RESEARCH

Association of serum stromal cell-derived factor 1 levels with EZSCAN score and its derived indicators in patients with type 2 diabetes

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Abstract

Background: The aim of the study was to explore whether plasma stromal cell-derived factor 1 (SDF-1) levels are associated with the EZSCAN score and its derived indicators in patients with type 2 diabetes (T2D).

Methods: From July 2020 to December 2020, a total of 253 patients with T2D were consecutively recruited. Serum SDF-1 levels were measured by sandwich ELISA. EZSCAN test was applied to evaluate the sudomotor function of each patient, and based on the results, EZSCAN score, cardiac autonomic neuropathy risk score (CANRS) and cardiovascular risk score (CVDRS) were calculated by particular algorithms. In addition, other relevant clinical data were also collected.

Results: With increasing tertiles of serum SDF-1 levels, the CANRS and CVDRS significantly increased (both *P* for trend <0.001), while the EZSCAN score significantly decreased (*P* for trend <0.001). Moreover, serum SDF-1 levels were significantly and positively correlated with the CANRS and CVDRS (r = 0.496 and 0.510, respectively, both *P* < 0.001), and negatively correlated with the EZSCAN score (r = −0.391, *P* < 0.001). Furthermore, multivariate linear regression analyses were constructed, and after adjusting for other clinical covariates, serum SDF-1 levels were independently responsible for EZSCAN score (β = −0.273, *t* = −3.679, *P* < 0.001), CANRS (β = 0.334, *t* = 5.110, *P* < 0.001) and CVDRS (β = 0.191, *t* = 4.983, *P* = 0.003).

Conclusions: SDF-1 levels in serum were independently associated with the EZSCAN score and its derived indicators, such as CANRS and CVDRS in patients with T2D.

Introduction

The rising prevalence of type 2 diabetes (T2D) has posed a great threat to public health, affecting approximately 400 million people in 2017 (1). Uncontrolled and untreated T2D may lead to a variety of chronic complications (2). In 2015, approximately 5.0 million deaths may be attributed to T2D and its complications (3). Compared with individuals without diabetes, those with T2D suffer a severe decrease in quality of life due to the heavy burden of treatment and the development of diabetic complications (4). Therefore, in patients with T2D, identifying the risk of developing complications and timely intervention is the focus of the management of T2D.

The EZSCAN test is noninvasive detection technology for the assessment of electrochemical skin conductance (ESC) by reverse iontophoresis and chronoamperometry, which is clinically useful for evaluating sudomotor function (5). Since sudomotor function is dominated by small sympathetic C fibers, the EZSCAN test is available for assessing autonomic neuropathy and small-fiber neuropathy in diabetes (6). Cardiac autonomic neuropathy risk score (CANRS), derived from ESC, age and BMI, can serve as a good screening tool for cardiac autonomic neuropathy (CAN) (7). In addition, the EZSCAN test also functions to evaluate the risks of peripheral artery disease (PAD) (8), diabetic kidney disease (DKD) (9) and diabetic retinopathy (DR) (10) in patients with diabetes. Therefore, the EZSCAN test can be applied to evaluating the risk of diabetic complications in patients with T2D.

Stromal cell-derived factor 1 (SDF-1) belonging to the CXC chemokine family is widely expressed in various tissues and regulates several aspects of stem cell function (11). Sustainable inflammation and chronic ischemia can induce SDF-1 production in systemic tissues through hypoxia-inducible factor 1 (HIF-1) (12). It has been confirmed that elevated SDF-1 levels can promote the onset and progression of T2D by inducing islet inflammation (13) and mediating insulin desensitization in adipocytes (14). Our previous study demonstrated that serum SDF-1 levels are closely related to hyperglycemia, hypercoagulability, and inflammation in patients with T2D (15). Since chronic complications of diabetes share a common pathogenesis (16), we speculated that serum SDF-1 levels may be closely related to CAN and cardiovascular disease (CVD) in patients with T2D. However, no studies have focused on this aspect.

