Functional Predictors of Treatment Induced Diabetic Neuropathy (TIND): a Prospective Pilot Study Using Clinical and Neurophysiological Functional Tests

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Research Article

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Abstract

Background: A sudden drop of HbA1c has been linked to TIND.

Method: From 60 recruited patients with severe diabetes only 21 patients adhered to the study protocol over one year with autonomic nervous system tests before and after antidiabetic treatment initiation.

Results: With a pronounced drop of HbA1c some parameters tended to deteriorate with later improvement.

Conclusion: Poor adherence appears as major obstacle in this type of study.

Trial registration: Ethic Committee University of Leipzig 439/15-ek. Registered 22 April 2016

Background:

Treatment-induced neuropathy of diabetes (TIND) is a subacute type of diabetic neuropathy affecting small peripheral nerve fibers.[1,2] It is characterized by acute neuropathic pain and autonomic dysfunction starting within 8 weeks of therapy initiation[3,4] and concomitant rapid decrease in HbA1c of more than 2 percent points over 3 months.[2,5–7] In a retrospective study with a 5-year observation period, Gibbons and Freeman (2015) found that 11% of patients with diabetes developed TIND.[5] The importance of a fast decline in HbA1c as a pathogenic factor in TIND manifestation has been further supported by a rodent diabetes model.[8]

Prospective studies investigating potential predictive autonomic nervous system (ANS) factors for developing TIND are in need. We, therefore, initiated a single center, prospective pilot study in patients with diabetes and baseline HbA1c levels above 8.5%. At baseline and after receiving adequate treatments over a period of 1 year, we aimed to detect neural abnormalities predicting the risk for TIND utilizing non-invasive neurophysiological functional tests.

Patients And Methods:

Sixty patients (23 women, 37 men), diagnosed with diabetes mellitus type 1/2 and HbA1c values higher than 8.5%, were screened. Out of these, 21 patients (16 men, 5 women) agreed to be repeatedly examined over a period of one year. Clinical and neurophysiological examinations were planned for all patients at baseline (T0) and after 3 (T1), 6 (T2), and 12 months (T3). We conducted the following non-invasive neurophysiological functional tests: cardiovascular autonomic reflex tests (30:15-ratio, Valsalva-ratio, E/I-ratio), sympathetic skin responses (SSR), pupillography (pupil diameter in darkness, PDD), thermography (cold/warm perception threshold, CPT/WPT), quantitative sudorimotor axon reflex tests (QSART), in addition to blood analyses (e.g., HbA1c)[3]. The study protocol was approved by the Ethics Committee (No. 241-2009-0911209). All participants gave written informed consent. The differences between the HbA1c values and the differences of the neurophysiological tests between T0 and T1 were calculated and used

for Pearson's correlation analysis. Patients were grouped according to the treatment-related reduction of HbA1c. Group A consisted of patients whose HbA1c dropped by 2 percent points or more and group B dropped less than 2 percent points. We expected deterioration in neurophysiological test results at T1 as compared to T0, with further deterioration during the subsequent course.

Results:

Twenty-one of the 60 patients agreed to participate over 1 year und recieved a full battery of tests while receiving effective antidiabetic medication and dietary recommendations. In the 13 patients of group A, mean reduction in HbA1c from T0 at T1 was 4.8 percent points (p = 0.001). Of, these, only one patient suffered from neuropathic pain at T1, which later regressed. In the 8 patients of group B mean reduction of HbA1c was 0.13 percent points (p = 0,53) suggesting insufficient antidiabetic treatment adaptation or poor treatment adherence (Table 1).

While values of functional tests were similar at baseline (T0) in both groups, group A tended to display abnormal test results in 30:15 ratio, E/I-ratio, CPT at T1, followed by subsequent improvement. In contrast, in group B test results gradually deteriorated over 1 year. The course of the 30:15 ratio over 1 year is shown as an example in the figure.

Discussion:

Our study aimed at testing the hypothesis that a rapid reduction of HbA1c after anti-diabetic treatment initiation in patients with severe diabetes (HbA1c > 8.5%) may be associated with induction of neuropathy (TIND). Neurophysiological clinical tests performed over one year did not reveal distinctive patterns of abnormality in groups stratified by their HbA1c response to treatment initiation. However, the high drop-out rate and low adherence to the study meant that we were unable to obtain a sufficient number of observations to formally confirm or refute our hypothesis.

