Assessment of Small Fiber Neuropathy through a Quick, Simple and Non Invasive Method in a German Diabetes Outpatient Clinic

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Abstract

Introduction: Sudomotor dysfunction is one of the earliest neuropathologic abnormalities to manifest in distal small fiber neuropathy. SUDOSCAN® was developed to provide a non invasive, quick, simple and quantitative measurement of sweat function. The aim of this observational study was to assess sweat function in a diabetes outpatient consult clinic in Germany.

Methods: The study was conducted from February 2009 to March 2011 on patients of a diabetes outpatient clinic in Germany with type 1 and type 2 diabetes, and was conducted parallel to standard care. Sweat function was evaluated by measuring the electrochemical conductance (ESC) of the hands and feet. The method’s reproducibility between 2 devices and a follow-up according to insulin administration were also assessed.

Results: 52 patients with type 1 diabetes and 115 patients with type 2 diabetes (69 receiving insulin) were involved in this observational study. Hand and foot conductances were lower in patients with type 2 diabetes when compared to patients with type 1 diabetes. A slight decrease in hand and foot conductances was observed in patients with type 2 diabetes without insulin, while an increase was observed in patients receiving insulin (~3.8±9.7 vs. 1.0±9.7μS, p<0.02 for the hands and ~2.2±7.5 vs. 4.1±8.8μS, p<0.001 for the feet). Coefficient of correlation between measurements performed with the 2 different devices was 0.85 for hands and 0.93 for feet, p<0.001. No safety concern was reported and none of the subjects experienced discomfort during the tests.

Conclusion: This preliminary study shows that the assessment of small C fiber neuropathy can be performed non invasively, quickly and effectively in standard diabetes outpatient practice with very good reproducibility. The observation that electrochemical skin conductance improves with intensified insulin treatment must be confirmed in a clinical study performed on a larger population.

Introduction

Different forms of somatic and autonomic neuropathy can function as predictors or contributors to a number of chronic diseases, but the disparity between the association of intensive therapy, mortality, and the expression of chronic disease remains unclear[1,2]. Changes in peripheral autonomic nervous system function may be the earliest manifestation of distal small fiber neuropathy [2]. The eccrine glands are innervated by a rich supply of blood vessels and sympathetic C nerve fibers and are responsible for the sweat response. Thus, sudomotor function can represent an attractive tool to evaluate the peripheral autonomic system [3]. Low et al., using the quantitative sudomotor axon reflex test (QSART), showed that sudomotor function decreases in patients with diabetes [4]. Studying skin biopsies, it was confirmed that the density of epidermal C-nerve fibers is decreased in patients with diabetes [5]. The evaluation of sudomotor function therefore can be a direct and indirect indicator for the degree of neuropathy in diabetes patients or those at risk. This is especially important because it is known that intensive therapy with insulin can delay the onset and slow the progression of retinopathy, nephropathy and peripheral neuropathy [6]. Additionally, lifestyle change can improve impaired nerve function [7,8]. SUDOSCAN®, a simple, non invasive and quick test, was recently developed to allow the measurement of sweat gland function in order to evaluate peripheral neuropathy [9–11].
underlying technology is based on the electrochemical reaction between the chloride in sweat and nickel-based plate electrodes, on which the subject’s hands and feet are placed [12, 13]. A low voltage (<4 V) is applied through the electrodes, attracting chloride ions from the sweat glands (which are most densely concentrated on the palms and soles). A measurement of conductance for the hands and feet is generated from the derivative current associated with the applied voltage[14]. The aim of this observational follow-up study was to evaluate sudomotor function in patients at a German diabetes outpatient clinic. Patients with type 1 or type 2 diabetes and a variation of oral and insulin treatment were assessed. Furthermore, the method’s reproducibility between devices and 1 year follow-up were also assessed.

**Methods**

**Patients**

The study was conducted from February 2009 to March 2011 on patients of a diabetes outpatient clinic in Germany. All participants gave their written informed consent. The observational study was performed parallel to the patients’ standard care. General examination was performed to gather weight, waist and biochemistry, including HbA1C. Retinopathy status and renal function — through the measurement of Modification of Diet in Renal Disease (MDRD) — were also assessed in a subgroup of patients.

**SUDOSCAN®** (Impeto Medical, Paris, France) is a new patented device designed to perform a precise evaluation of sweat gland function based on the electrochemical reaction between the chlorides in sweat and stainless-steel electrodes at low DC voltage [6–10]. The apparatus consists of 2 sets of electrodes in contact with the palms of the hands and soles of the feet, where sweat gland density is the highest, connected to a computer for recording and data management purposes. To conduct the test, the individual is required to stand still for 2 min. During the test, 4 combinations of 15 different low direct current (DC) incremental voltages ≤4 volts are applied. A time/ampere curve is recorded for each derivation. Electrochemical skin conductance (ESC) in the hands and feet, i.e., the ratio between current generated and the constant DC stimulus, are displayed on a monitor immediately after the test. Neither special subject preparation nor specially trained medical personnel are required. The reproducibility of this sweat function measurement had been successfully validated in previous studies, but inter-device reproducibility had to be confirmed through measurement in a subgroup of patients with two different devices [11]. The follow-up was also assessed by 2 measurements separated by a mean interval of 360 days. A blind analysis of the data was performed by an independent party  

**Results**

52 patients with type 1 diabetes and 115 patients with type 2 diabetes (69 receiving insulin) were involved in this observational study. Baseline population characteristics according to diabetes type and insulin treatment, together with changes in hand and foot ESC after a 1-year follow-up, are also indicated in the Table 1. No adjustments have been performed, as differences between insulin and no-insulin groups for age and BMI were not significant.

