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Discussion of EZSCAN Parameters for Diabetes Screening in Chinese

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Abstract

Objective: To study the parameters of EZSCAN as a screening tool for diabetes in Chinese.

Methods: 6270 subjects participated in the study. All subjects underwent tests of EZSCAN, fasting plasma glucose (FPG), oral glucose tolerance test (OGTT) and HbA1c.

Results: 1) All subjects were divided into 4 groups: the normal group, sugar metabolic abnormalities as low-risk group, middle-risk group and high-risk group. The difference of diabetes incidence among the 4 groups was statistically significant. With the increase of EZSCAN score, the prevalence of diabetes increased significantly. But there is no statistically difference between the low-risk group and the middle-risk group. 2) After adjustment for other variables, there is significantly positive relationship among EZSCAN risk score and the risk of diabetes. Meanwhile there is no statistically difference between the low-risk group and the middle-risk group. 3) The cut-off point of EZSCAN for diabetes was 44.5% with the sensitivity was 73.2% which was higher than of FPG and HbA1c.

Conclusion: As EZSCAN-diabetes risk score increases, the risk of diabetes increases. EZSCAN can be used as a tool for screening for diabetes. At the best screening diabetes cut-off point value 44.5%, the sensitivity is higher than traditional method of FPG and HbA1c.

Keywords: Diabetes; EZSCAN; Screening; Sensitivity; Specificity

Introduction

Diabetes mellitus (DM) has become one of the most-common non-communicable diseases which threaten the human health in the world. According to the most recent nationwide report in China [1], the prevalence of Diabetes and impaired glucose metabolism was 9.7% and 15.5% respectively. Since DM is asymptomatic for many years [2], early detection can result in appropriate interventions that can reduce the incidence of complications. Currently, screening tests for type 2 diabetes include risk assessment questionnaires, biochemical tests and combinations of both. The biochemical tests currently available are measurement of blood glucose or HbA1c [3]. Since the main purpose of screening is to detect asymptomatic people with undiagnosed diabetes, questionnaires which are based on the symptoms of diabetes are not adequate. The fasting plasma glucose (FPG) test is recommended for initial screening for non-pregnant adults. However it is an invasive test which has a low sensitivity in many populations. Hence a tool which is easy to administer, non-invasive, with high sensitivity and specificity and cost-effective would be of advantage and of great benefit for diabetes screening. The value of such a tool would increase if it can be used by non-clinical personnel, who assist the doctors.

The new EZSCAN device is designed to perform a precise evaluation of sweat gland function through reverse iontophoresis, allowing the measurement of sweat chloride concentrations [4,5]. In the present Chinese study, we first compared the accuracy of EZSCAN device and the original electrochemical conductance measurement with concentrations of fasting plasma glucose (FPG) and serum HbA1c in the diagnosis of diabetes mellitus, and then investigated the specific cut-off point for diagnostic tests of diabetes in Chinese people.

Methods

Study subjects

The study was performed between January 2012 and June 2015. The subjects were recruited from individuals visiting the Third Xiangya Hospital of Central South University (Changsha, China) for routine health checks. The exclusion criteria were as follows: Previous diagnosis of pre-DM or DM; cancer; epilepsy; pregnancy; consumption of drugs known to affect blood glucose levels (corticosteroids, diuretics, epinephrine, lithium, phenytoin); consumption of drugs known to affect the sympathetic nervous system (β-blockers); arm or leg amputation; electrical implantable device (pacemaker, defibrillator). A total of 6270 qualifying subjects were invited to participate in the study and all agreed to undergo oral glucose tolerance test (OGTT), FGP and glycated hemoglobin (HbA1c). Informed consent was obtained from all participants and the study protocol was approved by the Medical Ethics Committee of the Third Xiangya Hospital of Central South University.

OGTT and laboratory methods

All participants' weight, height, waist circumference, blood pressure and blood lipid were measured by trained nurses and their medical histories recorded. Body mass index (BMI) was calculated as weight in kg/height in m^2. Blood pressure was measured 3 times following standardized procedures. Blood samples about 2ml were collected respectively 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. Each subject was asked to consume 75g liquid glucose for an OGTT. The blood specimen was taken 2h after administering the oral glucose load. Plasma glucose was measured by glucose oxidase method. HbA1c was measured by high performance liquid chromatography. Serum lipid profiles, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein (LDL-C) were measured by standard enzymatic procedures.

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Based on the OGTT results, participants were categorized as no diabetes (2h-OGTT plasma glucose < 11.0 mmol/L); and diabetes (2h-OGTT plasma glucose ≥ 11.0 mmol/L) according to the 1999 World Health Organization criteria [6].

