Evaluation of EZSCAN as a screening tool for impaired glucose metabolism

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ABSTRACT

Aims: To evaluate the performance of EZSCAN as a screening tool for impaired glucose metabolism (IGM), including impaired glucose tolerance, impaired fasting glucose and undiagnosed diabetes in a Chinese population.

Methods: 876 subjects participated in the study. All subjects underwent tests of EZSCAN, glycated hemoglobin, fasting plasma glucose (FPG), and oral glucose tolerance test (OGTT). Correlation of electrical skin conductance (ESC) with glucose level was evaluated by Pearson correlation coefficient. EZSCAN performance was assessed by receiver operating characteristic curve.

Results: Among the 876 subjects, 53% had normal glucose tolerance (NGT), and 47% had IGM. The ESC for the hands and feet was $72 \pm 10 \mu S$ and $75 \pm 7 \mu S$, respectively, in NGT group; and $64 \pm 13 \mu S$ and $67 \pm 11 \mu S$, respectively, in IGM group. The ESC at hands and feet was significantly correlated with both 2h-OGTT and FPG ($p < 0.001$). NGT group demonstrated a EZSCAN score of $33 \pm 11\%$, which is significantly lower than that of IGM group ($44 \pm 12\%$, $p < 0.001$). The cut-off point of EZSCAN for IGM detection was 40% with a sensitivity of 80% and a specificity of 72%.

Conclusions: EZSCAN is a useful screening tool for identifying subjects at increased risk for impaired glucose metabolism in prediabetes and diabetes. Diagnostic laboratory test should be performed in subjects with EZSCAN scores greater than 40%.

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1. Introduction

The prevalence of diabetes is increasing rapidly in mainland China [1]. Strong evidence has shown that diabetes can be prevented by diet and lifestyle modification in high risk individuals [2–4]. Therefore it is important to have a screening tool for early identification of individuals at high risk of diabetes. Prediabetes, including impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), is a state with intermediate hyperglycemia and is a risk factor for diabetes. An

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Abbreviations: IGM, impaired glucose metabolism; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; OGTT, oral glucose tolerance test; ESC, electrical skin conductance; ROC, receiver operating characteristic; NGT, normal glucose tolerance; OR, odds ratio; CI, confidence interval; AUC, area under the ROC curve.

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estimated 5–10% of individuals with prediabetes will progress to diabetes [5]. Lifestyle modification can lower the relative risk for diabetes by 40–70% [5]. Therefore, any screening tool that can detect prediabetes will be significant in the context of diabetes prevention.

Currently recommended screening tools include measurement of fasting plasma glucose (FPG), and oral glucose tolerance test (OGTT). However, they are invasive and/or time consuming (especially OGTT). Risk assessment questionnaire is another approach to evaluate risk of diabetes. A recently developed EZSCAN system (Impeto Medical, Paris, France) provides a new approach for the detection of diabetes by evaluating sweat gland function [6]. The basic pathophysiological mechanism behind this technology is that small autonomic nerve fibers innervating the eccrine glands are injured with poor glycemic control and respond differently to electric current stimulus [7–10]. As a rapid, noninvasive and reproducible measurement, EZSCAN has gained increasing attention and has been tested in several countries for its validity as a screening tool for the detection of diabetes [11–13]. However, no previous studies have clearly demonstrated a specific cut-off point for further diagnostic tests after EZSCAN. Moreover, most studies have focused on the detection of diabetes with limited consideration of prediabetes [11–13]. Individuals with IGT and IFG have a high risk for the future development of diabetes [14]. Therefore, the aim of present study was to evaluate the performance of EZSCAN as a screening tool for detecting individuals with impaired glucose metabolism (IGM), including prediabetes and undiagnosed diabetes, in an urban Chinese population, and to determine the cut-off point of EZSCAN score for further diagnostic testing.

2. Subjects, materials and methods

2.1. Subjects

The study was performed between August 2012 and October 2012. The subjects were recruited from individuals visiting Peking University People’s Hospital (Beijing, China) for routine health checks. Subjects were included if they were over 18 years old. Exclusion criteria included previously diagnosed prediabetes or diabetes, cancer, severe psychiatric disturbance, epilepsy, pregnancy, use of medications known to influence blood glucose levels (corticosteroids, diuretics, epinephrine, lithium, phenytoin), use of medications known to influence the sympathetic nervous system (beta-blockers), amputation of arm or leg, implantable electrical devices (e.g. pacemaker and defibrillator), known sensitivity to nickel or any other standard electrodes.