Hence, the present study was designed to assess whether serum SDF-1 levels are related to the EZSCAN score and its derived indicators, such as CANRS and CVD risk score (CVDRS).

Methods

Study design and participants

From July 2020 to December 2020, this observational cross-sectional study was conducted on patients with T2D at the inpatient department of the Second Affiliated Hospital of Nantong University. The diagnostic criteria for T2D were based on the statement of the American Diabetes Association in 2011 (17). The exclusion criteria were as follows: (1) type 1 diabetes (T1D); (2) foot deformity; (3) a previous history of uses of medications such as steroids; (4) previous and current malignant tumors; (5) chronic heart and renal failure; (6)

acute diabetic complications, such as diabetic ketoacidosis, hyperosmolar hyperglycemic state and hypoglycemic coma; (7) complications with infection or autoimmune diseases. This study completely adhered to the Declaration of Helsinki, and written informed consent was provided by all participants. The medical research ethics committee of the Second Affiliated Hospital of Nantong University fully evaluated and approved the study protocol. Ultimately, 253 patients with T2D were enrolled in the present study.

Basic data collection

Information on demographics, including age, sex, height, weight, smoking history, drinking history, duration of diabetes, PAD, DKD, DR, antihyperglycemia therapy and use of lipid-lowering agents, was collected using self-report questionnaires with the assistance of an experienced clinician.

Assessment of serum SDF-1 level

Fasting blood samples were collected the morning after enrollment for the measurement of laboratory parameters and serum SDF-1 levels. After fully centrifuged, all blood samples were stored at –80°C. Sandwich ELISA kits purchased from Elabscience (Wuhan, China) were used to measure serum SDF-1 levels.

EZSACAN test

During the test, patients placed their hands, feet and foreheads on nickel electrodes, as the skin in these regions is rich in sweat glands. Then, an incremental low direct voltage (less than 4 V) was applied to the electrodes, and the ESC was calculated as the ratio of the resulting voltage and the generated current. Through a proprietary algorithm, an EZSCAN score was calculated based on the ESC measured on hands and feet. The CANRS and CVDRS were calculated with algorithms controlling for demographic data, including age, BMI, HbA1c and gender, and had a range from 0 to 100.

Laboratory examination and calculation

An automated biochemical analyzer (Model 7600, Hitachi) was used to detect lipid profiles, blood urea nitrogen, creatinine, cystatin C and uric acid (UA) levels. An ion exchange-based HPLC method in a hemoglobin analysis system (D-10, Bio-Rad) was adopted to measure glycosylated hemoglobin (HbA1c) levels. The estimated

glomerular filtration rate (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration creatinine-cystatin C equation (2012) (18).

Statistical analyses

Normally distributed continuous variables are presented as the mean ± s.d., and skewed distributed continuous variables are presented as the median (25 and 75% interquartile). Categorical variables are described as frequencies (percentages). The total participants were divided according to the SDF-1 tertiles, and the clinical variables of each subgroup are presented. To compare differences in normally distributed data, skewed data and categorical data among the three subgroups, one-way ANOVA, the Kruskal–Wallis test, and the chi-square test were conducted. Pearson's bivariate correlation analysis was

constructed to explore the correlations of SDF-1 levels with the CANRS and CVDRS. Multiple linear regression analysis was performed to investigate the independent effects of SDF-1 levels on the CANRS and CVDRS. SPSS statistical software 18.0 (IBM SPSS Inc.) was used to data analyses. A value of $P < 0.05$ was identified as statistical significance.

Results

Basic characteristics

The clinical characteristics of the participants were presented in Table 1. 253 patients with T2D were recruited in the present study, and the range of SDF-1 levels was 0.54–9.29 pg/mL. From the first to third tertiles of SDF-1 levels, age, diabetes duration, the prevalence of PAD and DKD, use of insulin and insulin sensitizing agents,

Table 1 Clinical characteristics of the study participants. Normally distributed values in the table are given as the mean ± s.d., skewed distributed values are given as the median (25 and 75% interquartiles), and categorical variables are given as frequency (percentage).