20 subjects presented with nephropathy (MDRD < 60 ml/mn/1.73 m²). The hand and foot conductances of these patients were lower than those of the 104 patients without nephropathy (63 ± 18 vs. 72 ± 15 p = 0.07 and 73 ± 16 vs. 82 ± 11 p = 0.009 respectively).

The mean difference was −1.15 ± 3.1 μS for hand conductances and 0.59 ± 5.3 μS for foot conductances (n = 28).

The type 2 diabetes patients had very good levels of HbA1c at the baseline assessment. No significant evolution of HbA1c was observed at the follow-up investigation. A slight decrease in hand and foot ESC was observed in patients with type 2 diabetes without insulin while a significant increase was observed in patients receiving insulin (−3.8 ± 9.7 vs. 1.0 ± 9.7 μS, p = 0.02 for the hands and −2.2 ± 7.5 vs. 4.1 ± 8.8 μS, p < 0.001 for the feet).

Coefficient of correlation between measurements performed with the 2 different devices was 0.85 for hands and 0.93 for feet, p < 0.001. The SUDOSCAN® test was accepted by the subjects without complain, no safety concern was reported, and none of the subjects experienced discomfort during the tests.

**Fig. 1** Correlation between measurements performed with 2 different devices in a subgroup of 28 patients for hand ESC (a, r = 0.85, p < 0.001 and foot ESC (b, r = 0.93, p < 0.001).

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Discussion

This observational study performed in a German diabetes outpatient clinic showed:

1. that electrochemical skin conductance measured using SUDOSCAN is impaired in type 2 diabetes, with a progressive impairment in those with longer diabetes duration and requiring more intensified treatment,

2. that electrochemical skin conductance improves over a 1 year period in patients with type 2 diabetes receiving intensified insulin therapy compared to patients not receiving insulin, and

3. that the measurement of electrochemical skin conductance can be performed non invasively, quickly and effectively in standard diabetes outpatient practice with very good reproducibility.

This study is interesting in its observation, because it shows for the first time observational data comparing patients with type 1 diabetes and type 2 diabetes with various degrees of treatment and disease-associated complications. We observe an association of impaired electrochemical skin conductance with the occurrence of diabetes-associated complications, which was expected based on previous experimental data [15,16] and suggested by studies testing similar technologies [17]. Additionally, this impairment progresses over time for those patients with type 2 diabetes without insulin, which is consistent with a pathomechanistic understanding of the development of diabetes-associated complications [18]. This also underlines the importance of continuous glucose control, during the later period of diabetes, for the development of diabetic peripheral neuropathy [15]. Unique is that intensive insulin therapy was associated with improvements of electrochemical skin conductance, which is shown here for the first time.

We can extrapolate from this that intensified insulin therapy may have led to an improvement of nerve function and improvement of neuropathy in those patients. Data which support this hypothesis has been shown to delay the onset of microvascular complications [6]. The observation of a significant difference in ESC, between type 2 diabetes patients receiving insulin and those not receiving insulin, has to be confirmed in a larger population assessing patients with insulin therapy in various stages of diseases progression.

Another attractive result is that the patients in this observational study did not experience any relevant evolution of HbA1c values, leading to the conclusion that the changes observed, based on measuring electrochemical skin conductivity, are not related to mean glycaemia in these patients. What can explain this finding? One option could be that increasing insulin resistance may have a stronger effect on impairing nerve function than overall glycaemia [19]. Furthermore, increased glycaemic variability in non-insulin treated type 2 diabetes patients which are treated predominantly with sulfonylurea can be another driving factor for progression of impairment of autonomic nerve function [20].

In our study we observe sweat dysfunction in type 1 and type 2 diabetes patients. This is supported by data on sweat disturbances in diabetes patients observed with Q5ART [4]. Due to small C fiber neuropathy, partly explained by poor glycaemic control, patients with type 2 diabetes are at higher risk of peripheral neuropathy. This effect will also be associated with later disease diagnosis because often early signs of neuropathy develop in stages of insulin resistance and prediabetes, as observed by skin biopsies [7].

A compelling finding of this study is that SUDOSCAN, a non-invasive fast test to assess neuropathy, can be used in standard clinical practice to reduce the need for biopsies, and is furthermore independent from patients’ self-reported outcomes. If this data can be confirmed by additional studies, SUDOSCAN can be developed as an objective test to monitor neuropathic changes in patients with diabetes mellitus. The method’s reproducibility has already been shown in previous studies, with measurements performed several hours apart on the same device [12,21]. This study assessed inter-device reproducibility. The good correlation between measurements performed on 2 different devices strengthens the case for this method’s adoption for use in standard outpatient diabetes clinics.

One important limitation of this preliminary study is that peripheral neuropathy was not confirmed by complete neurological clinical examination, which generally assesses large fiber neuropathy.

This preliminary study shows that the assessment of small C fiber neuropathy through the measurement of electrochemical skin conductance can be performed non invasively, quickly and effectively in standard diabetes outpatient practice with very strong evidence for the diagnostic accuracy of this method.
good reproducibility. The observation that electrochemical skin conductance improves with intensified insulin treatment must be confirmed in a clinical study performed on a larger population. These results suggest the potential utility of SUDOSCAN® for the early diagnosis of neuropathy in type 2 diabetes.

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Conflict of interest statement: JD and JHC are employees of Impeto Medical. HW and PS have no conflict of interest.

References