A total of 1100 qualifying subjects were invited to participate in the study and 876 (79.6%) agreed to undergo an OGTT. Informed consent was obtained from all participants and the study protocol was approved by the Medical Ethics Committee of the Peking University People’s Hospital.

2.2. Anthropometric and laboratory measurements

All participants’ weight, height, waist circumference and blood pressure were measured by trained nurses and their medical histories recorded. Body mass index (BMI) was calculated as weight in kg/height in m². Blood pressure was measured 3 times following standardized procedures. Blood samples were collected after an overnight fasting for FPG, glycated hemoglobin (HbA1c) and lipid profile analyses, then a standard OGTT was performed according to the WHO recommendations in subjects without known diabetes mellitus [15]. Plasma glucose was measured by glucose oxidase method. HbA1c was measured by high performance liquid chromatography. Serum lipid profiles, including total cholesterol, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein, were measured by standard enzymatic procedures.

Based on the OGTT results, participants were categorized as having normal glucose tolerance (NGT, fasting plasma glucose < 6.1 mmol/L and 2h-OGTT plasma glucose < 7.8 mmol/L); IGT (2h-OGTT plasma glucose 7.8–11.0 mmol/L); IFG (fasting plasma glucose 6.1–6.9 mmol/L), and diabetes (fasting plasma glucose ≥ 7.0 mmol/L and/or 2h-OGTT plasma glucose ≥ 11.0 mmol/L) according to the 1999 World Health Organization criteria [16].

Individuals with IFG, IGT and diabetes were categorized collectively as the group with IGM.

2.3. Measurement of EZSCAN scores

The EZSCAN device is designed to accurately evaluate the sweat gland function through reverse iontophoresis and chromoamperometry. Essentially, EZSCAN measures electrochemical skin conductance (ESC) based on an electrochemical reaction between sweat chlorides and nickel electrodes.

The apparatus consists of two sets of large-area nickel electrodes, as well as a headband. Six electrodes in total are connected to a computer for data recording and management. During the test, each electrode was placed on areas of skin enriched in sweat glands, namely the forehead, the palmar side of the hands, and the plantar side of the feet. A direct-current at an incremental voltage of ≤4 V is applied to the electrode and the ESC (measured in μS; the ratio between current generated and the constant DC stimulus) was calculated for the face, hands, and feet. EZSCAN score is then derived from these ESC measurements with an algorithm that accounts for sex, age, BMI, and systolic blood pressure. The EZSCAN score ranges from 0 to 100%. The test requires no preparation and takes 2–3 min to complete.

2.4. Statistical analysis

Statistical analyses were performed using the SPSS software package version 16.0 (SPSS, Chicago, USA). The data are presented as mean ± SD, median (25–75th percentile), or percentage. Student’s t test and Mann–Whitney test were used for comparisons between continuous variables and chi-squared test was used for categorical variables. The receiver operating characteristic (ROC) was used to evaluate the performance of EZSCAN for the detection of IGM. The area under the ROC curve (AUC) with 95% confidence interval (CI) was calculated and the optimal cut-off point was the peak of the curve where the sum of sensitivity and specificity is maximal. Pearson correlation coefficient was used to evaluate
the correlation of original ESC with 2h-OGTT and FPG. p-Value < 0.05 was considered statistically significant.

3. Results

The demographic, clinical and laboratory characteristics of participants are presented in Table 1. Of the 876 subjects included in the study, 412 were diagnosed with IGM, with an overall prevalence of 47%. The other 464 subjects had NGT. When compared with NGT group, subjects in IGM group were generally older, had larger waist circumferences, higher BMI, systolic blood pressure and triglycerides, and higher FPG, 2h-OGTT and HbA1c levels.

As shown in Table 2, the ESC in both hands and feet (64 ± 13 μS and 67 ± 11 μS, respectively) was significantly decreased in the IGM group compared with the NGT group (72 ± 10 μS and 75 ± 7 μS for hands and feet, respectively, p < 0.001). IGM group had an EZSCAN score of 44 ± 12%, which was significantly higher than that of NGT group (33 ± 11%, p < 0.001). The difference remained significant after the scores were adjusted for age, waist circumference, BMI, systolic blood pressure, triglycerides, FPG, 2h-OGTT, and HbA1c (p < 0.001). Furthermore, the ESC was negatively correlated with both 2h-OGTT and FPG in the hands (r = -0.282 and r = -0.203, respectively) and feet (r = -0.354 and r = -0.281, respectively).