The observations in Group A patients are consistent with involvement of parasympathetic and sympathetic C- and A-delta fibres as a potential indicator of treatment-related small fiber neuropathy.[1] Only one patient of group A developed a painful clinical episode over the first 3 months as an indicator of mild TIND.

This futile pilot trial underscores the problem of poor adherence and treatment compliance in patients with very high HbA1c values.[9] Moreover, reduced adherence to prescribed medication may also be associated with poor motivation to follow the test protocol which involved a number of visits.

Conclusions:

In conclusion, our study failed to define ANS (autonomic nervous system) predictors for TIND in patients with type 1 and type 2 diabetes because of the inability to recruit and motivate participants. Given the observed standard deviation of 0.16[10] at T1 in our present pooled data, a future TIND trial would need to

enroll about 500 patients to detect this MCID (minimal clinically important difference) at a power of 80%. Therefore, a multi-center design effort is encouraged for achieving a high number of patients.

Declarations:

Ethics approval and consent to participate: The study protocol was approved by the Ethics Committee of University Leipzig (No. 241-2009-0911209). All participants gave written informed consent.

Consent for publication: Not applicable

Availability of data and materials: The datasets generated during the current study are not publicly available due privacy but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: PB analyzed and interpreted the patient data regarding the research question. YH performed the clinical investigations and was instrumental in writing the manuscript. KVT further adapted the manuscript for publication. All authors read and approved the final manuscript.

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Tables:

Table 1

Baseline characteristics

	All patients (n = 21)	**Group A (n = 13)**	**Group B (n = 8)**	**p value**
Male sex	16 (73%)	10 (77%)	6 (67%)	0.6*
Age (years)	49.9 ± 3.7	50.5 ± 3.9	49.1 ± 7.2	1*
HbA1c (%) at T0	10.5 ± 1.7	11.2 ± 1.6	9.4 ± 1	**0.03***
HbA1c (%) at T1	7.4 ± 0.4	6.4 ± 0.3	9.2 ± 1.1	**0.01***
difference T0 - T1	3 ± 2.9	4.8 ± 3	0.1 ± 1.1	**< 0.001***

*: comparisons between group A and B. p value calculated according to Mann-Withney -U-Test.

Table 2
Electrophysical parameters of group A and B and correlation analysis of all participants

	T0	T1	p value	T3	p value
30:15 ratio	1 ± 0.12	0.95 ± 0.1	0.12	1 ± 0.13	0.62
	(1.1 ± 0.3)	(1 ± 0.2)	(0.8)	0.9 ± 0.2	(0.3)
E/I ratio	2.91 ± 2.7	2 ± 0.9	0.18***	2.4 ± 0.9	0.65
	(2.6 ± 1)	(2.6 ± 0.7	(0.8)	2.7 ± 1	(0.3)
PDD (mm)	5.6 ± 0.5	5 ± 1.3	**0.02**	5.4 ± 1	0.3
	(5.4 ± 1.7)	(5.3 ± 1.5	(0.6)	(5.4 ± 1.5)	(0.6)
CPT (°C)	27.3 ± 3	25.1 ± 5.9	0.1***	26.2 ± 4.5	0.4***
	(22 ± 9)	(24 ± 3.2)	(0.4***)	(20 ± 10)	(0.6***)
NES	2.8 ± 2.3	1.2 ± 1.3	0.04	1.8 ± 1.9	0.2
	(4.1 ± 4)	(2.4 ± 2.3)	(0.2)	(3.1 ± 2.9)	(0.7)
NSS	4 ± 5	3.2 ± 5	0.3	4.8 ± 8	0.5
	(4.5 ± 5)	(10.9 ± 11)	(0.08)	(11.2 ± 15)	(0.2)
Correlation analysis					
Difference between T0 and T1		Pearson correlation coefficient		p value	
30:15 ratio		0,121		0,6	
Valsalva ratio		0,02		0,94	
E/I ratio		0,4		0,08	
PDD		0,2		0,45	
CPT		0,21		0,37	
WPT		0,06		0,81	
Latency of SSR right hand		-0,16		0,5	
Sweat rate		-0,034		0,9	

