Non-invasive Screening of Diabetes Risk by Assessing Abnormalities of Sudomotor Function

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Key words
- sudomotor function
- insulin resistance

Abstract

Background: The early detection of diabetes, and subsequent lifestyle intervention, may reduce the burden of diabetes and its complications. Several studies have identified a link between sudomotor dysfunction, insulin resistance, and pre-diabetes. The aim of this study was to evaluate the ability of a new non-invasive device EZSCAN evaluating sudomotor function to detect pre-diabetes in a German population at risk for diabetes.

Methods and findings: 200 German subjects at risk for diabetes (mean age 56 ± 14 years, BMI 28.4 ± 5.4 kg/m^2) were measured for anthropometric data on inflammatory parameters, including high sensitivity C reactive protein (hs-CRP). The subjects also underwent an oral glucose tolerance test with measurements of plasma glucose, insulin, proinsulin, C-peptide and free fatty acids during 2 h following glucose challenge. Indexes for sensitivity to insulin were calculated: S_I using minimal model, HOMA-IR and Matsuda index. Based on the measurement of electrochemical sweat conductance, subjects were classified as no risk, moderate risk or high risk. According to this risk model classification, a significant difference was observed between OGTT-1 h ($p = 0.004$), AUC glucose ($p = 0.011$), AUC C-peptide ($p < 0.001$), HOMA-IR ($p = 0.009$), Matsuda ($p = 0.002$), S_I ($p < 0.001$) and hs-CRP ($p = 0.025$) after adjustment for age. Among the 54 subjects with impaired fasting glucose or impaired glucose tolerance according to WHO classification, 37 had a moderate risk and 15 a high risk according to the EZSCAN risk model classification. Among the 12 subjects with newly diagnosed diabetes, 2 had a moderate risk and 10 a high risk according to the risk model classification. No adverse event was reported during or after the study.

Conclusions: These results, in accordance with a previous study performed in India, show that EZSCAN could be developed as a screening tool for diabetes risk, and could help to improve diabetes screening strategies. Results obtained from an at-risk population would have to be confirmed in a larger population.

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Introduction

Diabetes is a growing global concern that is affecting 285 million people today. By 2030, according to the IDF Diabetes Atlas, that number of people will have risen to 438 million [1], and double that if figures for metabolic syndrome or pre-diabetes are included. These statistics also reveal a disturbing trend: the increase in number of children and adolescents developing type 2 diabetes. Major prevention trials have shown that diabetes can be delayed or prevented in individuals with impaired glucose tolerance (IGT) using lifestyle intervention or medication [2]. However, incorporating the evidence from trials into clinical practice represents one of the major challenges for public health and clinical care. Currently an evidence-based guideline for the prevention of type 2 diabetes [3] and a practice tool kit for the implementation of programs for the prevention of chronic metabolic diseases [4], especially diabetes mellitus, have been developed to promote improved patient compliance. There is growing evidence that interventions to prevent diabetes from developing are more efficient when applied earlier in subjects identified at risk for normoglycemic, exhibiting insulin resistance but not hyperglycemic.

Diagnosing type 2 diabetes and screening for the different pre-diabetic stages of risk require often resource-intensive measurements of a set of biomarkers, which are yet to be universally standardized. Attempts to employ questionnaire-based risk scores, for which there is some valid predictive

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efficacy, are unfortunately limited in the practical sense. An added value to clinical practice would be to have a fast, non-invasive, and reproducible diagnostic method to efficiently identify those with increased diabetes risk.

Presently, several methods – including risk models based on HbA_{1c} [5,6] and 1-h post-load glucose values [7] – are employed in diagnosing diabetes and pre-diabetes. However, debate continues over which single tool is ideally suited for assessing diabetes risk or identifying individuals with increased metabolic risk factors in a population-based public health setting. In general, measurements that require blood sampling are time consuming, have low sensitivity and cannot be used for screening of large population. On the other hand, questionnaire-based methods used for early screening which require individual data such as age, BMI, and blood pressure [8–10], have their own limitations. Clearly a simple-to-use and effective diagnostic or screening tool is needed for preventive intervention programs where overall cost and population receptivity are overriding factors.

