DETECTION OF MICROVASCULAR COMPLICATIONS OF TYPE 2 DIABETES BY EZSCAN AND ITS COMPARISON WITH STANDARD SCREENING METHODS

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ABSTRACT

BACKGROUND

EZSCAN is a new, noninvasive technique to detect sudomotor dysfunction and thus neuropathy in diabetes patients at an early stage. It further predicts chances of development of other microvascular complications. In this study, we evaluated EZSCAN for detection of microvascular complications in Type 2 diabetes patients and compared accuracy of EZSCAN with standard screening methods.

MATERIALS AND METHODS

104 known diabetes patients, 56 males and 48 females, were studied. All cases underwent the EZSCAN test, Nerve Conduction Study (NCS) test, Vibration perception threshold test (VPT), Monofilament test, Fundus examination and Urine micral test. The results of EZSCAN were compared with standard screening methods. The data has been analysed and assessed by applying appropriate statistical tests within different groups.

RESULTS

Mean age of the subjects was 53.5 ± 11.4 years. For detection of diabetic neuropathy, sensitivity and specificity of EZSCAN was found to be 77.0 % and 95.3%, respectively. Odd's ratio (OR) was 68.82 with $p < 0.0001$. AUC in ROC curve was 0.930. Sensitivity and specificity of EZSCAN for detection of nephropathy were 67.1% and 94.1%, respectively. OR = 32.69 with $p < 0.0001$. AUC was 0.926. Sensitivity of EZSCAN for detection of retinopathy was 90% while specificity is 70.3%. OR = 21.27; $p< 0.0001$). AUC came out to be 0.920.

CONCLUSION

Results of EZSCAN test compared significantly to the standard screening methods for the detection of microvascular complications of diabetes and can be used as a simple, noninvasive and quick method to detect microvascular complications of diabetes.

KEYWORDS

Type 2 Diabetes, EZSCAN, Microvascular Complications.

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INTRODUCTION: Type 2 diabetes often progresses silently, without developing clinically evident symptoms. It frequently remains undiagnosed until complications appear. So, as soon as a patient is diagnosed with diabetes, she/he must be screened for the complications of the disease simultaneously because by this time the disease would have already progressed pretty long in its course. Timely screening and early detection of diabetes and its complications will enable clinicians to intervene early in the course of the disease, preventing adverse outcomes and possible regression of the complications associated with the disease.

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There are a number of macro as well as microvascular complications of diabetes, among which neuropathy is considered to be the earliest to occur.[1,2] Autonomic neuropathy develops very early in the course of the disease and it may be either clinically evident or subclinical with dysfunctions of cardiovascular, gastrointestinal, genitourinary systems and sudomotor or ocular functions. Among these, sudomotor dysfunction has been regarded as the initial component of autonomic neuropathy. In the presence of neuropathy, the possibility of nephropathy and retinopathy is increased too.

The conventional methods used to screen for microvascular complications are time taking and invasive. Moreover, multiple tests are needed for different complications which might reduce the patient's compliance. This creates a need for methods which are quick, safe, non-invasive and can be used to screen all the three complications by a single test. EZSCAN is one such method which has already proven its effectiveness in detecting

diabetes and pre-diabetes at mass level[3-7] and can be used further to detect the presence of microvascular complications in persons having diabetes.

AIMS AND OBJECTIVES: Use of EZSCAN for detection of microvascular complications in patients of Type 2 diabetes and comparison of EZSCAN results with standard screening methods for complications of diabetes.

MATERIALS AND METHODS:

Study Design: This single point cross sectional study was conducted over 104 subjects at MLN Medical College, Allahabad and its associated SRN Hospital, Allahabad and Nazareth Hospital, Allahabad during a period from March 2014 to July 2015. Subjects ≥ 18 years who were already diagnosed with diabetes according to American Diabetes Association 2014 guidelines were selected as cases. There was no separate control group for the study. Conventional screening methods to detect microvascular complications of diabetes here served as control. Patients having secondary diabetes due to chronic pancreatitis, haemochromatosis, cystic fibrosis, drug- or chemical-induced (such as in the treatment of HIV/ AIDS or after organ transplantation) and Gestational diabetes mellitus were excluded from the study.

