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ORIGINAL ARTICLE

Current glycaemic control has no impact on the advancement of diabetic neuropathy

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Abstract

The aim of the study was to assess the association between glycemic control understanding as a glycated haemoglobin level and indices of diabetic neuropathy.

Methods: We evaluated 204 patients with diabetes (type 1 – 29; type 2 – 175). Glycated haemoglobin was determined using The Diabetes Control and Complications Trial/ National Glycohemoglobin Standardization Program method. Evaluation of complaints from the lower extremities was based on the Neuropathy Syndrome Total Score questionnaire. We used a monofilament for evaluation of touch sensation (Semmes-Weinstein 5.07-10 g), a 128 Hz calibrated tune-fork for the vibration perception test, Tip-Therm to assess temperature sensation.

Results: The mean glycated haemoglobin level was assessed on 8.53±1.87%. The mean Neuropathy Syndrome Total Score: 11.45±6.37. Decreased sensation of touch on both sides was determined in 30% of cases, decreased sensation of temperature in 59% and decreased sensation of vibration in 30%. For Neuropathy Syndrome Total Score and glycated haemoglobin the Pearson's correlation test was 0.00910 ($p \approx 0.99$), Spearman's rank correlation test was 0.00523 ($p \approx 0.95$). Persons with sensation deficits and neuropathy symptoms had not significantly higher (Neuropathy Syndrome Total Score, temperature sensation disturbances) and not significantly lower (vibration and touch) glycated haemoglobin level compared to patients without neuropathy.

Conclusion: There is no correlation between prevalence and advancement of sensorial neuropathy and current diabetes control in patients with long–term established diabetes.

Key words

diabetic neuropathy, glycemic control, glycated haemoglobin, diabetes complications, long term diabetes

INTRODUCTION

Diabetic neuropathy is one of the most common and devastating complication of diabetes mellitus (DM). Approximately 10-50% of diabetic patients have some degree of diabetic neuropathy [1], independent of the type of DM (45% with type 2 and 54% with type 1, according to the Rochester Diabetic Neuropathy Study) [2]. In a UK community-based population, Abott established that 1/3 of patients suffered from painful neuropathic symptoms [3]. Despite the lower quality of life among diabetic patients with neuropathic pain, even 40% of them are not receiving proper treatment [4].

Approximately 15% of patients with DM develop foot ulcer during their lifetime [5], of which 70% have a neuropathic origin [6]. Screening of patients with neuropathic pain and its treatment is a first line prevention of diabetic foot ulcers [7].

The formation of an ulcer is the point from which begins the pathway to potential amputation and death. The risk of a leg amputation is 15-40 times greater in patients with DM than in the general population [8], and according to USA data, 50% of amputees will die within five years of amputation [9].

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The results of DCCT, EDIC/DCCT, UKPDS [10, 11, 12, 13] proved that decrease of the glycated haemoglobin level (HbA1c) lowers the incidence of diabetic neuropathy, or a slowdown in the progression of diabetic neuropathy; therefore, the recommendations of the Diabetic Foot European Group, American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) place a large emphasis on glycaemic control as a main element of neuropathy treatment.

The aim of the presented study was to assess the association between glycaemic control, understood as HbA1c and indices of the diabetic peripheral, and sensorial neuropathy in patients hospitalized in a Diabetology Ward due to chronic hyperglycaemia.

Patients and Methods. A total of 204 patients with DM admitted to Diabetology Ward at the Institute of Rural Health in Lublin between 14 December 2009 – 9 February 2011 were examined. The patients were admitted due to hyperglycaemia, which is difficult to control in ambulatory conditions. A fresh diagnosis of DM was an exclusion criteria.

Sensory symptoms were assessed according to the Neuropathy Total Syndrome Score (NTSS) questionnaire [14]. Numbness, prickling, sensation, aching pain, burning pain, lancinating pain and allodynia were evaluated.

A monofilament (Semmes-Weinstein 5.07-10 g) was used to assess the sensation of touch (clinical important deficits if less than 8 (+) for 10 points), Tip-Therm to assess temperature sensation (clinical important deficits if less than 8 (+) for 10 points), and a 128 Hz tuning fork (Rydel-Seiffer tuning fork) to assess perception of vibration (clinical important deficits if less than 6 (+) for 8 points in subjects under 40 years of age, and less than 5 (+) for 8 points in subjects aged 40 and over).