The ROC curve of EZSCAN for detecting IGM is shown in Fig. 1. The AUC for detecting IGM was 0.794 (95% CI: 0.753–0.831). The optimal cut-off point was 40%, with a sensitivity of 80% (95% CI: 73–86%), a specificity of 72% (95% CI: 67–78%), a positive predictive value of 63% (95% CI: 56–70%) and a negative predictive value of 87% (95% CI: 82–91%).

4. Discussion

Diabetes has become increasingly prevalent in China with more than one million new cases diagnosed each year, however, many with IGM remain undetected until complications developed [17]. Dysglycemia alone is a major risk for microvascular and macrovascular complications [17]. Therefore, the early detection of dysglycemia and controlling glycaemia are essential to prevent or delay the vascular and other diabetes complications [18]. EZSCAN, a new noninvasive technology, was originally developed for assessing diabetes risk but has recently also been used to evaluate conditions with altered glucose metabolism, such as metabolic syndromes [6,19]. The present study was designed to evaluate the performance of EZSCAN for identifying individuals with IGM in a Chinese population.

Our study showed that EZSCAN performed strongly in detecting individuals with IGM. The AUC for detection of IGM was 0.794. With an optimal cut-off point of ≥40%, sensitivity was 80%, and specificity was 72%. These results are in line with results from previous studies [11–13]. One study from France, where the device was developed, demonstrated that EZSCAN was highly accurate in detecting IGM with a sensitivity of 87% and specificity of 91% [19].

Table 1 - Baseline characteristics of study subjects.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NGT</th>
<th>IGM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>464</td>
<td>412</td>
<td>–</td>
</tr>
<tr>
<td>Age, years (years)</td>
<td>56.5 ± 9.7</td>
<td>60.5 ± 8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>43.5</td>
<td>46.6</td>
<td>0.377</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.9 ± 4.3</td>
<td>25.9 ± 4.5</td>
<td>0.020</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>89.4 ± 9.7</td>
<td>92.8 ± 9.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>129.7 ± 21.0</td>
<td>139.2 ± 21.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>78.6 ± 11.2</td>
<td>80.6 ± 9.7</td>
<td>0.067</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.88 ± 1.00</td>
<td>5.05 ± 1.02</td>
<td>0.084</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.37 (1.01–1.87)</td>
<td>1.64 (1.18–2.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.25 ± 0.28</td>
<td>1.26 ± 0.28</td>
<td>0.676</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.07 ± 0.99</td>
<td>3.02 ± 1.12</td>
<td>0.640</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>5.32 ± 0.43</td>
<td>6.67 ± 2.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2h-PG, mmol/L</td>
<td>6.13 ± 1.04</td>
<td>10.08 ± 4.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>5.8 ± 0.5</td>
<td>6.3 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(mmol/mol)</td>
<td>(40 ± 5.5)</td>
<td>(45 ± 12)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± standard deviation, median (25–75th percentile), or percentage; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low density lipoprotein; FPG: fasting plasma glucose; 2h-PG: 2 h plasma glucose; HbA1c: glycated hemoglobin. * Log-transformed before testing.

Table 2 - Electrochemical skin conductance (ESC) values and EZSCAN score.

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IGM</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECS of hands (μS)</td>
<td>72 ± 10</td>
<td>64 ± 13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ECS of feet (μS)</td>
<td>75 ± 7</td>
<td>67 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EZSCAN (%)</td>
<td>33 ± 11</td>
<td>44 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted EZSCAN (%)</td>
<td>35 ± 6</td>
<td>42 ± 7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Adjusted for age, waist circumference, BMI, systolic blood pressure, TG, FPG, 2h-OGTT, and HbA1c.