**: comparisons between T0 and T3.

p-value according to Wilcoxon-test, ***: t-test

Figures

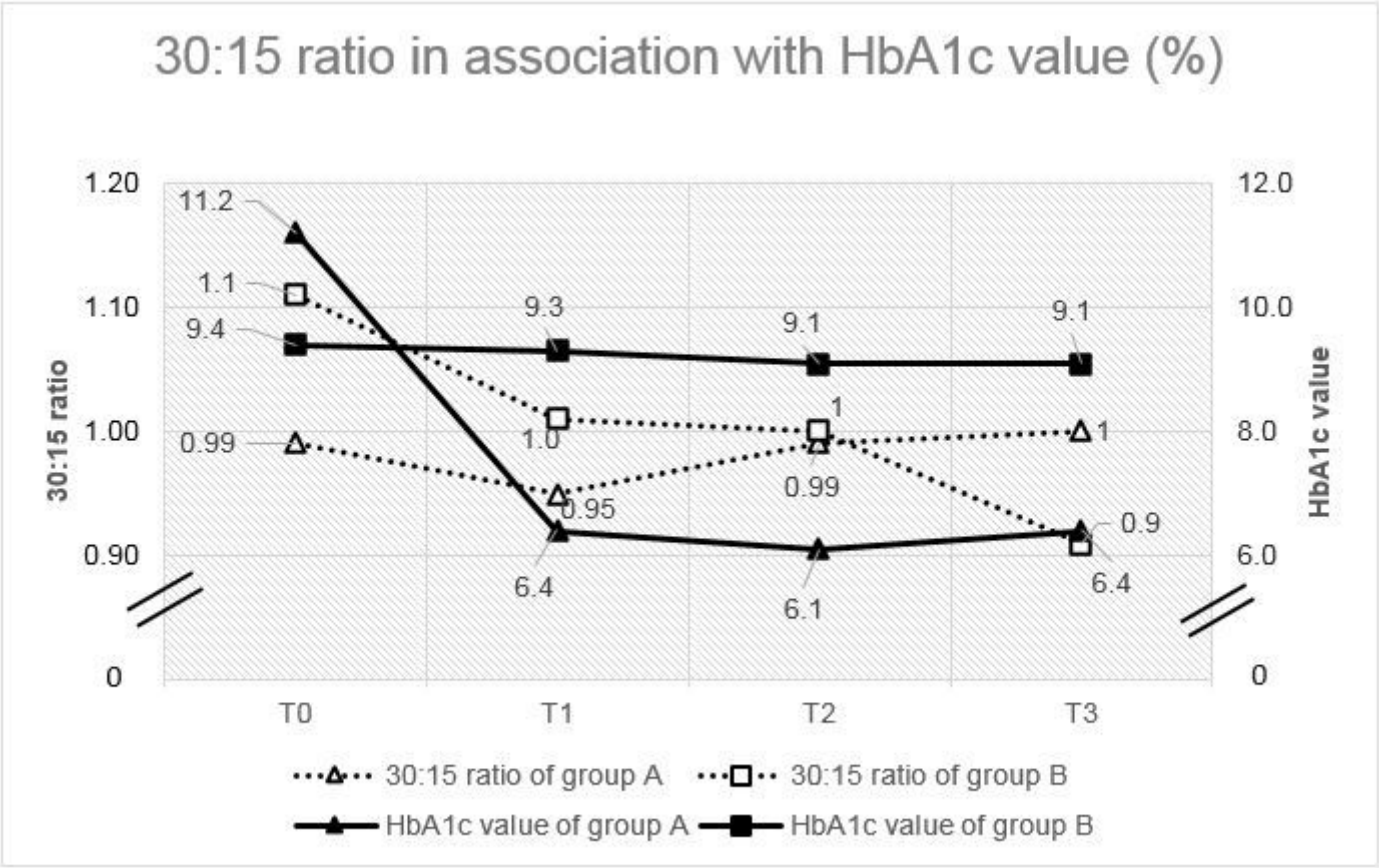

Figure 1

30:15 ratio of group A and B over one year: Group A: HbA1c values improved by 4.8 percentage points at T1 and leveled off at around 6.3% during the course. 30:15 ratios tended to deteriorate after 3 months (T1) and subsequently improved over the following 9 months. Group B: HbA1c values exceeded those of group A at all time points after treatment initiation. 30:15 ratios deteriorated continuously over a year.