HbA1c was determined at the admission to hospital. The measurements were performed by accredited laboratory using DCCT/NGSP method, which is one of the recommended methods [15]. The test incorporates a latex-enhanced competitive turbidimetric immunoassay, which determines HbA1c concentration with a colorimetric quantification of total haemoglobin.

The analyse of coincidence between the degree of complaints intensity and the different HbA1c level groups was performed in general population and in groups dependent to HbA1c level. Group A: HbA1c <7.5%, B: ≥ 7.5% and <8.5%, C: ≥ 8.5% and <9.5% and D: ≥ 9.5%.

Statistical analysis was performed using STATISTICA 8.1 Stat-Soft package. Descriptive statistics of analysed continuous variables includes: average, median, standard deviation and range (maximum and minimum). Variables distribution was tested by normality Lillefors statistics. Non-parametric Mann-Whitney statistics were used to test the difference of continuous variable value between discrete variable categories; chi-square exact test was used to analyse distribution difference in two-way tables for comparison of two discrete variables. Parametric Pearson correlation and non-parametric Spearman correlation, respectively, were used to test two continuous variables coincidence, and with variable value prediction in the linear regression model.

RESULTS

There were no statistically significant differences of HbA1c, NTSS, and sensation disturbances in both DM types, it was therefore decided to analyse these two groups of patients together, despite the age disparity.

Characteristic of the examined population is presented in Table 1. Descriptive statistics of NTSS results and HbA1c value are shown in Table 2. Clinically important deficits of vibration threshold measurements, touch and temperature sensation, are presented in Table 3. Decreased sensation of touch on both sides was determined in 30% of cases,

Table 1. Characteristics of studied population: gender, age and type of diabetes

		Females	Males	Total
Type 1	n	14	15	29
	%	48.28	51.72	14.22
Type 2	n	73	102	175
	%	41.71	58.29	85.78
All	n	87	117	204
	%	42.65	57.35	100.00
mean age (years)			All	59.2±11.7
mean BMI (kg/m^2)			All	32.0±6.9
mean DM duration (years)			All	14.6±10.4

Table 2. Descriptive statistics of NTSS and HbA1c levels

		N	Mean	Median	Min.	Max.	SD	p
HbA1c	Type 1	29	8.80	8.62	4.71	12.07	1.60	0.07
	Type 2	175	8.48	8.18	5.47	16.50	1.91	
	All	204	8.53	8.30	4.71	16.50	1.87	
NTSS	Type 1	29	10.81	12.00	0.00	18.99	5.67	0.5
	Type 2	175	11.56	12.66	0.00	21.96	6.49	
	All	204	11.45	12.00	0.00	21.96	6.37	

Table 3. Deficits of vibration, temperature, touch sensation and type of diabetes

sensation disturbances		type 1	type 2	total	P
vibration	n	5	57	62	0.10
	%	17.24	32.57	30.39	
temperature	n	14	106	120	0.21
	%	48.28	60.57	58.82	
touch	n	6	55	61	0.24
	%	20.69	31.43	29.90	
Total	n	14	113	127	0.09
	%	48.28	64.57	62.25	

decreased sensation of temperature in 59% and decreased sensation of vibration in 30%. 21 (10%) of the examined patients had foot ulcers and 9 (4%) had Charcot arthropathy. There were no significant differences in prevalence of sensation disturbances in the examined groups (Fig. 1-3),

