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Assessment of small fiber neuropathy to predict future risk of type 2 diabetes

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ABSTRACT

Objective: Sudomotor dysfunction due to small fiber neuropathy can be observed very early in pre-diabetes. The aim of this study was to assess the predictive power of EZSCAN, a non invasive, quick and simple measurement of sudomotor function to identify glucose impairment.

Research design and methods: The study was performed in 76 German subjects at risk of diabetes. Glucose metabolism was assessed by using, oral glucose tolerance test (OGTT) at baseline and after 2 year follow-up. Sudomotor function was evaluated by measuring hand and foot electrochemical sweat conductances to calculate a risk score.

Results: At baseline, 38 patients had normal glucose tolerance (NGT), 34 had pre-diabetes (impaired fasting glucose, IFG and/or impaired glucose tolerance, IGT) and 4 had newly diagnosed type 2 diabetes. The AUC values for FPG, 2 h-OGTT glucose, 1 h-OGTT glucose, HbA_{1C} and EZSCAN score to predict pre-diabetes were 0.50, 0.65, 0.64, 0.72 and 0.76, respectively. Subjects having a moderate or high EZSCAN score (>50) at baseline had a substantially increased risk for having IFG and/or IGT at follow-up visit presented by an odds ratio of 12.0 [1.4–100.5], the OR for having 1 h-OGTT $\geq$ 8.6 mmol/L at follow-up was 9.8 [1.0–92.8] and for having $HbA_{1C} \geq 5.7\%$ was 15.7 [1.9–131.5] compared to subjects with low EZSCAN risk.

Conclusions: This preliminary study, which must be confirmed in a larger population, shows that EZSCAN risk score is associated with diabetes progression which have implications for prevention and disease management.

1. Introduction

The prevalence of type 2 diabetes and pre-diabetes—i.e. impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)—is increasing worldwide [1]. As early identification and treatment of persons with pre-diabetes have the potential to reduce or delay progression to diabetes [2], there is a distinct need for simple, non-invasive, sensitive and quick tools for pre-diabetes screening [3–5].

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The eccrine glands are innervated by a rich supply of blood vessels and sympathetic C nerve fibers and are responsible for the sweat response [6]. Small fiber neuropathy (observable in metabolic syndrome and pre-diabetes) may induce autonomic dysfunction [7], including decreased sudomotor response, which may be the earliest manifestation of distal small fiber neuropathy [8]. The assessment of sudomotor function has been proposed as a method to evaluate the peripheral autonomic system [9]. However recommended methods such as Quantitative Sudomotor Axon Reflex Test (QSART) and skin biopsies are time consuming, highly specialized or invasive [10,11]. EZSCAN, a device recently developed to allow quick, quantitative and non-invasive assessment of sudomotor function, has been shown to detect sudomotor dysfunction in diabetes or pre-diabetes [12,13]. This method has been validated in previous studies as a screening tool for glucose metabolism disturbances [14,15].

The aim of this follow-up study, performed in German subjects at risk of diabetes, was to compare the predictive power of EZSCAN versus other common methods to identify subjects with pre-diabetes after two years, based on HbA_{1C} values and IFG/IGT, type 2 diabetes thresholds.

2. Research design and methods

Seventy-six subjects from the city of Dresden and adjoining areas were recruited in the clinic's Department for Prevention and Care of Diabetes. Written informed consent was obtained from all subjects prior to the start of any study procedures. Clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. Ethical approval was obtained by the University of Dresden (approval No. 198062010). Most of the subjects came from German families with a family history of type 2 diabetes, obesity, or dyslipoproteinaemia. The average age of the subjects was 64 ± 8 years; average BMI was $27.6 \pm 3.7\,kg/m^2$. Exclusion criteria were: known diabetes mellitus, severe renal disease, disease with a strong impact on life expectancy, and therapy with drugs known to influence glucose tolerance (thiazide diuretics, beta blockers, and steroids) or pregnancy. Subjects were invited for study participation at baseline and for an average two-year follow-up. Anthropometric data (weight, height, BMI, waist circumference), fasting plasma glucose (FPG) and HbA_{1C} were recorded. FINDRISC was assessed by personal interview. All individuals underwent a 75 g 2 h oral glucose tolerance test (OGTT) following an overnight period of fasting (10 h minimum) with measurements of plasma glucose and insulin taken at fasting and at 30, 60, 90 and 120 m after glucose challenge as previously published [5,16]. Based on these data, homeostasis model assessment-insulin resistance (HOMA-IR) and MATSUDA index were also calculated. The population was divided into four glucose tolerance groups according to the results of FPG and OGTT: Normal glucose tolerance (NGT, FPG < 5.6 mmol/L and 2 h-OGTT < 7.8 mmol/L), IGT (2 h-OGTT 7.8–11.0 mmol/L), IFG (FPG 5.6–6.9 mmol/L), and type 2 diabetes (FPG ≥ 7.0 mmol/L and/or 2 h-OGTT ≥ 11.1 mmol/L), based on ADA clinical practice recommendations. Pre-diabetes was defined as HbA_{1C} 5.7–6.4% and/or FPG 5.6–6.9 mmol/L and/or 2 h-OGTT7.8–11.0 mmol/L.

Measurements were performed at baseline and during a follow-up visit.

2.1.1. *Measurement of sudomotor function*

EZSCAN, a patented device designed to perform a precise evaluation of sweat gland function based on a reverse iontopheresis electrochemical reaction between sweat chlorides and stainless-steel electrodes when a low DC voltage is applied, as previously described [13,14]. The apparatus consists of two 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 minutes. During the test, 4 combinations of 15 different low direct current (DC) incremental voltages (≤4 v) are applied. A time/ampere curve is recorded for each derivation. Hand and foot electrochemical sweat conductances (ESC) expressed in microsiemens (μS), i.e. the ratio between current generated and the constant DC stimulus, are displayed on a monitor immediately after the test. No special subject preparation or specially trained medical personnel are required. Patients were classified according to their risk score using a color classification allowing easy patient understanding—green: no risk, yellow: moderate risk and orange/red: high risk of diabetes.

2.1.2. *Statistical analysis*

Results for quantitative variables are shown as mean values ± standard deviations (SD). Log transformation was performed for variables not normally distributed. Group means were globally compared using a Student's *t*-test. Analysis of variance (ANOVA) adjusted for age has been performed to compare quantitative variables. Assessment of the predictive discrimination of the various parameters was made using the receiver-operating characteristic (ROC) curve with calculation of the area under the ROC curve (AUC). Confidence intervals for odds ratios (OR) have been calculated using the Woolf method. The statistical analysis was done using R 2.13.1 (the R-project for statistical computing [17]). As a rule, a *p*-value < 0.05 was regarded as statistically significant.

Blind analysis of the data was performed by an independent party.

3. Results

Seventy-six patients at risk of diabetes were involved in the study. At baseline, 38 of them had NGT, 34 had pre-diabetes (i.e. IFG and/or IGT) and 4 had newly diagnosed diabetes. Among the 38 subjects with IFG, IGT or diabetes, 95% of them were at moderate or high risk according to EZSCAN classification. The mean time between baseline and follow-up was 677 ± 207 days. Baseline and follow-up characteristics are displayed in the Table 1. Subjects having a moderate or high EZSCAN score (≥50) at baseline had a substantially increased risk for having IFG and/or IGT at follow-up visit presented by an odds ratio of 12.0 [1.4–100.5], the OR for having 1 h-OGTT ≥ 8.6 mmol/L at