Procedures: A detailed history, clinical examination and relevant investigations were done in each subject to assess the disease progression and presence of microvascular complications. Each subject also underwent EZSCAN to assess the presence of microvascular complications of diabetes. History included duration of diabetes, symptoms of neuropathy and other related complications, any drug intake, any concurrent or chronic illness. Diabetic neuropathy was confirmed if the patient complained of any symptoms of neuropathy after ruling out other disorders that can cause neuropathy on the basis of history and clinical examination or any of the three tests done to detect neuropathy was abnormal viz. 10 gram monofilament test, vibration perception threshold test and nerve conduction study (NCS). Retinopathy was assessed by an experienced ophthalmologist using a direct ophthalmoscope with dilated pupils. Any form and grade of retinopathy was taken as presence and normal retinal examination was considered as absence of retinopathy. Screening for diabetic nephropathy was done by detecting microalbuminuria by urine micral test. Nephropathy was considered present when the spot urine albumin level was more than 20 mg/L of urine in a spot urine sample. Fasting blood glucose (FBG), Post-prandial blood glucose (PPBG) and HbA1c level were measured in the hospital laboratory.

EZSCAN Test: EZSCAN is being used for early screening and assessment of early diabetes, devised by Impeto Medical (Paris, France). It is non-invasive and provides immediate results, without any need for patient preparation, fasting or a blood draw. It uses reverse iontophoresis and chronoamperometry methods to assess the sudomotor dysfunction. Data processing results in a score representative of the individual's risk to show pre-diabetes (IGT), diabetes and complications.[8] EZSCAN risk score was recorded which ranges from 0 to 100% and risk assessment was done as: no risk (<25 %), intermediate risk (25-50 %) and high risk (>50%). These threshold values were issued from the previous clinical studies. 37% was taken as the cut-off for detection of the microvascular complications (optimal according to Youden index).

STATISTICAL ANALYSIS: The data were analysed and assessed with appropriate statistical methods within different groups. Software used is SPSS-IBM version 21.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Odd's ratio (OR) were calculated. Receiver Operator Characteristic (ROC) curve were plotted to test the accuracy of EZSCAN for all the three microvascular complications. Confidence interval used is 95% and p value <0.05 was taken as significant.

OBSERVATIONS AND RESULTS: Out of 104 subjects studied, 56 were males and 48 females. Mean age of subjects was 53.5 ± 11.4 (years) with a range between 24 to 76 years. Among 49 subjects labelled to have microvascular complication by EZSCAN, 47 were having diabetic neuropathy as confirmed by standard methods of detection of neuropathy viz. Monofilament test, VPT and NCS and 2 were found to be normal. Whereas among 55 subjects found to be having no microvascular complication, 14 were detected having neuropathy by standard methods. EZSCAN was found highly specific to detect neuropathy in diabetics with specificity being 95.3% but a little less sensitive (77%). PPV came out to be 95.9% while NPV was 74.5%. Odd's Ratio (OR) was calculated 68.8214 and p value was <0.0001 which is highly significant (Table 1). When ROC curve was plotted, the Area Under Curve came out to be 0.93 which signifies that EZSCAN can very accurately predict (93.0%) the abnormal results shown by standard methods to detect neuropathy (Fig. 1). Out of 49 subjects detected to have microvascular complications by EZSCAN, 27 were found to have retinopathy on fundus examination while 22 were normal. Among 55 normal subjects according to EZSCAN, only 3 were having retinopathy on fundus examination and rest 52 were normal. EZSCAN was highly sensitive in detecting retinopathy with 90% sensitivity but specificity was 70.3 %. PPV was 55.1 % while NPV was 94.5 %. Odd's Ratio (OR) came out to be 21.2727 with p<0.0001 which is significant (Table 2). The Area Under Curve in the ROC curve for retinopathy was 0.920 (Fig. 2). Out of 49 subjects predicted to have complication by EZSCAN method, 47 were found to be having nephropathy as detected by Urine Micral test and 2 were normal. While among 55 subjects found to be normal by EZSCAN, 23 were found to be positive for Urine micral test and 32 were negative. Sensitivity of EZSCAN was 67.1% whereas specificity was 94.1%. PPV and NPV were 95.9% and 58.2% respectively. Odd's ratio was 32.6957 with p<0.0001 (Table 3). The AUC in the ROC curve plotted was 0.926 which signifies that EZSCAN can very accurately predict (92.6%) the abnormal results detected by standard method i.e. urine micral test (Fig. 3).