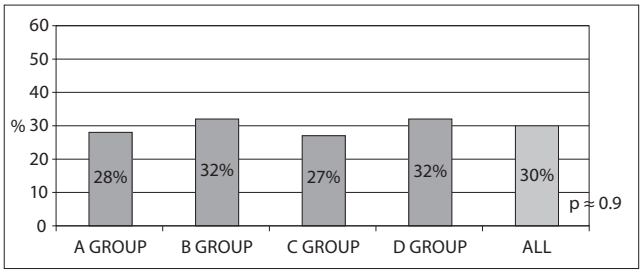

Figure 1. Prevalence of touch sensation disturbances in study groups

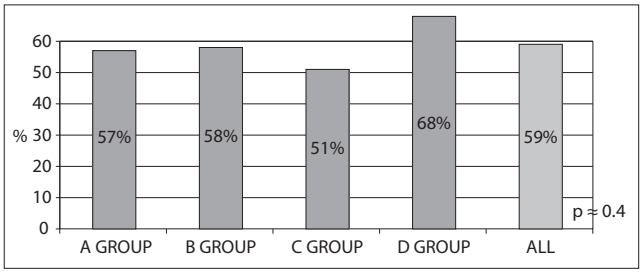

Figure 2. Prevalence of temperature sensation disturbances in study groups

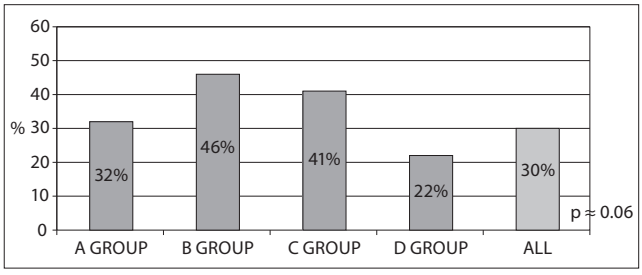

Figure 3. Prevalence of vibration disturbances in study groups

but vibration sensation disturbances were found more often in group B and less often in group D. Decreased temperature sensation was most often in all groups (Fig. 4).

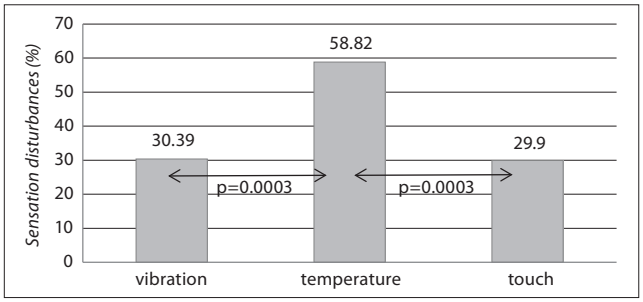

Figure 4. Different types of sensation disturbances in study sample

First, the bivariate relationships between HbA1c level and other variables (NTSS count, touch, vibration and temperature senses) were examined. The absence of significance relationships is shown in Table 4, and the NTSS vs HbA1c scatter plot in Figure 5. There were also no significant parameters in multivariate linear regression analysis that was performed next. For NTSS and HbA1c levels, the Pearson's correlation test was 0.00910 (p≈0.99) and Spearman's rank correlation test – 0.00523 (p≈0.94).

Table 4. Deficits of vibration, temperature, touch sensation and level of HbA1c

sensation disturbances		N	mean	median	SD	p
vibration	absent	142	8.65	8.35	2.05	0.38
	present	62	8.25	8.19	1.32	
temperature	absent	84	8.51	8.14	1.93	0.54
	present	120	8.54	8.35	1.83	
touch	absent	143	8.54	8.30	1.89	0.91
	present	61	8.51	8.30	1.83	
Total	absent	77	8.57	8.20	1.99	0.79
	present	127	8.51	8.30	1.80	

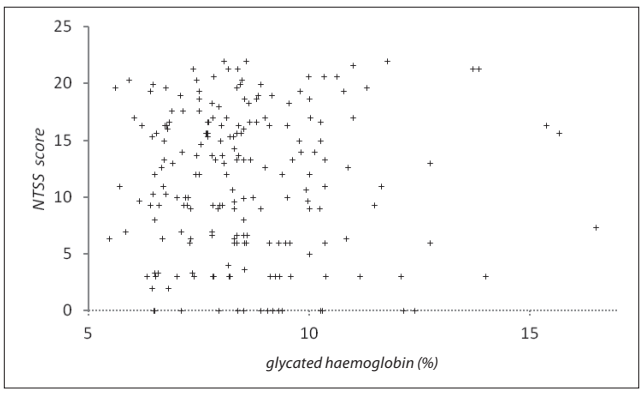

Figure 5. Scatterplot of NTSS score vs. glycated haemoglobin level

Persons with sensation deficits and neuropathy symptoms have HbA1c levels that are a little different, both higher (NTSS, temperature, all sensation disturbances together) and lower (vibration and touch sensations), but the differences were extremely small (maximum 0.2% of glycated haemoglobin). This means that 5% HbA1c increase (for instance from 6.1% to 11.1%) is related to only 0.15 point higher NTSS.