Variable	Total	T1	T2	T3	*P* for trend
SDF-1 (ng/mL)	4.46 ± 1.49	<3.91	3.91-4.94	>4.94	
n	253	84	86	83	
Age (years)	56.0 (47.0–64.0)	49.0 (37.3–55.0)	57.0 (50.0–65.0)	61.0 (54.0–68.0)	<0.001
Male, *n* (%)	172 (68.0)	60 (71.4)	56 (65.1)	56 (67.5)	0.392
Diabetic duration (years)	5.0 (1.0–10.0)	4.0 (0.0–8.0)	7.5 (1.0–10.0)	8.5 (1.8–13.3)	<0.001
BMI (kg/m^2)	25.48 ± 3.98	26.03 ± 3.82	25.51 ± 3.63	24.89 ± 4.44	0.191
SBP (mmHg)	133.0 (124.0–148.0)	131.5 (120.3–143.5)	132.5 (123.8–150.0)	136.0 (126.0–152.0)	0.089
DBP (mmHg)	82.43 ± 10.79	82.51 ± 10.72	82.33 ± 9.67	82.46 ± 12.01	0.993
Smoking history, *n* (%)	34 (13.4)	10 (11.9)	13 (15.1)	11 (13.3)	0.827
Drinking history, *n* (%)	29 (11.5)	13 (15.5)	5 (5.8)	11 (13.3)	0.117
Antidiabetic treatments					
Insulin treatment, *n* (%)	59 (23.3)	12 (14.3)	18 (20.9)	29 (34.9)	0.006
Metformin, *n* (%)	111 (43.9)	40 (47.6)	40 (46.5)	31 (37.3)	0.340
Acarbose, *n* (%)	17 (6.7)	5 (6.0)	8 (9.3)	4 (4.8)	0.479
Insulin-secretagogues, *n* (%)	78 (30.8)	20 (23.8)	29 (33.7)	29 (34.9)	0.230
Insulin-sensitisers, *n* (%)	43 (17.0)	5 (6.0)	9 (10.5)	29 (34.9)	<0.001
DPP-4 inhibitors, *n* (%)	11 (4.3)	4 (4.8)	3 (3.5)	4 (4.8)	0.886
Statins medications, *n* (%)	6 (2.4)	2 (2.4)	2 (2.3)	2 (2.4)	0.999
HbA1c (%)	9.51 ± 2.25	9.01 ± 2.05	9.29 ± 2.12	10.23 ± 2.41	0.001
TG (mmol/L)	1.69 (1.04–3.19)	1.69 (1.17–2.98)	1.69 (0.99–3.49)	1.69 (1.00–3.79)	0.954
TC (mmol/L)	4.52 ± 1.26	4.77 ± 1.31	4.41 ± 1.41	4.38 ± 0.98	0.082
HDL-c (mmol/L)	1.11 ± 0.24	1.11 ± 0.21	1.09 ± 0.22	1.13 ± 0.27	0.499
LDL-c (mmol/L)	2.75 ± 0.93	2.87 ± 0.93	2.63 ± 0.99	2.76 ± 0.86	0.236
UA (µmol/L)	334.02 ± 108.62	343.85 ± 114.28	321.48 ± 105.14	337.06 ± 106.33	0.388
eGFR (mL/min/1.73m^2)	104.35 ± 28.48	123.52 ± 27.48	101.32 ± 17.90	89.08 ± 28.24	<0.001
PAD, *n* (%)	121 (47.8)	31 (36.9)	42 (48.8)	48 (57.8)	0.025
DKD, *n* (%)	43 (17.0)	5 (6.0)	9 (10.5)	29 (34.9)	<0.001
DR, *n* (%)	18 (7.1)	3 (3.6)	7 (8.1)	8 (9.6)	0.282
EZSCAN score (%)	40.10 ± 12.85	45.60 ± 10.81	39.72 ± 11.95	35.06 ± 13.56	<0.001
CANRS (%)	59.20 ± 24.79	43.57 ± 21.87	61.71 ± 22.97	72.42 ± 20.61	<0.001
CVDRS (%)	42.66 ± 15.50	33.36 ± 13.05	42.70 ± 14.59	52.05 ± 12.93	<0.001