Fig. 1 – Receiver operating characteristic curve (ROC) of EZSCAN for detection of unknown impaired glucose metabolism vs. OGTT.
at a cut-off point of 50% had a 75% of sensitivity and a 100% specificity for detecting diabetes [11]. Another study from India reported a 75% sensitivity for detecting diabetes when using a cut-off point of 50% EZSCAN score [12]. The same group of authors then conducted an 8-month longitudinal study on NGT subjects from the initial study in India [20]. EZSCAN test was performed at the beginning and end of the study. They found that for subjects with an initial EZSCAN score > 65%, the odds ratio (OR) of having IGT 8 months later was 6.19 when compared with subjects with an initial EZSCAN score < 50%. The OR decreased to 3.0 for subjects with an initial EZSCAN score between 50 and 65% [20]. The increased OR of having IGT in individuals with initial high EZSCAN scores suggests that changes in ESC may occur even before the onset of IGT. This finding provided supporting evidence for the use of EZSCAN in detecting prediabetes.

Results from the present study indicate that EZSCAN is almost equally sensitive in detecting IGM and diabetes, as the sensitivity of 80% for detecting IGM in the present study is similar to the 85% sensitivity for detecting diabetes reported in a recent study from China with a cut-off point of 40% EZSCAN [13]. This similarity in sensitivity could be attributed to the same ethnic background of study participants. Another explanation may lie in the correlation coefficients between the electrical conductivity at hands/feet and 2h-OGTT glucose level. Sheng et al. [13] reported a significant negative correlation between 2h-OGTT glucose level and electrical conductance in the hands and feet (0.35 and 0.29, respectively). We also detected a significant negative correlation between 2h-OGTT glucose level and ESC in the hands and feet (0.282 and 0.354, respectively). The correlation data indicate that electrical conductance in the hands and feet are correlated with glucose level within a certain range, with the glucose levels for IGT and diabetes both falling in this range. Therefore, EZSCAN score based on ESC should correlate well with glucose level in both IGM and diabetes, which is reflected by the similar sensitivity of EZSCAN in detecting IGM and diabetes in the previous and present study [12,13], despite a big difference in the EZSCAN score between IGM (a mean of 44) in the present study and diabetes (a mean of 66.6) reported by Sheng et al. [13].

The ORs of having IGT with different levels of initial EZSCAN scores from the India longitudinal study and the significant correlation between ESC and 2h-OGTT/FPG glucose level in the present study provide evidence that EZSCAN can be a reliable tool in detecting IGM. This finding could have important clinical implications because many individuals with IGM are unaware of their glycemic state and the high risk for developing type 2 diabetes. If IGM, especially those with prediabetes, can be diagnosed earlier through EZSCAN screening, lifestyle modification and pharmacologic intervention could be implemented to prevent and delay progression to type 2 diabetes. Therefore, we recommended that subjects with an EZSCAN score of 40% or higher should be further tested for IGT, IFG and undiagnosed diabetes. This practice should reduce the need for invasive diagnostic glucose tolerance tests in the screening phase. Meanwhile, subjects with EZSCAN score > 40% should be informed of the increased risk for prediabetes/diabetes and educated/encouraged to make lifestyle changes.

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 prediabetes/diabetes risk assessment [21]. The most successful approaches have been risk scores such as FINDRISC [21]. 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 noninvasive, technically simple, and low cost with reasonable sensitivity and specificity; however, questionnaires designed for longitudinal studies do not take into account rapid changes in lifestyles, which is especially prominent in China. 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 evaluate. In comparison, noninvasive EZSCAN is an objective test requiring no input from the subjects and operator, and the test takes only a couple minutes to complete and provides immediate results with higher sensitivity and specificity. Neuropad® is another noninvasive test assessing the sweat chloride and sympathetic cholinergic innervation and has a reported sensitivity of 65.1–100% and specificity of 32–78.5% for the diagnosis of diabetic peripheral neuropathy, but the use of Neuropad® for early diabetic neuropathy and IGM has not been verified [24].

The main limitation of the present study is its cross-sectional design. Further longitudinal studies should be designed to evaluate the performance of EZSCAN in detecting prediabetes with a larger sample size and the cost-effectiveness of EZSCAN should also be assessed.

In conclusion, EZSCAN appears to be a useful screening tool for identifying individuals at high risk of prediabetes and diabetes. Our findings suggest that diagnostic laboratory tests should be performed in individuals with an EZSCAN score higher than 40%.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Authors’ contributions

Lizhu Chen and Xiaolu Chen designed the research, analyzed data and wrote the manuscript. Rongjing Ding designed the research and edited the manuscript. Qiting Shi collected and analyzed the data. Dayi Hu reviewed and revised the manuscript.

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