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Long-Term Follow-up of the Autonomic Function Among Patients with Type 1 Diabetes Treated with Insulin Pump

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Introduction

Autonomic neuropathy (AN) is an independent risk factor for mortality in type 1 diabetes, particularly explained by the relatively increased activity of the sympathetic nervous system due to an attenuated parasympathetic function [Spallone 2011]. Further etiological factors of the poor life expectancy in patients with AN are the impaired cardiovascular adaptation, the development of diastolic dysfunction and the increased rate of arrhythmias that may be associated with sudden cardiac death or respiratory arrest [Spallone 2019]. As AN is a critical determinant of the cardiovascular integrity, it is mandatory to apply all possible therapeutic options to prevent the development or to reduce the progression of this diabetic complication.

In type 1 diabetes, one of the most important tools to achieve these aims is to keep the glycaemic control strictly in the target range. It is a well-known fact, that there is an association between long-term glycaemic control and the prevalence of neuropathy, as it was shown in several previous studies including large numbers of patients. Pirart's early results in the 25-year long follow-up of 4 400 patients showed that the incidence of neuropathy depends on the quality of metabolic control and the duration of diabetes [Pirart 1978]. At the closeout of the Diabetes Control and Complications Trial (DCCT) after 6.5 years of follow-up of 1 441 patients, the investigators reported that intensive insulin treatment significantly reduced the incidence of diabetic neuropathy, similarly to findings for diabetic retinopathy and nephropathy [The Diabetes Control and Complications Trial Research Group 1998]. By the end of the DCCT the prevalence of AN remained the same in the intensively treated group, while it almost doubled in participants on conservative treatment. The progression of AN was reduced by 45 % with intensive treatment compared to the conventionally treated group during the course of the DCCT [The Diabetes Control and Complications Trial Research Group 1998]. The observational Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up was established to monitor the long-term effects of the prior intensive treatment in the DCCT cohort on the development and progression of neuropathy. All of the study participants in EDIC were advised to follow intensive treatment regimens after the conclusion of the DCCT. At 13 – 14 years of EDIC the groups receiving previous intensive or conservative insulin treatment differed primarily in their R-R variation to deep breathing. This cardiovascular test remained significantly higher in the group with intensive treatment in the original DCCT, compared with the group applying conservative treatment in that period of the trial. The R-R variation to deep breathing is a sensitive marker of the parasympathetic function and becomes abnormal early during the progression of AN. This observation underlines the importance of the role of the early glycaemic control in the long-term progression of AN and provides evidence for the dominance of the parasympathetic impairment in the initial phase of AN [Martin 2014]. The EURODIAB IDDM Complications Study identified a number of risk factors for AN in type 1 diabetes, including long-term glycaemic control and duration of diabetes [Kempler 2002]. A meta-analysis of 17 randomized trials revealed, as part of the Cochrane database, that effective glucose control significantly prevented the development of clinical neuropathy in type 1 diabetes mellitus, whereas this association in type 2 diabetes is less evident [Callaghan 2012].

There is no doubt that the long-term glycaemic control plays an important role in the development of neuropathy in type 1 diabetes, but some remark-

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able observations in small numbers of patients suggest that even short-term changes of glucose levels may also affect the nervous system function in both types of diabetes or even in healthy subjects. Eight months after starting subcutaneous pump therapy, peripheral nerve conduction measurements and vibratory sensory threshold improved compared to those receiving conservative insulin therapy in patients with type 1 diabetes [Service 1985]. Four weeks following initiation of intensive insulin therapy, improvements in vibratory sensation were observed in Japanese patients with type 2 diabetes [Kitano 2004]. Only 2 hours of hyperglycaemia increased the corrected QT interval at electrocardiogramm (ECG) in patients with type 2 diabetes [Santini 2007] and in healthy men as well [Marfella 2000]. In addition, a 150 minute-long hyperglycaemia increased the supine heart rate and altered a parasympathetic reflex test in healthy individuals [Yeap 1996]. Moreover, acute hyperglycaemia inhibited basal and stimulated pancreatic polypeptide secretion in non-diabetic participants suggesting an actual vagal inhibition induced by high glucose levels [Lam 1997]. These latter observations point to a reversable decreased parasympathetic activity and a relatively increased sympathetic activity in the case of currently high glucose. The data from the literature clearly suggest that well-treated glucose metabolism is the only way to prevent or to reduce the progression of neuropathy. The most intensive form of the treatment and optimisation of the glycaemic control in type 1 diabetes is the introduction of subcutaneous pump therapy which ensures the continuous insulin supply by the basal rate of the administration supplemented with bolus doses before main meals.

