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EZSCAN as a Screening Tool for Prediabetes and Diabetes in a Large Mexican Population

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Abstract

Objective: Autonomic neuropathy especially small C-Fibers innervating sweat glands is common in diabetes and occurs in pre-diabetes. EZSCAN, a new and non-invasive device that precisely assesses sudomotor function was evaluated as a screening tool for pre-diabetes and diabetes in a large Mexican population.

Methods: The study was performed in Hospital Regional "Lic. Adolfo Lopez Mateos" ISSSTE center. Subjects were classified as pre-diabetic or diabetic according to ADA criteria for fasting plasma glucose (FPG) and HbA_{1C}. EZSCAN test was performed and subjects were classified as no risk, moderate risk or high risk and its performance as a screening tool was assessed through ROC curve analysis.

Results: Among the 1414 subjects involved in the study 357 had pre-diabetes and 64 had diabetes according to FPG confirmed by HbA_{1C} for 52 of them. Area under the Curve for EZSCAN to detect pre-diabetes or diabetes using FPG as reference were 0.65 and 0.73 respectively. Using 27 and 34 as threshold values for EZSCAN risk score for detection of pre-diabetes and diabetes sensitivity was 69% and 73%, specificity 56% and 70% and negative predictive value 82% and 98% respectively. The Odds Ratio (OR) for a patient classified as moderate risk with EZSCAN test was 2.06 (1.59-2.67) to have pre-diabetes and 15.8 (3.8-65.5) to have diabetes as compared to a subject with no risk. The OR was 4.32 (2.49-7.50) for pre-diabetes and 18.3 (3.3-102.5) for diabetes for a subject with high risk as compared to a subject with no risk.

No adverse events during and after measurement with EZSCAN were reported.

Conclusion: EZSCAN allowing quick and quantitative assessment of sudomotor function could be used as an early screening tool for pre-diabetes and diabetes in a large population before performance of more sophisticated and specific, but time-consuming and expensive tests.

Keywords: Sudomotor function; Peripheral neuropathy; prevention

Introduction

Type 2 diabetes is now recognized as an immense and growing public health challenge worldwide affecting about 382 million adults in 2014 and predicted to rise to 592 million by 2035 [1]. In Mexico, the prevalence of pre-diabetes and diabetes were 10.7% and 12.7%, respectively in 2006 with an economic burden of more than US$750 million [2]. Early diagnosis of pre-diabetes and diabetes can result in appropriate interventions which can reduce the incidence of negative complications including myocardial infarction, stroke, retinopathy, nephropathy and neuropathy [3]. Therefore, it is of paramount importance to adopt simple and inexpensive methods in screening for individuals with high risk of pre-diabetes or diabetes. Autonomic neuropathy is common in diabetes populations with potential dysfunctions of cardiovascular, gastrointestinal, genitourinary systems and sudomotor or ocular functions [4,5]. In addition, recent studies have shown that individuals with oral glucose intolerance can also develop autonomic neuropathy [6-8]. Sudomotor function disturbance is considered one of the initial components of autonomic neuropathy, and its assessment may contribute to the detection of autonomic dysfunction in diabetics; in fact, the American Diabetes Association suggests that sudomotor function assessing small fiber status should be included in the diagnostic tests for the detection of neuropathies in diabetes [5]. However lack of a simple and quick method has not allowed widespread use of sudomotor function testing as a screening tool for diabetic neuropathies [9]. EZSCAN, a new device recently developed to allow a precise evaluation of sweat gland function based on sweat chloride concentrations has been shown to detect sudomotor dysfunction in people with diabetes or pre-diabetes when compared to controls [10-14].

The aim of this study was to evaluate EZSCAN as a screening tool for pre-diabetes and diabetes on a large Mexican population.

Materials and Methods

The individuals invited to participate in the study were all recruited in the Clinic Automated Detection and Diagnosis of the Institute for Social Security and Services for State Workers-ISSSTE (CLIDDA). After signing the informed consent a blood sample was taken and a test with the ESZCAN was performed. Individuals over 18 years old of both sexes, apparently healthy, who attended a full check up at CLIDDA were

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included. Individuals with a diagnosis of diabetes, chronic degenerative diseases, cancer, pregnant women and individuals with amputations were excluded. The protocol was approved by the committee of research and research ethics committee for the Hospital Regional "Lic. Adolfo Lopez Mateos" with registration number 226.2013.

Laboratory measurements

Fasting plasma glucose (FPG) was measured using the glucose oxidase method on an autoanalyser (Miura 200). Triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured using chemiluminescence methods on the autoanalyser (Miura 200). The HbA1c level was measured by Immuno-turbidimetric Test Particle Enhanced (Fully-automated Clinical Chemistry Analyzer Miura 200, logotech-ise)

Prediabetes and diabetes were defined by FPG according to ADA criteria (FPG between 100 and 125 mg/dL for prediabetes and ≥126 mg/dL for diabetes) [15].