EZSCAN Test

The EZSCAN device is designed to accurately evaluate the sweat gland function through reverse iontophoresis and chronoamperometry. 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. Following the placement of the electrodes, the patient was asked to stand still for 2–3 min. 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% and categorized as the normal group (0-25%), sugar metabolic abnormalities as low-risk group (26-50%), middle-risk group (51-75%) and high-risk group (76-100%).

Statistical methods

Statistical analyses were performed using the SPSS software package version 17.0 (SPSS, Chicago, USA). The data are presented as mean ± SD. 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, FPG and HbA1c for the detection of diabetes mellitus. 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 EZSCAN score with risk of diabetes incidence. $p < 0.05$ was considered statistically significant.

Results

The demographic, clinical and laboratory characteristics of participants are presented in Table 1. Of the 6270 subjects included in the study, 3957 were men and 2313 were women. All subjects were classified 4 groups: normal group (0-25%), sugar metabolic abnormalities as low-risk group (26-50%), middle-risk group (51-75%), and high-risk group (76-100%). Compared among 4 groups, the difference is significant in the clinical and laboratory characteristics ($p<0.01$). And the differences between 4 groups are shown in the Table 1. The incidence of the diabetes were significant among 4 groups (F=112.629, p=0.000) and the data compared between 4 groups are shown in the Table 2 and Figure 1.

Logistic analyze showed that there existed correlation between EZSCAN evaluation system and risk of diabetes after adjusted for age, systolic blood pressure (SBP), diastolic blood pressure (DBP), waist hip ratio (WHR), BMI, TC, TG, LDL-C, HDL-C. Compared with normal groups, the risk of diabetes was gradually increasing among other 3 risk groups. The OR of low-risk group was 1.974 (95% CI: 1.497-2.603), of middle-risk group was 2.374 (95% CI: 1.674-3.366), of high-risk group was 30.977 (95% CI: 19.492-49.228) showed in Table 3.

The ROC curve showed the diagnostic accuracy of the derived EZSCAN diabetes index for the diagnosis of diabetes mellitus (Figure 2). The area under the curve (AUC) was 86.6% of the total square (95% CI: 0.851-0.882). And the cut-off point of EZSCAN for diabetes was 44.5% with the sensitivity and specificity were 73.2% and 83%, respectively (Table 4 and Figure 2).

	normal group	low-risk group	middle-risk group	high-risk group	*P*
n	2506	2031	1050	683	
Age, years	43.09 ± 8.67	49.74 ± 8.73[a]	51.48 ± 9.45[ab]	55.72 ± 9.24[abc]	0.000
BMI	24.67 ± 3.22	25.80 ± 3.36[a]	25.67 ± 3.52[a]	26.35 ± 3.14 [a]	0.000
WHR	0.89 ± 0.066	0.92 ± 0.24[a]	0.91 ± 0.067[a]	0.96 ± 0.053[abc]	0.000
SBP, mmHg	125.24 ± 15.05	130.08 ± 16.89[a]	129.04 ± 17.98[a]	134.57 ± 17.47[abc]	0.000
DBP, mmHg	80.05 ± 11.44	82.69 ± 12.13[a]	81.94 ± 11.81[a]	83.02 ± 13.08 [a]	0.000
FPG(mmol/l)	5.30 ± 1.18	5.59 ± 1.33[a]	5.65 ± 1.46[a]	8.73 ± 3.46[abc]	0.000
OGTT(mmol/l)	7.00 ± 2.72	7.92 ± 3.41[a]	8.07 ± 3.63[a]	14.97 ± 7.05[abc]	0.000
HbA1c (%)	5.40 ± 0.78	5.61 ± 0.84[a]	5.72 ± 0.95[a]	7.73 ± 1.94[abc]	0.000
TC(mmol/l)	5.23 ± 0.97	5.52 ± 1.02[a]	5.49 ± 0.87[a]	5.56 ± 1.03[abc]	0.000
TG(mmol/l)	1.31 ± 0.87	1.56 ± 1.01[a]	1.52 ± 0.98[a]	1.61 ± 1.03[abc]	0.000
LDL-C(mmol/l)	3.15 ± 0.92	3.31 ± 0.89[a]	3.28 ± 1.02[a]	3.35 ± 0.88[abc]	0.000
HDL-C(mmol/l)	1.41 ± 0.23	1.38 ± 0.29[a]	1.37 ± 0.33[a]	1.34 ± 0.32[abc]	0.000

Data are presented as mean ± SD, or number of subjects; BMI: body mass index; WHR: waist hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; HbA1c: glycated hemoglobin; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein; HDL-C: high-density lipoprotein; a. compared with normal group, $p < 0.05$; b. compared with low-risk group, $p < 0.05$; c. compared with middle-risk group, $p < 0.05$

Table 1: Baseline characteristics of subjects.