EZSCAN Results	Neuropathy present by Standard methods	Neuropathy absent by standard methods	Total
Abnormal (n)	47	2	49
Normal (n)	14	41	55
Total	**61**	**43**	**104**

Table 1: Comparison of EZSCAN results with Standard tests for Neuropathy

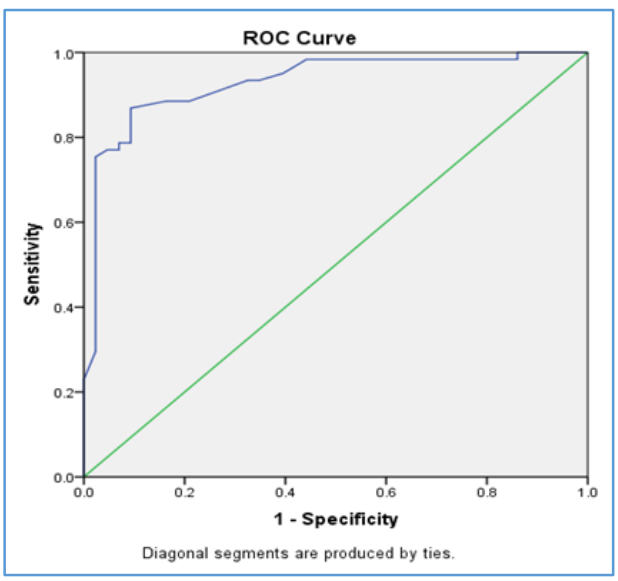

Fig. 1: Receiver Operator Characteristic (ROC) curve showing Comparison of EZSCAN with Standard Method to detect Neuropathy

EZSCAN Results	Retinopathy present by standard method	Retinopathy absent by standard method	Total
Abnormal	27	22	49
Normal	3	52	55
Total	**30**	**74**	**104**

Table 2: Comparison of EZSCAN results with Standard tests for Retinopathy

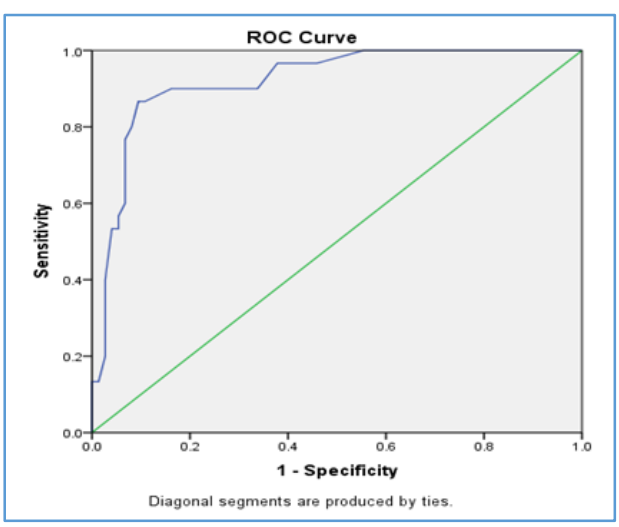

Fig. 2: Receiver Operator Characteristic (ROC) curve showing Comparison of EZSCAN with Standard method to detect Retinopathy

EZSCAN Results	Nephropathy present (n)	Nephropathy absent (n)	Total
Abnormal (n)	47	2	49
Normal(n)	23	32	55
Total	**70**	**34**	**104**

Table 3: Comparison of EZSCAN results with Standard tests for Nephropathy

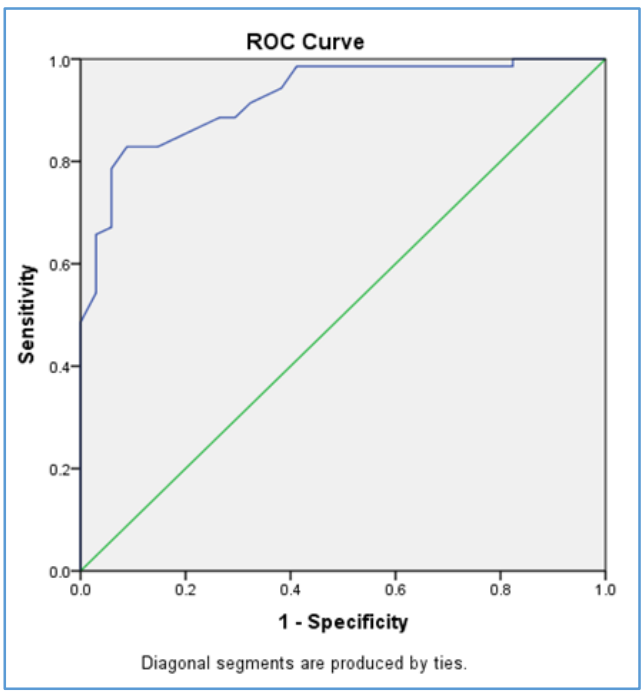

Fig. 3: ROC plot showing Comparison of EZSCAN with Standard test to detect Nephropathy (Urine Micral)