Measurement of sweat function

EZSCAN is a patented device designed to perform a precise evaluation of sweat gland function based on an electrochemical reaction between sweat chloride and stainless-steel electrodes on which a low Direct Current (DC) is applied and has been described previously [16-19]. It's a dynamic method based on stimulation of sweat glands by the low-level voltage, allowing evidence of sweat dysfunction not detectable under physiological conditions. The device consists of two sets of electrodes for the feet and hands which are connected to a computer for recording and data management (Figure 1). This is a non-invasive test lasting approximately two minutes, during which four combinations of 15 different low DC voltages are applied. No subject preparation such as fasting is required for this test. The subject places their dry, clean palms of the hands and soles of the feet on the electrodes. The device measures the Electrochemical Skin Conductance (ESC) of the hands and feet (right and left sides) using the ratio of the current measured over the constant power applied, expressed in microSiemens (μS). A risk score for prediabetes or diabetes is calculated from these conductances and additional biometric data (age and BMI): no risk (≤ 25), moderate risk (25-50) and high risk scores (>50). These threshold values were issued from previous clinical studies. To improve understanding of the results by the patient a color code for each risk category is used (green for no risk, yellow for moderate risk and orange for high risk).

Statistical analyses

Results for quantitative variables are shown as means ± SD. Quantitative variables were globally compared using ANOVA analysis. As a rule, a p-value <0.05 was regarded as statistically significant. EZSCAN performance was assessed using Receiver Operating Curve (ROC) Analysis with calculation of the Area Under the Curve (AUC). Odds ratios were calculated using logistic regression adjusted for gender. The data management and statistical analysis were done using SAS version 9.4 and R version 2.13.1 [20].

Results

Among the 1414 subjects involved in the study 357 had prediabetes and 64 had diabetes (among them 52 were confirmed by HbA_{1C} ≥ 6.5%). Demographic data of the population are displayed in the table. EZSCAN score values were higher in subjects with prediabetes and diabetes as compared to subjects with normal glucose tolerance. Performance of EZSCAN to detect pre-diabetes and diabetes using FPG as reference is displayed in Figure 2. AUC for HbA_{1C} were 0.68 for pre-diabetes and 0.92 for diabetes. Using 27 as a threshold value for EZSCAN score for detection of pre-diabetes (optimal according to Youden index), sensitivity was 69%, specificity 56% and negative predictive value 82%. Using 34 as threshold value for EZSCAN score for detection of diabetes (optimal according to Youden index), sensitivity was 73%, specificity 70% and negative predictive value 98 %. Among the 52 diabetic patients diagnosed through FPG and HbA1C only 2 had normal EZSCAN (no risk, ≤ 25). The OR for a patient classified as

Figure 1: EZSCAN device with hand and foot electrodes. On the screen is displayed a typical presentation of results after the test for a subject with moderate risk.

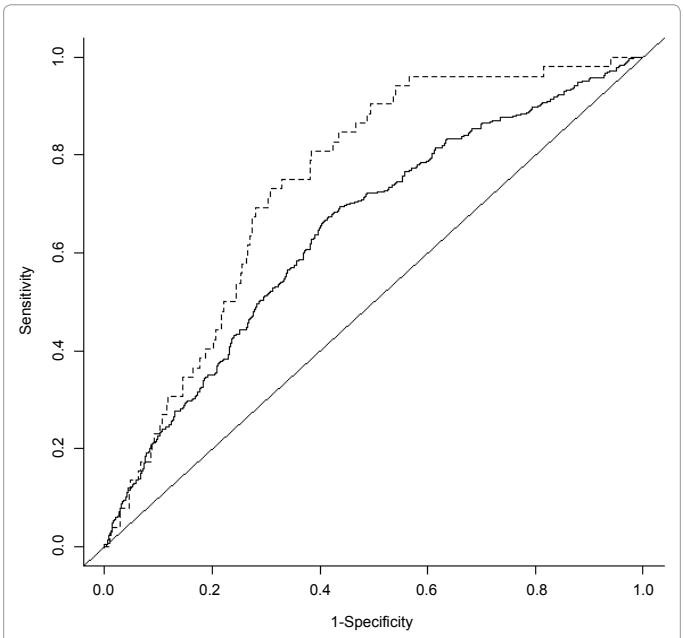

Figure 2: Diagnostic performance of EZSCAN by receiving-operating charactersitics (ROC) curve analysis for pre-diabetes (solid line) and diabetes (dotted line) using fasting plasma glucose threshold values as a gold-standard. Area under the curve are 0.65 for pre-diabetes 0.74 for diabetes.

moderate risk with EZSCAN test as compared to a subject with no risk was 2.06 (1.59-2.67) to have pre-diabetes and 15.8 (3.8-65.5) to have diabetes. The OR for a patient classified as high risk was 4.32 (2.49-7.50) for pre-diabetes and 18.3 (3.3-102.5) for diabetes as compared to a subject with no risk according to EZSCAN test (Table 1).

