association between mean HbA_{1c} over 18 years and nerve conduction at 18-year follow-up was studied.

RESEARCH DESIGN AND METHODS

— A total of 39 of the patients from the Oslo study of type 1 diabetes were included in the present study. The design of the Oslo study is described in detail elsewhere (8,9). At inclusion in the present study, in 1982, the patients were between 18 and 42 years of age with disease duration between 7 and 23 years. In all patients, type 1 diabetes had been diagnosed before 30 years of age. The mean age for diagnosis of diabetes was 12.5 years, and 90% cases were diagnosed before 21 years of age. At initial inclusion into the study, the patients had either minor diabetes complications or none at all. For example, six patients had one single NCV slightly below the normal range with values between 35 and 39 m/s (mean 38). There was no evidence of alcohol abuse in any patients. A general neurological examination did not reveal any clinical signs of neuropathy.

The original study included 45 patients and was designed to study the effect of intensive insulin treatment on microvascular complications. After 2 and 4 years of intensive insulin therapy with multiple insulin injections or insulin pump treatment, this therapy was shown to be superior to the traditional treatment with two injections of insulin daily in slowing down the development of microvascular late complications of diabetes (8,10). After 4 years, all patients were of-

From the [1]Diabetes Research Center, Aker and Ulleval University Hospitals, Oslo, Norway; the [2]Pediatrics Department, Ulleval University Hospital, Oslo, Norway; the [3]Neurophysiology Department, Ulleval University Hospital, Oslo, Norway; the [4]Endocrinology Department, Aker University Hospital, Oslo, Norway; and the [5]Center for Clinical Research, Ulleval University Hospital, Oslo, Norway.

Address correspondence and reprint requests to Jakob R. Larsen, MD, Departement of Pediatrics, Aker and Ullevaal Diabetes Research Center, Ullevaal University Hospital, Oslo, Norway 0407. E-mail: j.r.larsen@ioks.uio.no.

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Abbreviations: DPN, diabetic polyneuropathy; NAPA, nerve action potential amplitude; NCV, nerve conduction velocity.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

fered intensified insulin treatment. At the time of the present study, in 1999, the patients had been followed for 18 years. A total of 39 patients are still being followed and 2 patients have died, 1 of breast cancer and 1 of lung disease. Four patients have declined further participation.

Written informed consent was obtained from all participants at baseline and at the last follow-up visit. The study protocols were approved by the regional ethics committee.

Laboratory examinations

HbA_{1c} was measured prospectively by ion-exchange chromatography until 1987 and by high-performance liquid chromatography (Variant; Bio-Rad, Richmond, CA) thereafter, except for a short period with DCA 2000 (Bayer Diagnostics, Tarrytown, NY) in a few patients. The methods correlated closely ($r = 0.97$ and 0.96, respectively), and no corrections of HbA_{1c} values were considered necessary (reference values 4.1–6.4%). The intra-assay coefficient of variation was 5% for the first method and <3% for the later methods. Lipid profiles were measured by conventional methods in the fasting state, and blood pressure was measured in the sitting position after at least 15 min of rest. Information about smoking habits and use of medication was obtained through questionnaires. Urine samples (24 h) were collected and analyzed to determine urinary excretion of albumin. Microalbuminuria was defined as urinary albumin excretion >30 mg/24 h in two of three samples, and overt nephropathy was defined as albumin excretion >300 mg/24 h in two of three samples. Height and weight were measured, and BMI was calculated as body weight (kg) divided by height squared (m^2).