CANRS, cardiac autonomic neuropathy risk score; CVDRS, cardiovascular disease risk score; DR, diabetic retinopathy; DKD, diabetic kidney disease; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin A1c; insulin-secretagogues, insulin secretagogues; insulin-sensitisers, insulin sensitizing agents; PAD, peripheral arterial disease; SBP/DBP, systolic/diastolic blood pressure; SDF-1, stromal cell-derived factor 1; TC, total cholesterol; TG, triglyceride.

HbA1c level, CANRS and CVDRS significantly increased (*P* for trend <0.05), eGFR and EZSCAN score decreased (both *P* for trend <0.001). However, among the tertiles of SDF-1 levels, there were no significant differences in the gender distribution, smoking and drinking history, the prevalence of DR, blood pressure, other antidiabetic treatment, use of statin medications, lipid profile or UA level (*P* for trend >0.05).

Association of serum SDF-1 levels with CANRS and CVDRS

We constructed Pearson's bivariate correlation analysis to explore the association of serum SDF-1 levels with EZSCAN score, CANRS and CVDRS. As illustrated in Figs 1, 2 and 3, serum SDF-1 levels were negatively associated with EZSCAN score ($r = -0.391$, $P < 0.001$), and positively associated with CANRS ($r = 0.496$, $P < 0.001$) and CVDRS ($r = 0.510$, $P < 0.001$).

Multiple linear regression models displayed the effects of SDF-1 on EZSCAN score, CANRS and CVDRS

The associations between SDF-1 and EZSCAN score, CANRS and CVDRS evaluated by multiple linear regression analyses are shown in Table 2. In the basal unadjusted Model 0, SDF-1 was significantly associated with EZSCAN score ($\beta = -0.391$, $t = -6.657$, $P < 0.001$, adjusted $R^2 = 0.153$), CANRS ($\beta = 0.496$, $t = 9.044$, $P < 0.001$, adjusted $R^2 = 0.246$) and CVDRS ($\beta = 0.510$, $t = 9.403$, $P < 0.001$, adjusted
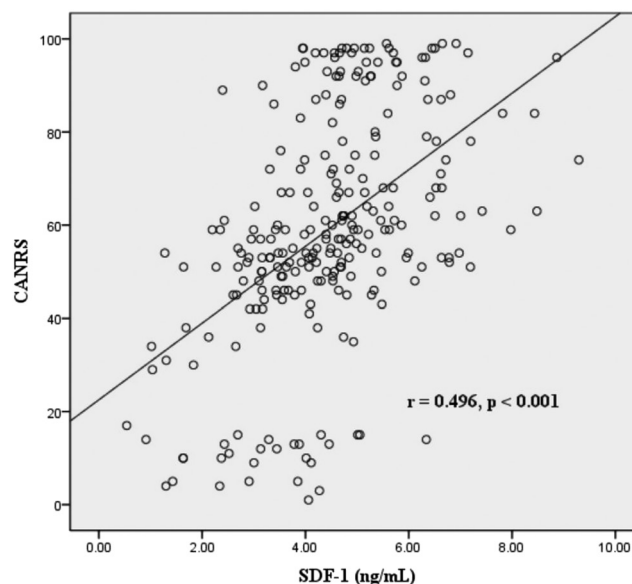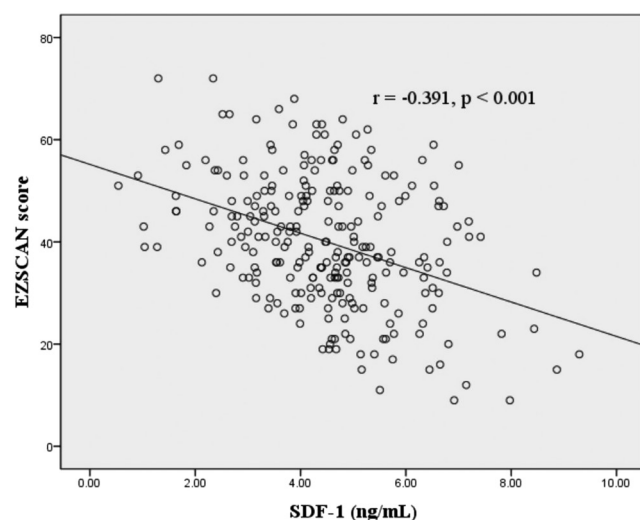