No adverse event or discomfort during and after measurement with EZSCAN was reported by any subject involved in the study.

Discussion

This study evidenced that the EZSCAN negative predictive values for detection of pre-diabetes and diabetes were 82 and 98% respectively.

Similar studies have been performed in countries with a high prevalence of diabetes requiring a simple, quick and non-invasive method for screening of pre-diabetes and diabetes on large populations. In a study performed in China on more than 5800 subjects with a prevalence of pre-diabetes and diabetes of 21.9% and 17.5% respectively, Zhi Yang et al. showed that the optimal cut-off value for detection of pre-diabetes and diabetes was 30% for EZSCAN risk score [11]. Sensitivity was 73% for pre-diabetes and 81% for diabetes with specificities of 46 and 43% respectively. In another study performed in 876 subjects including 47% with impaired glucose metabolism the AUC of EZSCAN for detecting Impaired Glucose Metabolism (IGM) was 0.79 and with a cut-off of 40% EZSCAN score had a sensitivity of 80%, a specificity of 72% and a negative predictive value of 87% for the detection of IGM [10]. These two studies are in accordance with a previous study performed in India. Ramachandran et al. evidenced that EZSCAN had a sensitivity of 75% to detect diabetes and 70% to detect pre-diabetes in patients diagnosed through an oral glucose tolerance test [12].

According to the results observed in this study, the performances of EZSCAN and HbA_{1C} to detect pre-diabetes seem comparable while HbA_{1C} has a higher capacity to detect diabetes. Based on this and on the low number of false negatives for diabetes (2 out of 52 diagnosed by FPG and confirmed by HbA_{1C}), EZSCAN – a quick, non-invasive and easy to perform test – could be suggested as a first screening test for metabolic diseases in large populations. HbA_{1C} is invasive, and requires time and cost to obtain the results; it would be performed only in subjects with moderate or high risk according to EZSCAN test results. This strategy would dramatically reduce costs avoiding performance of numerous useless HbA_{1C} tests whose individual cost is around $20 US. There have been numerous attempts over the past 30 years to develop non-invasive methods to measure glucose or to use questionnaires/scores based on anthropometric data or other parameters for pre-diabetes/diabetes risk assessment as a first diagnostic step [21]. The most successful approaches have been risk scores such as FINDRISC. A sensitivity rate of 67–84% and specificity rate of 61–67% for IGM have been reported from several studies [22,23]. Risk questionnaires are non-invasive, technically simple, and low cost with reasonable sensitivity and specificity; however, questions in a questionnaire can sometimes be interpreted incorrectly if researchers are not available to clarify those questions, and the result of a questionnaire may also be at risk of "response bias". Furthermore, questionnaires often take a considerable amount of time to complete and score. In comparison, the non-invasive EZSCAN is an objective test requiring no input from the subjects or operator, and the test takes only a couple of minutes to complete and provides immediate results with comparable sensitivity and specificity. The other approach is FPG; however it requires individuals to fast and has low sensitivity [24].

	Whole population (n=1414)
Age (yrs)	44.7 ± 6.8
Male, n(%)	702 (49.6)
EZSCAN risk score (%)	29.8 ± 10.7
BMI (kg/m²)	28.6 ± 4.5
Waist circumference (cm)	95.5 ± 11.0
Hips circumference (cm)	103.5 ± 10.1
Fasting plasma glucose (mg/dl)	98.3 ± 25.6
HDL (mg/dl)	45.4 ± 12.1
Triglycerides (mg/dl)	169.4 ± 101.8
HbA_{1C} (%)	6.2 ± 1.1
Data are Mean ± SD	

Table 1: Characteristics of the study population (n=1414).

EZSCAN was well accepted by the patients, in accordance with previous study populations [13]. As results are quantitative and easy to understand they could also be used as a motivational tool for lifestyle improvement. An exercise study in Finland of individuals at cardiometabolic risk showed that subjects with higher weekly activity - i.e. with a greater improvement in lifestyle - experienced a greater decrease in EZSCAN risk score after 12 months [25]. The results of this last study were in line with small fiber recovery observed through skin biopsy performed in patients involved in a lifestyle improvement program [26]. In this way EZSCAN would be preferable for the follow-up of a patient to questionnaires that do not take into account rapid changes in lifestyle.

One important limit of our study is that FPG was used as reference. Oral glucose tolerance test (OGTT) would have been more suitable but could not be performed on such a large scale. The low percentage of diabetics in our population (around 4%) as compared to a percentage of 15-16% in the Mexican population could be explained by the recruitment in a centre where patients have good follow-up. It underlines the importance of prevention.

This study shows that EZSCAN—a simple, non-invasive, quick and quantitative method—could be used as a screening test for prediabetes or diabetes before more specific, specialized, and time-consuming tests such as 2-hour OGTT or HbA_{1C}. This will allow earlier detection of populations with high risk of developing or presenting diabetes, allowing implementation of preventive measures in this population.

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