Diabetic neuropathy is a known complication of diabetes mellitus and manifests as impairment of nerve function due to hyperglycemia and insulin resistance [11]. To understand diabetic neuropathy development, several studies have explored sudomotor dysfunction by using quantitative sudomotor axon reflex test (QSART) or sympathetic skin response [12,13]. These studies have shown a direct link between impairment of sudomotor function and insulin resistance and pre-diabetes [14,15]. Skin biopsies confirmed damage to the sympathetic C nerve fibers innervating sweat glands in hyperglycemic and insulin resistance conditions; while, on the contrary, the positive effects of lifestyle intervention led to the rejuvenation of those fibers [16]. However, skin biopsies and traditional tests used to assess sudomotor function are time-consuming and/or invasive and are not efficient for screening.

EZSCAN® (Acronym for "Easy Scan") was recently developed to perform a noninvasive evaluation of sweat gland function through measurement of electrochemical skin conductance, based on an electrochemical reaction between sweat chloride and nickel electrodes in contact with palms of the hands and soles of the feet [17–21]. A risk model based on hand and foot conductance values adjusted for age and BMI was developed and evaluated in both controls and patients with diabetes, to predict insulin resistance and current diabetes. This predictive model was tested and evaluated in Indian and Chinese subjects at risk of diabetes according to ADA criteria [22,23], which approved the risk model in persons with normal glucose tolerance and diabetes mellitus. Persons with IGT presented a unique picture and expressed repeatedly elevated foot conductance. This was explained by the presence of an inflammatory process influencing sweat gland innervation, previously explored through skin biopsies performed in patients with pre-diabetes [24]. The risk model had to be adjusted using relative values of hand and foot conductances and systolic blood pressure.

The aim of this study was to assess the ability of this new risk model previously validated in India to detect pre-diabetes or diabetes in a German population at risk for these conditions.

Methods

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Participants and biochemical measurements

200 subjects from the city of Dresden and adjoining areas were recruited in the Division for Prevention and Care of Diabetes mellitus as previously described [25]. Written informed consent was obtained from all subjects and all subjects were able to give the consent themselves. 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 56 ± 14 years; average BMI was 28.4 ± 5.4 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, steroids) or pregnancy of the proband. Anthropometric data (body weight, body height, BMI, waist circumference), HbA_{1C}, lipids (triglycerides, total cholesterol, HDL-C, LDL-C) and inflammatory parameters including hs-CRP were recorded. All individuals underwent a 75 g oral glucose tolerance test following an overnight period of fasting (10 h minimum) with measurements of plasma glucose, insulin, proinsulin, C-peptide and free fatty acids (NEFA) at fasting and at 30, 60, 90 and 120 min after glucose challenge. The cohort was divided into 4 glucose tolerance groups according to the results of the baseline and follow-up OGTT: normoglycemic (NGT), impaired glucose tolerance (IGT), those with impaired fasting glucose (IFG), and type 2 diabetes mellitus based on the WHO criteria of 1997, which was previously reported [25–27].

Insulin sensitivity, Matsuda index, HOMA-IR

The Minimal model was used to calculate insulin sensitivity (S_I) index based on the following formula [28].

$$S_{I(OGTT)} = \frac{f \cdot D_{OGTT} \cdot \frac{AUC[\Delta G(t)/G(t)]}{AUC[\Delta G(t)]} - GE \cdot AUC[\Delta G(t)/G(t)]}{AUC[\Delta I(t)]}$$

Where G is plasma glucose concentration; ΔG and ΔI are glucose and insulin concentrations above basal, respectively; AUC denotes the area under the curve calculated from time 0 to $t \to \infty$, GE is glucose effectiveness (dl.kg^{-1}min^{-1}); DOGTT is the dose of ingested glucose per unit of body weight (mg/kg); and f is the fraction of ingested glucose that actually appears in the systemic circulation. Calculation of S_I requires insertion of values for GE and f. Values proposed by Monti et al. were used: GE = 0.024 dl.kg^{-1} · min^{-1} and f = 0.8 [29]. Homeostasis model assessment – insulin resistance (HOMA-IR) and Matsuda index were also calculated.