Neurophysiologic examinations

NCV and NAPA in the lower limbs were measured by experienced specialists in neurophysiology using the same methods. However, the long observation time made it necessary to change the registration equipment used for optimal registrations. The neurophysiologic studies at the last examination were performed with Key Point Equipment (Medtronic, Denmark). At the initial inclusion, Medelec MS 92 (Oxford Instruments Medical, Old Woking, U.K.) equipment was used and, after 8 years, measurements were performed with DISA Neuromatic electromyography equipment (Electronic, Skovlunde, Denmark). Standard recording sites and temperature control between 32 and 33°C were ensured at all occasions. Reference values are the same for the three methods. The coefficient of variation of NCV is 5–10% with all three methods. The reference values for NCV and NAPA used are based on a large number of volunteers (11). For NCV, the lowest reference value is 40 m/s (−2 SD) for all nerves, and for NAPA, the lowest reference value (−2 SD) is 5 μV for the sural nerve and 2 mV for the peroneal and tibial nerves. NCV and NAPA were analyzed for the sensory sural, motor peroneal, and motor tibial nerves. Due to the gradual disappearance of the NAPA in diabetic patients at this velocity level, NCVs below or just below 30 m/s were displayed as 0 m/s. Therefore, in such situations, NCV was scored as 15 m/s to avoid exaggeration of the glycemic effect.

Statistics

Spearman's correlation coefficient was used to analyze the association between two continuous variables. Multiple linear regression analysis was used to study the association between mean HbA_{1c} and the number of nerves with abnormal electrophysiological parameters when corrected for age and height. A significance level of 5% was used. The Statistical Package for Social Sciences software (version 10.0; SPSS, Chicago, IL) was used for all calculations.

RESULTS

A total of 39 patients with type 1 diabetes (23 men and 16 women) were studied. The mean age of the patients at the last electrophysiological examination was 43 years (range 35–58) and the mean duration of disease was 30 years (23–39). Mean HbA_{1c} over 18 years was 8.2% (6.6–11.3), with a reference value of 4.1–6.4%. Some demographic data of the participants grouped according to tertiles of HbA_{1c} are shown in Table 1.

The nerve conduction parameters at the last examination were significantly associated with mean HbA_{1c} for all nerves tested ($P < 0.05$), which was also true when corrected for age and height. Only minor changes in NCV and NAPA were seen when HbA_{1c} was <8.4%, whereas patients with HbA_{1c} ≥8.4% (highest tertile) had marked reductions of nerve conduction as shown in Table 2. In 1982, there was no significant difference between the values of NCV and NAPA between the groups of patients. From 1982 to 1999, there was a significant reduction in nerve function for HbA_{1c} ≥8.4% for all nerves (noted by an asterisk in Table 2). The number of patients with undetectable NCV in 1999 is also shown in Table 2 for each nerve and HbA_{1c} group.

The number of nerves with reduced NCV below the reference level was significantly associated with mean HbA_{1c} ($P < 0.01$), as was the NAPA ($P = 0.01$). The numbers of patients within each tertile of HbA_{1c} with 0–1 nerves or at least two nerves with results below the reference level are shown in Table 3. As shown in Table 3, 47% of the patients with HbA_{1c} ≥8.4% had at least two nerves with reduced NCV as opposed to 8 and 9% in the groups with HbA_{1c} <8.4%. For NAPA below the reference level, the frequency in those with HbA_{1c} ≥8.4% was 47% vs. 23 and 27% in the groups with HbA_{1c} <8.4%. In univariate analysis, there was a significant correlation between the number of nerves affected and HbA_{1c} ($r = 0.42$, $P < 0.01$). When adjusting for age and height (multivariate analysis), there was a significant association between the number of nerves with nerve conduction below the reference values (NAPA and/or NCV) and the mean HbA_{1c} over 18 years ($r = 0.47$, $P < 0.001$). An augmentation of mean HbA_{1c} of 1% corresponded to an increase of 0.7 in the number of nerves with values below the reference value; an augmentation of 10 years of age implied the same changes.

No association was found between NCV or NAPA and sex, duration of disease, BMI, cholesterol, smoking, blood pressure, or microalbuminuria.