DISCUSSION

Symptoms of symmetric, distal, sensorial neuropathy were found in about 30% of the examined subjects. The results of NTSS questionnaire (mean score – 11.5) showed the symptoms were severe, with longer DM duration that in some other neuropathic studies (ALADIN study: 11.1-12.3 years) [16] and similar glycemic control (ALADIN HbA1c: 8.8-9.4%). The intensity of symptoms were difficult to compare to other studies dealing with neuropatic patient with long duration of diabetes since ALADIN and SYDNEY 2 studies used TSS with 4 point scale [16, 17] (SYDNEY 2 TSS: 9.02-9.40, ALADIN TSS score: 5.0-5.3). The duration of DM was similar in SYDNEY 2 (14-15 years), but glycemic control was better (SYDNEY 2 HbA1c: 7.53%-7.81%)[17].

HbA1c level analysed in groups had no impact on any neuropathy parameters; it can therefore be assumed that current glycaemic control has no affect on the presence of sensation disturbances and intensity of ailments assessed with NTSS questionnaire. This does not mean that proper glycaemic control has no effect on the development of chronic DM complications. Otherwise, it is very important.

There some reports confirming that in advanced stages of peripheral neuropathy, a long period of near normal glycaemic control – even for years – may slow down the progression of nerve dysfunction [12, 18, 19].

The benefits of early intervention are very well documented, both in type 1 and type 2 DM. Both DCCT (Diabetes Control and Complications Trial) and EDIC/DCCT (Epidemiology of Diabetes Interventions and Complications Trial) with type 1 DM patients [10, 12] and UKPDS (United Kingdom Diabetes Study) with type 2 DM patients [13] showed a statistically important lower prevalence of microvascular complications among intensively-treated patients with near normal glycaemia in early type 2 DM [13] or in long-term established type 1 DM with moderately low HbA1c (7.3% at the beginning and 7.8% at the end) [11, 12]. Even as in the case of DCCT [10], HbA1c was high (9.1%), but the DM duration was short (6 years). In the presented study, the mean duration of DM was longer (14.6 years) and HbA1c was higher (8.8% in type 1 and 8.5% in type 2).

The vision of reduction of neuropathy cases due to proper glycaemic control is unfortunately far from reality. Instead of reduction of diabetic neuropathy we should rather talk about slowing down the progression, but even this statement could sometimes be questioned. The prevalence of clinical neuropathy increased during 6.5 years of DCCT from 5% to 17% in conventional treatment groups, and from 7% to 9% in intensive treatment groups ($p<0.01$) [20]. In 13-14 years of follow-up normoglycaemia has still proved to be beneficial – the prevalence of diabetic neuropathy increased to 35% in former conventional treatment groups, and to 25% in former intensive treatment groups ($p<0.01$) [12]. At EDIC year 8 the difference in the prevalence of neuropathy persisted, despite a narrowing of prior glycaemic separation [21].

UKPDS showed that many of the newly-detected type 2 DM (36% of men and 21% of women), already have evidence of neuropathy. At 12 years from DM diagnosis, 71% of men and 51% of women have clinically significant neuropathy, and 64% of men and 44% of women free of neuropathy at baseline were found to be positive for at least one of these indices. HbA1c was a weaker risk factor for neuropathy

prevalence at diagnosis and incidence by 12 years than height and smoking habit [22].

In the case of the Kumamoto Study, improvement was observed only in the multiple insulin injection group, but only in nerve conduction velocity. The vibration thresholds in the multiple injection treatment group showed a slight, but not significant increase after 6 years, while those in the conventional insulin treatment group significantly increased after 6 years. Additionally, only when both cohorts (primary and secondary) were combined, the shortened DM duration was approximately 8.2 years. In a secondary cohort, quite similar to our group in DM duration (about 10.2 years), the level of glycaemia was 9.0 in the intensive insulin treatment group and 9.4 in the conventional insulin treatment group) [23]. Therefore, in the case of long-term established diabetes with a high elevation of HbA1c, it can only be hoped that intensification of antyhyperglycemic treatment will have positive influence on our patient neuropathy (both existing or to be developed). The question has to be asked, 'what method of treatment – intensification of hyperglycaemia treatment or different measures (such as off –loading) should be cost-effective in the treatment of diabetic neuropathy?'

Admittedly, the presented study has several weaknesses. It was not a randomised study, and deals with a special group of patients (hospitalised due to hyperglycaemia); therefore, the findings cannot be generalised. The results obviously need further clarification in a randomised study, and if possible, in a multicentre study. However, the lessons from the ACCORD [24] and VADT [25] studies which proved that patients with type 2 DM are not a homogenic group, and that sometimes the reduction of HbA1c does not work in the way we would like to work according to diabetological standards.