Analysing the previous papers, it is not clear when a better glycaemic condition should be achieved to improve neuronal function. The available data from small studies range from hours to years defining the glycaemic condition affecting the parameters of neuropathy.

The aim of our study was to explore the characteristics of autonomic cardiovascular function among patients with type 1 diabetes whose glycaemic control necessitated insulin pump therapy. Our further aim was to have a short-term and a long-term follow-up of the autonomic function during the treatment. In accordance with these aims cardiovascular autonomic function was detected at the initiation of the insulin pump treatment and was followed after 2 months and 6 years of pump treatment. We assessed the nature of the change in the tests and seeked for possible correlations between diabetes-specific parameters and autonomic nervous system function.

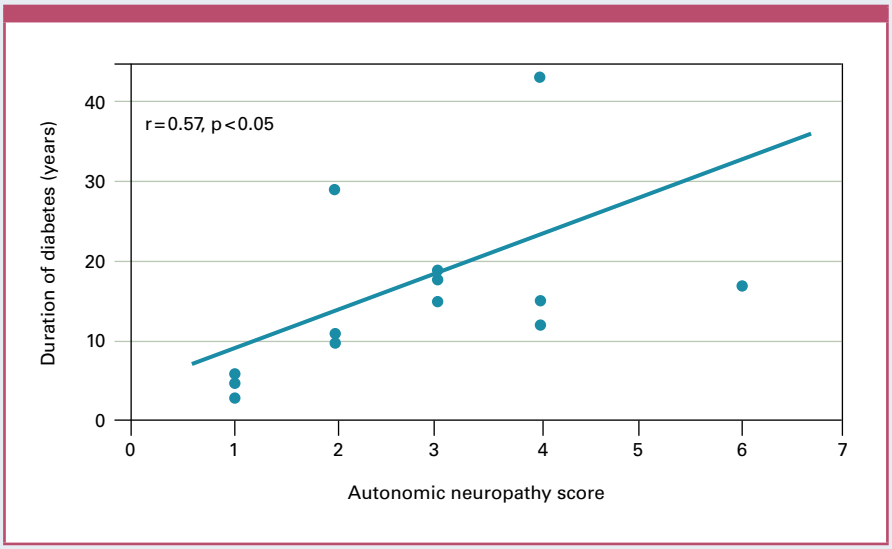

Fig. 1: Association between the duration of diabetes and the autonomic neuropathy score in patients with type 1 diabetes at the initiation of insulin pump treatment.

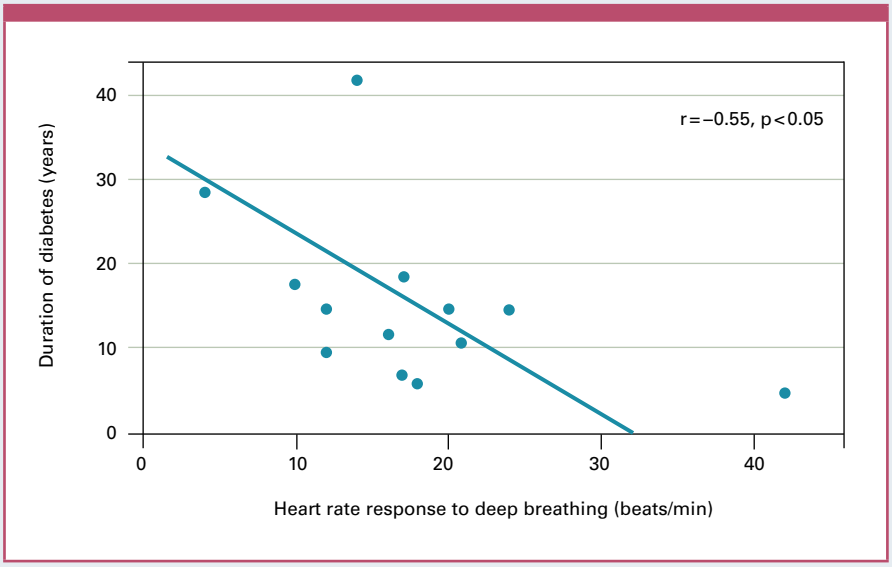

Fig. 2: Association between duration of diabetes and the heart rate response to deep breathing in patients with type 1 diabetes at the initiation of insulin pump treatment.

Study design

The first cardiovascular reflex tests (CRTs) were performed in all patients within 1 week before starting subcutaneous insulin pump therapy. The assessments of the cardiovascular autonomic function were performed 2 months and 6 years after the initiation of pump treatment. HbA_{1c} levels were determined at the time of all the three tests.