CONCLUSIONS

Our study shows that long-term blood glucose concentration in patients with type 1 diabetes predicts physiological peripheral nerve function in the lower limbs. We demonstrated a significant association between mean HbA_{1c} over 18 years with NCV and NAPA. The patients with the lowest mean HbA_{1c} values had better NCV and NAPA and also had the lowest number of nerves with reduced function. In the present study, HbA_{1c} <8.4% was associated with good nerve function. Ziegler et al. (12), who followed a group of patients from diagnosis and over 14 years, found that patients with mean HbA_{1c} <8.5% had a

Table 1—*Demographic data in 1999 at 18-year follow-up in groups according to tertiles of mean HbA_{1c} over 18 years*

	HbA_{1c} ≤7.8%	HbA_{1c} >7.8 and <8.4%	HbA_{1c} ≥8.4%
n	13	11	15
Sex distribution: men/women	6/7	8/3	9/6
Age (range)	43 (35–53)	42.5 (36–58)	43 (38–53)
Duration of diabetes (years)	29.5 ± 3.5	28.4 ± 3.6	32 ± 5
HbA_{1c} over 18 years (%)	7.3 ± 0.4	8.1 ± 0.1	9.1 ± 0.9
HbA_{1c} (%)	8.0 ± 0.8	8.6 ± 1.0	9.4 ± 1.5
Systolic blood pressure (mmHg)	128 ± 12	133 ± 21	126 ± 11
Diastolic blood pressure (mmHg)	79 ± 11	85 ± 9	77 ± 8
BMI (kg/m^2)	22 ± 2	23 ± 2	23 ± 6
Total cholesterol (mmol/l)	5.4 ± 0.8	5.2 ± 0.5	5.4 ± 0.7
LDL cholesterol (mmol/l)	3.1 ± 0.9	3.1 ± 0.6	3.2 ± 0.8
HDL cholesterol (mmol/l)	2.0 ± 0.3	1.7 ± 0.3	1.6 ± 0.4
Triglycerides (mmol/l)	0.7 ± 0.2	1.0 ± 0.3	1.4 ± 1.6
Total cholesterol/HDL cholesterol ratio	2.8 ± 0.7	3.2 ± 0.7	3.5 ± 1.0
Microalbuminuria	0	1	3
Overt nephropathy	0	0	2
Current smokers	0	6	6
Patients on antihypertensive treatment	2	2	3
Patients on lipid-lowering medication	0	0	5

Data are means ± 1 SD.

decline in nerve conduction not greater than the age-related fall within the physiologic range.

It is widely accepted that chronic hyperglycemia is a causal factor in the development and progression of DPN. The present study supports this view, as did our findings after 2 and 8 years in the Oslo study (8,9). The Diabetes Control and Complications Trial had a follow-up of 6.5 years (range 3–9) and in the Stockholm Diabetes Intervention Study, follow-up was 7.5 years; both of these studies showed that intensive insulin treatment could postpone or hinder progression of diabetic microvascular complications and polyneuropathy (6,13). The important role of long-term blood glucose control (mean HbA_{1c}) was also shown by Hyllienmark et al. (14). However, they studied a relatively young group of patients, with mean age 19 years (range 10–26) and mean disease duration of 12 years (range 7–20), and the nerve conduction studies were performed twice with an interval of 4 years. Padua et al. (15) found a positive association between