CONCLUSIONS

There was no correlation between the prevalence and severity of peripheral, sensorial neuropathy and current diabetes control evaluated as the level of HbA1c in patients with long-term established diabetes.

REFERENCES

1. Nicolucci A, Carinci F, Cavaliere D, Scorpiglione N, Belfiglio M, Labbrozzi D, et al. A meta-analysis of trials on aldose reductase inhibitors in diabetic peripheral neuropathy. The Italian Study Group. The St. Vincent Declaration. Diabet Med. 1996; 13: 1017-1026.
2. Dyck PJ, Kratz KM, Karnes JL, Litchy WJ, Klein R, Pach JM, 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.
3. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 2011; 34: 2220-2224.
4. Daousi C, MacFarlane IA, Woodward A, Nurmikko TJ, Bundred PE, Benbow SJ. Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. Diabet Med. 2004; 21: 976-982.
5. Boulton, AJ. The diabetic foot: a global view. Diabetes Metab Res Rev. 2000; 16 (suppl.1): 2–5.
6. Gonzalez, ER, Oley MA. The management of lower-extremity diabetic ulcers. Manag. Care Interface 2000; 13: 80-87.
7. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA 2005; 2: 217-228.
8. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. Diabetes Care 1990; 13: 513-521.
9. Kulkarni J, Pande S, Morris J. Survival rates in dysvascular lower limb amputees. Int J Surg. 2006; 4: 217-221.
10. DCCT Research Group. The effects of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med. 1993; 329: 977-986.
11. DCCT/EDIC Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002; 287, 2563-2569.
12. Albers JW, Herman WH, Pop-Busui R, Feldman EL, Martin CL, Cleary PA, et al. Effects of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Diabetes Care 2010; 33: 1090-1096.
13. Stratton IM, Adler AI, Neil AW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321: 405-412.
14. Bastyr, EJ 3rd, Price KL, Bril V; MBBQ Study Group. Development and validity testing of the Neuropathy Total Symptom Score-6: questionnaire for the study of sensory symptoms of diabetic peripheral neuropathy. Clin Ther. 2005; 27: 1278–1294.
15. Charuruks N, Milintagas A, Watanaboonyoungcharoen P, Ariyaboonsiri C. Determination of reference intervals of HbA1C (DCCT/NGSP) and HbA1C (IFCC) in adults. J Med Assoc Thai. 2005; 88: 810-816.
16. Ziegler D, Hanefeld M, Ruhnau KJ, Meissner HP, Lobisch M, Schütte K, Gries FA. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoidic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). Diabetologia 1995; 38: 1425-1433.
17. Ametov AS, Barinov A, Dyck PJ, Hermann R, Kozlova N, Litchy WJ; SYDNEY Trial Study Group. The sensory symptoms of diabetic polyneuropathy are improved with α-lipoic acid: the SYDNEY trial. Diabetes Care 2003; 26: 770-776.
18. Ziegler D, Dannehl K, Wiefels K, Gries FA. Differential effects of near-normoglycaemia for 4 years on somatic nerve dysfunction and heart rate variation in type 1 diabetic patients. Diabet Med. 1992; 9: 622-629.
19. Pisarczyk-Wiza D, Zozulińska-Ziółkiewicz D, Wysocki H, Wierusz-Wysocka B. Increase in glycaemia stimulates reactive oxygen species (ROS) production by polymorphonuclear neutrophils in type 2 diabetic patients. J Pre-Ciln Clin Res. 2011; 5(1):22-27
20. DCCT Research Group. Effects of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. Ann Neurol. 1995; 38: 869-880.
21. Martin CL, Albers J, Herman WH, Cleary P, Waberski B, Greene DA, et al. Neuropathy among the diabetes control and complications trial cohort 8 years after trial completion. Diabetes Care 2006; 29: 340-344.
22. Stratton IM, Holman RR, Bulton AJM. Risk factors for neuropathy in UKPDS. Diabetologia 2004; 47, suppl 1: 47.
23. Ocubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Matoyoshi S. et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6 year study. Diabetes Res Clin Pract. 1995; 28: 103-117.
24. The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. N Engl J Med. 2008; 358: 2545-2559.
25. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. N Engl J Med. 2009; 360: 129-139.