Measurement of sweat function

EZSCAN, a patented device designed to perform a precise evaluation of sweat gland function through reverse iontophoresis and chrono-amperometry, has been described previously [17,20]. The apparatus consists of 2 sets of large area nickel electrodes for the hands and the feet, which are connected to a computer for recording and data management purposes; electrodes are used alternatively as an anode or a cathode and a direct current (DC) incremental voltage ≤4 volts is applied on the anode. To conduct the test, patients are required to place their hands and feet on the electrodes and then to stand still for 2 min. Through reverse iontophoresis, the device generates a voltage on the cathode and a current (intensity of about 0.2 mA) between the anode and the cathode, proportional to electrochemical reaction between chlorides of the sweat and nickel electrodes. At low voltages, less than 10 V, the stratum corneum is electrically insulating and only sweat gland ducts are conductive [30]. The electrochemical sweat

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conductance (ESC), expressed in microSiemens (μS), is the ratio between current generated and the constant DC stimulus applied on electrodes. 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.

Statistical analyses

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 student t-test. Pearson Chi-square or Fisher's exact tests were used for the comparisons of percentages. Analysis of variance (ANOVA) and logistic regression, adjusted for age, have been performed to compare quantitative variables and percentages. The statistical analysis was done using R 2.13.1 (The R-project for statistical computing) [31]. As a rule, a p-value < 0.05 was regarded as statistically significant.

Results

Of the 200 men and women included in the study initially, 134 (67%) were diagnosed with NGT; 54 (27%) exhibited IGT/IFG; and 12 (6%) were newly diagnosed with type 2 diabetes according to WHO classification. Among the 54 subjects with IFG/IGT, 37 had a moderate EZSCAN risk score and 15 a high risk according to risk model classification based on sudomotor function assessment, whereas lower values mean lower risk and vice versa. Among the 12 subjects with diabetes, 2 had a moderate risk and 10 a high risk according to risk model classification. Considering subjects with no risk vs. subjects with moderate or high risk, sensitivity to diagnose IFG/IGT or diabetes was 97% and specificity 31% with a negative predictive value of 95%. Demography and main results according to risk classification based on sudomotor dysfunction assessments are displayed in **Table 1**. After adjustment for age a significant difference was observed between each risk model group in AUC glucose ($p = 0.011$), AUC C-peptide ($p < 0.001$), HOMA-IR ($p = 0.009$), Matsuda ($p = 0.002$), S_I ($p < 0.001$) and hs-CRP ($p = 0.025$). No association was detected between the risk model and the patient lipid profile. Blood concentrations during 2 h-OGTT for glucose, insulin, pro-insulin, C-peptide and free fatty acids are displayed on **Fig. 1**.

Mean EZSCAN risk score values for NGT, IFG/IGT and diabetes groups were 48 ± 26, 57 ± 15 and 66 ± 12, respectively.

No adverse event was reported during or after the study. More specifically, no patient perceived the voltage applied or the current produced. No reddening of the palms or soles was observed.

Discussion

The EZSCAN technology was evaluated in this study as a potential screening tool to detect diabetes risk. This technology has several advantages: reproducibility, non-invasiveness, and short test duration allowing numerous follow-up tests with very low supply costs.

This study, performed in a population of German subjects at risk for pre-diabetes or diabetes, shows that non-invasive assessment of sudomotor function could present an effective method to identify people with increased diabetes risk. The assessment of sweat function based on an electrochemical reaction between sweat chloride and nickel electrodes allows a valid detection of patients with insulin resistance or type 2 diabetes, with a very low rate of false negative test results.

It is known that long diabetes duration and inadequately managed diabetes treatment increase the risk of developing neuropathy. Neuropathy diagnosed in a clinical setting is often in its late, irreparable stages, due to the diagnostic tools involved (biothesiometer or turning fork measuring large fiber damages), and has already manifested as significant impairment of nerve function [32, 33]. From a clinical point of view there is only little known about very early stages of autonomic nerve function impairment as it relates to the development of insulin resistance. Recent studies have shown a link in patients with pre-diabetes between more severe stages of insulin resistance and peripheral autonomic nerve fiber impairment [15, 34] and also and association in childhood obesity were increased BMI and elevated HOMA-IR is associated with impaired autonomic function [35]. In addition a recent study evidenced that insulin resistance itself was independently associated with peripheral and autonomic neuropathy [36]. Impairment of these autonomic sympathetic C nerve fibers innervating sweat glands leads to sudomotor dysfunction. Applying electrodes with a current voltage inducing current linked to an electrochemical reaction between sweat chloride and electrodes allows a precise evaluation of the sweat dysfunction. The measured conductance (ratio of the current and voltage) is directly related to the impairment of the C nerve fibers innervating autonomic sweat glands. A proof of concept study has shown good correlation between conductance and sweat chloride concentration as measured by a sweat test in controls and patients with cystic fibrosis [17]. This is in conjunction with a current observational study showing that insulin treatment improves the neuropathy measured by EZSCAN [33]. The advantage of this technology, EZSCAN, is that it is non-invasive, can be performed quickly (in less than 3 min), and will allow qualitative assessment of pre-diabetic stages based on the subject's measured chloride-dependent conductance levels. Previous studies have presented evidence of the method's reproducibility [33, 37]. A risk assessment model has been developed first in patients with diabetes, has undergone validation in an Indian test population at risk of diabetes [22], and has now been confirmed in different stages of pre-diabetes risk in a German-Caucasian population. Tests for insulin resistance showed a difference between subjects without risk, according to the risk model, and subjects with moderate or high risk (**Table 1**). A significant difference could be seen in hs-CRP (a marker of inflammation) between subjects with moderate risk and subjects with no risk, in accordance with the inflammation process observed in sweat gland innervation of subjects with IGT [23]. This hypothesis has to be confirmed by assessment of other markers of inflammation. These data help to further support the EZSCAN risk score as a technology that may meet requirements for the screening of metabolic risk stages. EZSCAN could be developed as an alternative to other biomarker-based medical risk assessment strategies or questionnaire-based public health screening strategies.