Table 2—*Nerve function in 1982, 1990, and 1999 for tertiles of HbA_{1c}*

HbA_{1c} tertiles	HbA_{1c} ≤ 7.8% (*n* = 13)	HbA_{1c} 7.9%–8.3% (*n* = 11)	HbA_{1c} ≥ 8.4% (*n* = 15)
Sensory sural NCV in 1982	51 m/s (4)	49 m/s (5)	47 m/s (7)
Sensory sural NCV in 1990	45 m/s (5)	43 m/s (5)	39 m/s (7)
Sensory sural NCV in 1999	44 m/s (10)	44 m/s (11)	34 m/s (15)†
Number of patients with undetectable sural NCV in 1999	1	1	5
Sensory sural NAPA in 1982	7.7 μV (5)	8.3 μV (3)	7.5 μV (3)
Sensory sural NAPA in 1990	8.3 μV (4)	6.7 μV (2)	5.9 μV (4)
Sensory sural NAPA in 1999	9.8 μV (9)	4.8 μV (4)*	3.4 μV (4)†
Motor tibial NCV in 1982	48 m/s (5)	46 m/s (5)	47 m/s (7)
Motor tibial NCV in 1990	42 m/s (3)	43 m/s (4)	38 m/s (5)
Motor tibial NCV in 1999	43 m/s (6)*	43 m/s (4)	31 m/s (11)†
Number of patients with undetectable tibial NCV in 1999	0	0	4
Tibial NAPA in 1999	4.9 mV (3)	4.9 mV (2)	2.6 mV
Motor peroneal NCV in 1982	44 m/s (4)	46 m/s (4)	41 m/s (4)
Motor peroneal NCV in 1990	42 m/s (2)	44 m/s (4)	38 m/s (5)
Motor peroneal NCV in 1999	41 m/s (4)	42 m/s (4)	35 m/s (8)*
Number of patients with undetectable peroneal NCV in 1999	0	0	1
NAPA peroneal nerve in 1999	2.7 mV (1)	2.9 mV (1)	1.7 mV (1)

Data are means ± 1 SD. *$P < 0.05$; †$P < 0.01$.

Table 3—*Number of patients with none or one nerve with NCVs under the lower limit of the reference value and two or more nerves with NCVs under the lower limit of the reference value with patients grouped according to tertiles of mean HbA_{1c} over 18 years*

NCV:

Tertiles for HbA_{1c}	None or one nerve below references for NCV(a)	Minimum two nerves below references for NCV
$HbA_{1c} < 7.8\%$ ($n = 13$)	12 (92%)	1 (8%)
HbA_{1c} 7.9–8.4% ($n = 11$)	10 (91%)	1 (9%)
$HbA_{1c} \geq 8.4\%$ ($n = 15$)	8 (53%)	7 (47%)

NAPA:

Tertiles for HbA_{1c}	None or one nerve below references for NAPA(b)	Minimum two nerves below references for NAPA
$HbA_{1c} < 7.8\%$ ($n = 13$)	10 (77%)	3 (23%)
HbA_{1c} 7.9–8.4% ($n = 11$)	8 (73%)	3 (27%)
$HbA_{1c} \geq 8.4\%$ ($n = 15$)	8 (53%)	7 (47%)

Data are *n* (%).

HbA_{1c} over 2 years in a group of patients about the same age as ours but with 16-year duration of diabetes. In the present study, in patients having used intensive insulin therapy for 14–18 years, with disease duration of 30 years and mean age at diagnosis of 12.5 years, we demonstrated a protective effect of good blood glucose control over 18 years.

In our calculations, we used 15 m/s instead of 0 m/s for the patients with NCV registered as 0 m/s because, for this type of patient, the true value probably lies between the detection limit (~30 m/s) and 0 m/s. If we had used 0, the differences between the groups would have been greater, but this way of analyzing reduces the possibility of overestimating the effect of HbA_{1c}. Tkac et al. (16) showed an association between metabolic control and nerve conduction when studying a group of patients with mild neuropathy (they excluded patients with unobtainable NCV).

Electrophysiologic studies of peripheral nerve function are considered reproducible and reliable (17). The present results are very consistent and strongly show the importance of long-term hyperglycemia in the development of peripheral nerve damage in type 1 diabetes. We could not show any associations with duration of disease, sex, or other known risk factors such as hypertension, cholesterol, microalbuminuria, or smoking (18). This might be due to the small size of our study group. It could also be related to the selection criteria used in 1982, excluding patients with clinical DPN at baseline even after 7–23 years' duration of diabetes. It has been suggested that vascular risk factors for development of DPN are most important at an early stage or at a very late stage after diagnosis (19).

This small but long-lasting study of a small number of patients shows that mean HbA_{1c} is a strong predictor of nerve function. Even after 30 years of diabetes duration, most of the patients who managed to have good HbA_{1c} values during our 18-year study kept physiologic nerve conduction values.

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