Patients and methods

13 patients (7 women and 6 men) with type 1 diabetes were included in the study. The patients were young adults at the time of the study initi-

ation (30.4 ± 2.7 years, mean ± SE). Their disease started in childhood or puberty (duration of diabetes at baseline: 16.5 ± 2.7 years, age at baseline: 27.8 ± 2 years). All patients received intensive insulin treatment immediately after their diagnosis until the start of insulin pump therapy. The mean body mass index (BMI) of the patient group at the initiation of the pump was 24.2 ± 1.0 kg/m², while 8.85 ± 0.2 % was the mean HbA_{1c} at the same time.

The quantitative characteristics of AN were determined by four standard CRTs [Ewing 1982]. These procedures ensure a non-invasive, clinically applicable, reproducible and standardized measurement of the autonomic control [Pop-Busui 2017]. Three of these tests evaluate the change of the heart rate during specific manoeuvres while the 4th test follows blood pressure changes [Spallone 2011]. The heart rate tests mainly (but not exclusively) assess the parasympathetic function while the blood pressure response predominantly reflects the impairment of sympathetic functions [Ewing 1985].

The following tests were applied:

1. Heart rate variation to deep breathing. The difference between maximum and minimum heart rates (beats/min) during the 6 breathing cycles was analysed.
2. Heart rate response to Valsalva manoeuvre. The Valsava ratio was calculated as the ratio of the longest R-R interval after the procedure to the shortest R-R interval during the manoeuvre.
3. Heart rate response to standing (30:15 ratio) The 30:15 ratio was defined as the ratio of the longest R-R interval at around the 30th beat after standing up to the shortest R-R interval at around the 15th beat.
4. Blood pressure response to standing up as a detection of orthostatic hypotension. The largest difference from the systolic blood pressure from lying position to standing up was evaluated.

A final score was created from the results of the four separate tests expressing the overall severity of the cardiovascular autonomic function. This autonomic score rated the severity of AN from 0–8 points.

Cardiovascular test	Baseline	After 2 months	After 6 years
Deep breathing (beats/min)	18.6 ± 0.5	23.2 ± 2.2	19.0 ± 0.7
30:15 ratio	1.14 ± 0.1	1.25 ± 0.1	1.12 ± 0.1
Valsalva manoeuvre (beats/min)	2.4 ± 0.1	1.6 ± 0.1	1.5 ± 0.1
Orthostatic blood pressure (mmHg)	5.2 ± 1.9	2.3 ± 0.7	5.1 ± 1.1

Tab. 1: Cardiovascular reflex tests at baseline and during the follow-up (mean ± SE). All changes were non-significant.

Results

At the baseline tests, when the pump treatment was initiated, the autonomic score that defines a sum of the autonomic dysfunction correlated positively with the duration of type 1 diabetes (Fig. 1). The baseline disease duration also correlated with a cardiovascular test, the heart rate response to deep breathing. It was a significant negative correlation meaning that the longer duration of diabetes was associated with a less physiologic change of the heart rate to the procedure of deep breathing reflecting a parasympathetic impairment (Fig. 2). At baseline a moderate to severe AN was revealed (Fig. 3). During the follow-up an improvement of the total AN score was detected 2 months after the implementation of pump (2.85 ± 0.3 vs. 1.23 ± 0.3, $p < 0.01$). The AN score measured 6 years later was similar to the initial value (Fig. 3). Heart rate responses to deep breathing, to Valsalva manoeuvre and to standing up, as well as the blood pressure response to standing up did not differ significantly during the follow-up (Tab. 1). In 3 of the 4 tests there was a non-significant tendency of an improvement by the 2nd month (Tab. 1), while a progression was not revealed by the 6th year in comparison to the initial values at all of the tests (Tab. 1). Regarding the glycaemic control, the HbA_{1c} decreased by 0.7 % after 2 months as a mean (8.85 ± 0.2 % vs. 8.12 ± 0.3 %, $p = 0.07$) and it was significantly lower by the end of the follow-up (8.85 ± 0.2 % vs. 7.85 ± 0.3 %, $p < 0.05$) (Fig. 4).

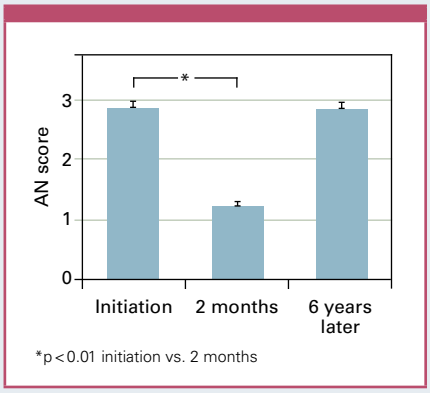

Fig. 3: Autonomic neuropathy (AN) score at baseline and during the follow-up (mean ± SE).