Several limitations warrant interpretation of the study results. First, the patients were not selected randomly, and were recruited based on their existing increased risk of diabetes. This may generate a bias – potentially an underestimation of the EZSCAN results. The second limitation of our study is that the association was only tested against the EZSCAN-developed risk model and not vice versa. In particular, investigating the differences

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Table 1 Demography and main results according to EZSCAN risk model classification.

	Overall n = 200	No risk (Green) n = 43	Moderate risk (Yellow) n = 86	High risk (Orange/red) n = 71	P	P adj.**
age (yrs)	56 ± 14	37 ± 11	58 ± 10	66 ± 8	< 0.001	–
gender (n men, %)	92 (46 %)	22 (51 %)	36 (42 %)	34 (48 %)	NS	–
BMI (kg/m^2)	28.4 ± 5.4	25.4 ± 3.9	29.4 ± 5.9	29.1 ± 5.1	< 0.001	< 0.001
waist (cm)	97.0 ± 13.3	88.8 ± 10.8	99.2 ± 14.1	99.3 ± 11.9	< 0.001	< 0.001
SBP (mm Hg)	135 ± 16	124 ± 13	138 ± 16	139 ± 16	< 0.001	0.019
HbA_{1C} (%)	5.7 ± 0.5	5.3 ± 0.3	5.7 ± 0.4	5.8 ± 0.5	< 0.001	0.098
FPG (mmol/L)	5.3 ± 0.7	4.9 ± 0.5	5.4 ± 0.6	5.5 ± 0.9	< 0.001	0.085
OGTT-1h (mmol/L)	9.3 ± 2.6	7.7 ± 2.1	9.6 ± 2.4	10.0 ± 2.6	< 0.001	0.004
OGTT-2h (mmol/L)	6.9 ± 2.3	5.5 ± 1.6	7.2 ± 2.1	7.4 ± 2.5	< 0.001	0.080
fasting free fatty acid (mmol/L)	0.52 ± 0.23	0.44 ± 0.20	0.52 ± 0.21	0.57 ± 0.25	0.009	NS
total cholesterol (mmol/L)	5.4 ± 1.0	5.1 ± 1.1	5.4 ± 0.9	5.6 ± 0.9	0.008	NS
triglycerides (mmol/L)	1.4 ± 0.9	1.3 ± 0.9	1.4 ± 1.0	1.4 ± 0.8	NS	–
HDLC (mmol/L)	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	1.6 ± 0.4	NS	–
LDLC (mmol/L)	3.3 ± 0.9	3.1 ± 1.0	3.3 ± 0.8	3.5 ± 0.8	0.054	NS
hs-CRP (mg/L)	2.2 ± 3.1	1.6 ± 2.3	2.0 ± 2.2	2.7 ± 4.1	0.015	0.025
AUC glucose 120 (mmol/Lmn)	983 ± 221	836 ± 174	1 009 ± 202	1 041 ± 233	< 0.001	0.011
AUC insulin-120 (mmol/Lmn)	60 698 ± 39 334	52 141 ± 33 466	65 595 ± 42 412	60 008 ± 38 342	0.061	0.010
AUC pro-insulin-120 (mmol/Lmn)	3 245 ± 2 560	3 185 ± 2 679	3 394 ± 2 810	3 102 ± 2 164	NS	–
AUC C-peptide-120 (mmol/Lmn)	103 ± 37	78 ± 31	111 ± 40	107 ± 31	< 0.001	< 0.001
HOMA-IR	2.9 ± 2.4	2.0 ± 1.5	3.2 ± 2.6	3.0 ± 2.5	0.028	0.009
MATSUDA	4.4 ± 2.9	5.9 ± 3.8	3.9 ± 2.5	4.0 ± 2.4	0.001	0.002
S_I	8.8 ± 8.2	14.5 ± 11.4	7.3 ± 6.4	7.3 ± 6.3	< 0.001	< 0.001
mean hands conductances (µS)	66 ± 16	74 ± 9	69 ± 14	58 ± 18	< 0.001	< 0.001
mean feet conductances (µS)	78 ± 11	85 ± 6	83 ± 6	70 ± 13	< 0.001	< 0.001
ratio (feet/hands)	1.26 ± 0.33	1.17 ± 0.16	1.26 ± 0.32	1.30 ± 0.40	0.100	NS
NGT (n, %)	134 (67 %)	41 (95 %)	47 (55 %)	46 (65 %)	< 0.001	< 0.001
IFG/IGT (n, %)	54 (27 %)	2 (5 %)	37 (43 %)	15 (21 %)	< 0.001	< 0.001
diabetes (n, %)	12 (6 %)	0 (0 %)	2 (2 %)	10 (14 %)	0.002	< 0.001