DISCUSSION: In this study, sensitivity and specificity of EZSCAN for detection of neuropathy were found to be 77.0% and 95.3%, respectively. In the study done by JH Calvet and et al, sensitivity and specificity of EZSCAN for detection of at least one microvascular complication were 82% and 61%, respectively.[9] AUC in ROC curve for detection of neuropathy was 0.93 in the present study while in the study of JH Calvet and et al, the AUC was found to be 0.75[9]. This signified that EZSCAN can very accurately predict neuropathy in diabetic patients and is significantly comparable with standard methods.

For detection of nephropathy, sensitivity and specificity of EZSCAN in this study were 67.1% and 94.1%, respectively. That means EZSCAN is not that much sensitive in detecting nephropathy in diabetes patients. It might be due to the fact that urine micral test may come positive in initial stages of diabetes, sometimes before the onset of neuropathic changes.[10] Thus, it shows that EZSCAN is significantly comparable to standard method in efficacy to detect diabetic nephropathy. When ROC curve was plotted for comparing EZSCAN with the standard methods for detecting diabetic nephropathy, AUC was 0.926 which signifies that EZSCAN can very accurately predict the nephropathy in diabetic patients comparable to the standard method. In the study conducted by Risa Ozaki and et al,[11] sensitivity and specificity of EZSCAN for

detection of diabetic nephropathy was found to be 94% and 78%, respectively. But they had taken the cut-off value of EZSCAN risk score as 55% whereas in the present study, 37% risk score has been taken as cut-off. In a similar study done by Barry I Freedman and et al,[12] evaluating SUDOSCAN for detection of kidney disease in African American and European American diabetic subjects, the electrochemical measure of skin conductance was positively associated with kidney function [parameter estimate (β)=3.42, standard error (SE)=1.2; p=4.9E−3]. Thus, observations of these two studies support the findings of the present study that EZSCAN is useful in predicting the presence of diabetic kidney disease.

In the present study, sensitivity of EZSCAN for detection of retinopathy came out to be 90% while specificity is 70.3%. Thus, EZSCAN is significantly comparable to standard method in efficacy to detect diabetic retinopathy. AUC in ROC was 0.92 which signifies that EZSCAN can very accurately predict retinopathy in diabetic patients comparable to the standard method i.e. fundus examination. This result is similar to the results found in study by JH Calvet and et al,[9] in which it was found that electrochemical conductance (ESC) was lower in T2DM patients with at least one microvascular complication as compared to patients without, and this difference was statistically significant. AUC of the ROC curve was 0.75 for SUDOSCAN risk score, with a sensitivity of 82% and specificity of 61%.

Among 49 subjects found to have microvascular complications by EZSCAN, 47 were having neuropathy and 47 were having nephropathy but these 47 subjects are not the same. And among the 2 subjects not having neuropathy, 1 was having nephropathy and same is the case with 2 subjects not having nephropathy. Only 27 patients were found to have retinopathy among these 49 subjects. This might be due to the fact that retinopathy develops later in the course of the disease as compared to neuropathy and nephropathy. Similar results were found in study done by Hari Kumar KVS and et al[10] on 1529 Indian subjects with T2DM. In their study, 37% subjects were having neuropathy while 20% and 17% subjects were having nephropathy and retinopathy respectively. This observation is further supported by many such studies done previously.[13-15]

Taking the results and observations of previous studies and the present study together, EZSCAN seemed to have significant sensitivity, specificity and accuracy in detecting microvascular complications of diabetes. And accuracy of EZSCAN in detecting microvascular complications in persons having diabetes is significantly comparable to the standard screening methods.

EZSCAN can be used as a non-invasive, easy to use and quick tool for casual as well as mass screening to detect microvascular complications in diabetics.

CONCLUSION: Diabetes is now recognised as an immense and growing public health challenge worldwide, especially India and other South East Asian countries. EZSCAN proved to be significantly sensitive, specific and accurate in detecting microvascular complications. So, considering the large number of patients needed to be screened, it can be used to detect microvascular complications at an early stage, even in the presence of a single complication.

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