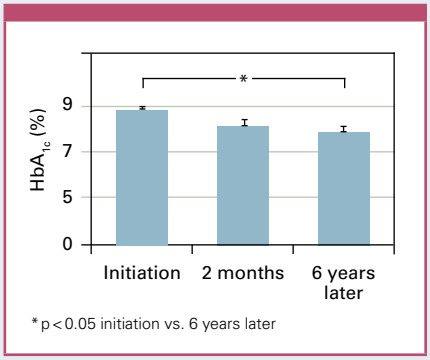

Fig. 4: HbA_{1c} at initiation and during the follow-up (mean ± SE).

Abbreviations

AN	autonomic neuropathy
BMI	body mass index
CRT	cardiovascular reflex test
DCCT	Diabetes Control and Complications Trial
ECG	electrocardiogramm
EDIC	Epidemiology of Diabetes Interventions and Complications
SE	standard error

Discussion

We had the opportunity to follow patients with type 1 diabetes whose glycaemic control necessitated the application of a subcutaneous insulin pump treatment. The observations at baseline

provide data on the characteristics of AN in a patient group who had a seriously bad glycaemic control. The overall grade of AN was not high, as the mean AN score was 2.85, but a strong relationship was found between the duration of diabetes and the severity of the autonomic dysfunction. In the presence of longer disease duration a more severe AN was documented. The patients had at least a 10-year long duration of type 1 diabetes and before the pump treatment several unsuccessful therapeutic efforts were performed due to their unstable glucose metabolism. These data are in accordance with our previous findings that the variability of the glucose levels is in close relationship with the severity of AN [Nyiraty 2018]. The detailed analysis of the possible correlation between each of the four CRTs and the duration of diabetes revealed that the results of the most sensitive parasympathetic test [Bernardi 2011], the heart rate response to deep breathing, are less physiologic in the presence of a longer metabolic dysregulation. This observation leads to the conclusion that mainly parasympathetic impairment is expected in patients with type 1 diabetes at the initiation of pump treatment. Moreover, this condition is frequently associated with a relative dominance of the sympathetic function resulting in an increased cardiovascular risk for these patients [Goldberger 2019].

A significant short-term improvement was found in the overall cardiovascular autonomic function during the follow-up of the pump treatment. Two months after the pump application, a significantly lower overall autonomic score was found. This parameter is accumulated from the scores of CRTs, thus it ensures a general characterisation of the autonomic function. The analysis of the separate tests did not reveal a significant change in the results by the 2nd month, however, 3 of the 4 tests suggested a tendency of improving the cardiovascular function. The significant reduction of the autonomic score might be a cumulative result of partial improvement in the parasympathetic and sympathetic functions. A beneficial effect during such a short period of intensified glycaemic control on the cardiovascular autonomic function was not observed earlier in type 1 diabetic patients. Our data might support the hypothesis that the moderate impairment of autonomic regulation might be sensitive for the short-term changes of the metabolic conditions and the pathogenetic process is particularly reversable. The results of the follow-up after 6 years reflected the same severity of neuropathy as it was recorded at the baseline tests. This means that the autonomic function was preserved during a 6-year period with the most intensive insulin treatment. The degree of glycaemic control characterized by HbA_{1c} did not change by the 2nd month but became significantly lower by the 6th year, although the mean value did not reach the glycaemic target. As HbA_{1c} did not decrease markedly during the follow-up despite of the preserved autonomic function might rise a hypothesis that the global stability of the glycaemic control has a more important role in the prevention than the average glycaemia characterized by HbA_{1c}. The initial moderate tendency of improvement in autonomic function seemed to be temporarily by the 6th year. There is no evidence from the literature about the shortest time interval with good glycaemic control which has a beneficial effect on autonomic function in diabetic patients. In the DCCT the prevalence of AN almost doubled in the conventional group during 6.5 years, while remained the same in the intensive group [Ang 2014]. Simultaneous pancreas-kidney transplantation improved Valsalva ratio in patients with type 1 diabetes by the 3rd year of follow-up [Ziegler 1991]. In a smaller study, heart rate variation was significantly less impaired within 24 months in a group of patients with type 1 diabetes with an HbA_{1c} of less than 8.3 % as compared to those having higher HbA_{1c} [Argente-Pla 2020]. Our data suggest that the beneficial effect might begin as early as some months after the start of the intensive treatment and lasts up to 6 years. The main limitation of our study is that only HbA_{1c} values were used to characterise glycaemic control. Data on glucose variability might also provide important information on the metabolic state of these patients. Moreover, the number of patients was relatively small. All patients were followed until the end of the study.

Conclusion

In summary, a moderate, initial improvement was followed by a preservation of autonomic function after 6 years of insulin pump treatment in patients with type 1 diabetes.

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