Groups in EZSCAN	OGTT normal	diabetes	Total subjects	Incidence (%)
normal group	2381	125	2506	4.99
low-risk group	1783	248	2031	12.21*
middle-risk group	903	147	1050	14.00*
high-risk group	286	397	683	58.06*#

Data are presented as number of subjects (%). Diabetes mellitus was defined as an OGTT test of at least 11.0 mmol/l. *compared with normal group, $p < 0.05$; #compared with low-risk group, $p < 0.05$.

Table 2: The incidence of diabetes among EZSCAN groups.

In the further analysis, we chose OGTT level as the gold standard for diabetes, then compared the sensitivity and specificity among EZSCAN (44.5%), FPG (7.0mmol/l) and HbA1c (6.5%) depending on the ROC curve (Table 5 and Figure 3).

Discussion

Diabetes has become increasingly prevalent in China with more than one million new cases diagnosed every year. However, many people with impaired glucose metabolism remain undetected until complication developed [7]. Dysglycemia alone is a major risk for microvascular and macrovascular complication. Therefore, the early detection of dysglycaemia and controlling glycemia are essential to prevent or delay the vascular and other diabetes complications [8]. EZSCAN, a new noninvasive technology, was originally developed for assessing diabetes. The present study was designed to evaluate the performance of EZSCAN and to find its suitable parameters for the diagnosis of diabetes in Chinese population.

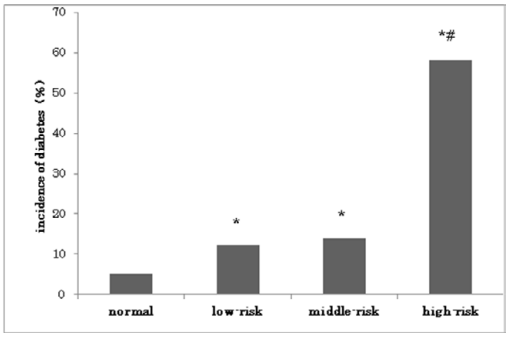

Figure1: The incidence of diabetes among EZSCAN groups.

variants	regression coefficient	Standard deviation	Wald test	OR (95%CI)	*p*
Low-risk group	0.680	0.141	23.221	1.974P (1.497-2.603)	0.000
Middle-risk group	0.864	0.178	23.548	2.374 (1.674-3.366)	0.000
High-risk group	3.433	0.236	211.023	30.977 (19.492-49.228)	0.000
WHR	0.052	0.226	0.054	1.054 (0.667-1.641)	0.817
Age	0.021	0.007	9.926	1.022 (1.008-1.035)	0.002
BMI	0.108	0.018	37.222	1.114 (1.076-1.153)	0.000
TC	0.302	0.084	11.032	1.098 (1.012-1.154)	0.001
TG	0.360	0.105	25.489	2.495 (1.631-2.962)	0.000
HDL-C	-0.102	0.106	0.351	0.931 (0.625-1.274)	0.382
LDL-C	0.401	0.098	18.377	1.465 (1.231-2.109)	0.000
SBP	0.006	0.005	1.137	1.006 (0.995-1.016)	0.286
DBP	0.020	0.007	7.074	1.020 (1.005-1.035)	0.008

Table 3: Logistics analyze between EZSCAN and diabetes.

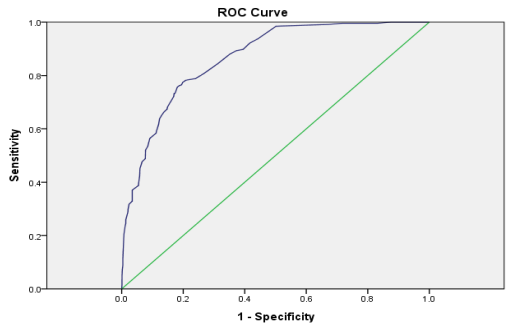

Figure 2: Accuracy of EZSCAN for the diagnosis of diabetes analyzed by Receiver operating characteristic curve (ROC).