**Adjusted on age

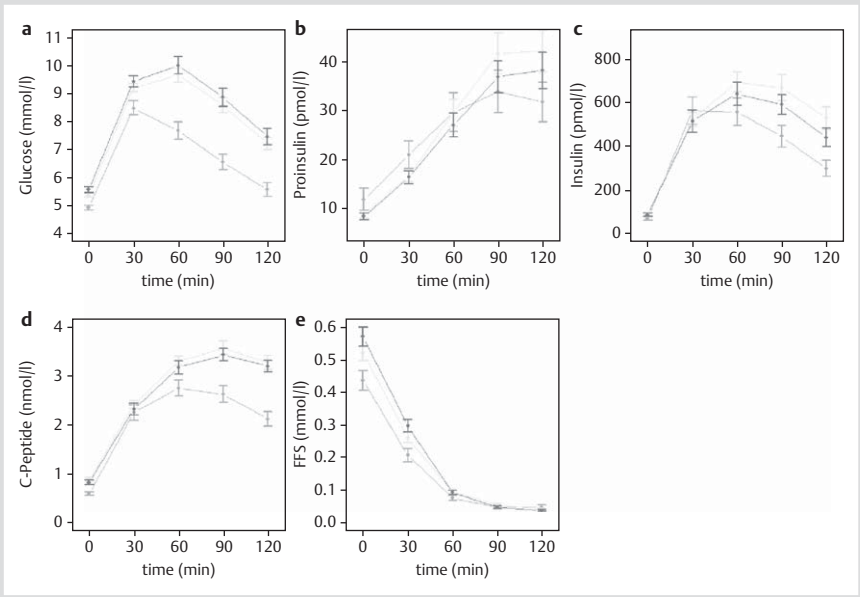

Fig. 1 AUC120 for Glucose **a**, insulin **b**, pro-insulin **c**, C-Peptide **d** and free fatty acid **e** according to risk classification defined by EZSCAN. Green: no risk, yellow: moderate risk and red: high risk. Values are mean ± SEM.

between patients with IFG or IGT would be an interesting topic to further evaluate the risk model against clinical patients' profiles. Therefore, it is necessary to validate the association between the risk model and insulin resistance in a randomized study, and also in larger populations. In addition a follow-up study seems necessary to assess the predictive power of the method.

The EZSCAN provides an interesting new technology for screening. The impairment of autonomic sudomotor dysfunction can be used as indicator to identify people with high risk for diabetes and maybe other metabolic and cardiovascular diseases. Recently, this technology is applicable to adult population, but the concept of impaired autonomic dysfunction is also visible in obese insulin resistant children. The validity of this technology needs to be

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further investigated: it is part of the large European prospective trial ePREDICE that just begins. Summarizing this, the EZSCAN provides an interesting non-invasive technology for screening of chronic diseases in various settings.

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