Cut-off point	sensitivity	specificity	Youden index
43.500	0.732	0.828	0.560
44.500	0.732	0.830	0.562
45.500	0.721	0.831	0.552
46.500	0.682	0.851	0.533

Table 4: Sensitivity and specificity of EZSCAN for the diagnosis of diabetes.

	AUC	95% CI	*P*	Cut-off point	sensitivity	specificity
EZSCAN	0.813	0.784-0.842	0.000	44.5%	73.2%	83.0%
FPG	0.792	0.759-0.825	0.000	7.0	59.9%	99.8%
HbA1c	0.816	0.785-0.847	0.000	6.5%	65.9%	98.7%

Table 5: Sensitivity and specificity of EZSCAN for the diagnosis of diabetes vs FPG and HbA1c.

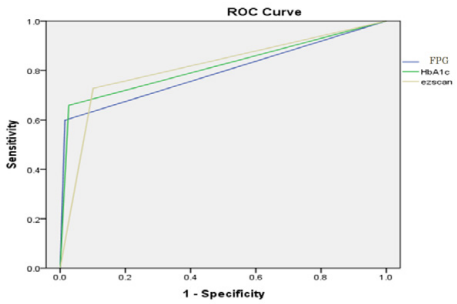

Figure 3: Receiver operating characteristic curve (ROC) of EZSCAN for the diagnosis of diabetes vs FPG and HbA1c.

Our study demonstrated that EZSCAN, as a screening tool, had an acceptable accuracy for the diagnosis of diabetes mellitus. The AUC for detection of diabetes was 0.813. With an optimal cut-off point 44.5%, the sensitivity was 73.2%, which is higher than the method of FPG (59.9%) and HbA1c (65.8%), and the specificity was 83.0%. It is well known that the sensitivity is more important for the screening method. In Mayaudon H [9] report recruited 133diabetes patients and 41 healthy volunteers in France, EZSCAN had a sensitivity of 75% and a specificity of 100% with the cut-off point 50%. One study from Chinese Shanghai 195 subjects demonstrated that EZSCAN at a cut-off point of 40% had a sensitivity of 85% and a specificity of 64% [10]. Another study from Chinese Beijing 1100 subjects reported 80% sensitivity for diabetes when using a cut-off point of 40% EZSCAN score [11]. All these studies found that sensitivity of EZSCAN is higher than of FPG. Taken these studies and our research together, EZSCAN seemed to have consistent and constant high sensitivity across population. The heterogeneous cut-off point might be attributable to the differences of participants in race, sample size and included criterion.

It is the first time to find that the grouping method of quartile in EZSCAN is not suitable in Chinese people. In the EZSCAN system, the subjects are divided into 4 groups: normal (0-25%), low-risk (26-50%), middle-risk (51-75%), high-risk (75-100%) according to the EZSCAN score. Our study found that the risk of diabetes increased with the increasing of EZSCAN score. Odds ratio (OR) showed that in our study, after adjusted for confounders, low-risk group was 1.974 (1.497-2.603), middle-risk group was 2.374 (95% CI: 1.674-3.366), high-risk group was 30.977 (95% CI: 19.492-49.228). Compared with the normal group, the variants of other 3 groups are significantly higher in age, BMI, WHR, TC, LDL-C, FPG, 2hPG, HbA1c, SBP and DBP, but lower

in HDL-C. However, compared the low-risk group with the middle-risk group, there were no significant difference in the all variants. And we furthered to find that the incidence of diabetes in the low-risk group was higher than of normal group and the incidence in high-risk group was higher than that of middle-risk and low-risk groups. In the same time, we also found that it is not significantly different between the middle-risk group and low-risk group. All these data implied that EZSCAN score is useful to evaluate the risk of diabetes. Nonetheless, the difference between low-risk group and middle-risk group is not significant. It is possible that the algorithm for the computation of diabetes index for the diagnosis of diabetes mellitus generated from the French population cannot directly be generalized to population of Chinese people.

In conclusion, our study found that the sensitivity of EZSCAN was higher than of FPG and HbA1c when the cut-off point was 44.5%, but the specificity was lower than of FPG and HbA1c. So EZSCAN is accurate in the diagnosis of diabetes mellitus as a screening tool. Our findings suggest that diagnostic laboratory tests such as OGTT should be performed in individuals with the EZSCAN score higher than 44.5%. EZSCAN appears to be a useful tool for identifying individuals at high risk of diabetes. But the main limitation of the present studies is cross-sectional design. Further longitudinal studies should be designed to find the suitable parameters such as cut-off point and evaluate the performance of EZSCAN in detecting pre-diabetes with a larger sample size and multi-center study in different race.

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