Figure 2

The relationship between SDF-1 and CANRS in patients with T2D.

$R^2 = 0.260$). The adjusted R^2 gradually increased as the other clinical covariates were gradually added to each model. In Model 3, SDF-1 was still independently associated with EZSCAN score ($\beta = -0.273$, $t = -3.679$, $P < 0.001$, adjusted $R^2 = 0.268$), CANRS ($\beta = 0.334$, $t = 5.110$, $P < 0.001$, adjusted $R^2 = 0.439$) and CVDRS ($\beta = 0.191$, $t = 4.983$, $P < 0.01$, adjusted $R^2 = 0.810$).

Discussion

The current study revealed the association between serum SDF-1 levels and the EZSCAN score and its derived indicators, such as CANRS and CVDRS in patients with T2D. The main findings are: first, across the ascending tertiles of serum SDF-1 levels in patients with T2D, CANRS and CVDRS significantly increased, and EZSCAN score significantly decreased; second, bivariate correlation analysis showed that serum SDF-1 levels were positively associated with CANRS and CVDRS, and negatively associated with EZSCAN score; third, after adjusting for other possible factors, serum SDF-1 levels were significantly and positively associated with CANRS and CVDRS, while negatively associated with EZSCAN score.

Eccrine glands mediating sweat responses are simple tubular glands with a rich supply of blood vessels and are innervated by sympathetic fibers (19). A review published in 2019 compared different tests for the detection of sudomotor dysfunction and found that ESC results achieved by the EZSCAN test might be more sensitive, less expensive, and easier to operate than other tests (20). A study that enrolled 83 patients with diabetes found that ESC results

Figure 1

The relationship between SDF-1 and EZSCAN score in patients with T2D.
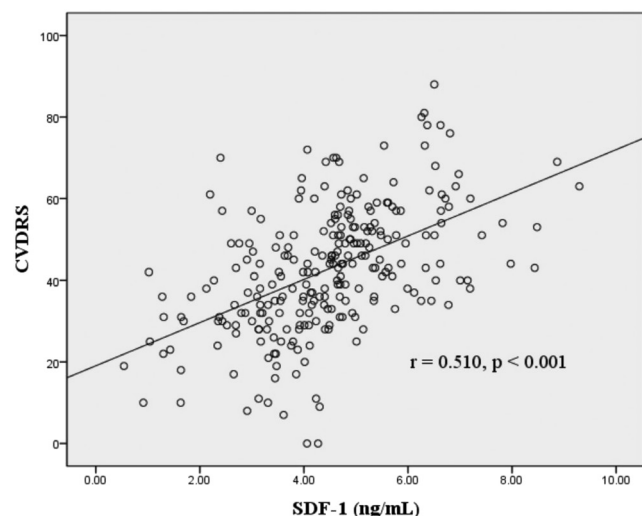
Figure 3
The relationship between SDF-1 and CVDRS in patients with T2D.

were significantly correlated with autonomic function testing assessed by quantitative autonomic function testing (QAFT) (21). Sympathetic overactivity possibly promotes vascular muscle growth and arterial wall fibrosis by regulating the renin-angiotensin-aldosterone system and other mechanisms. These conditions eventually lead to arterial stiffness (22), which is an independent predictor of CVD. Zeng *et al.* found a strong correlation between the EZSCAN scores and arterial stiffness in non-T2D and non-CVD participants (23). Moreover, Yajnik *et al.* revealed that compared with Ewing tests, CANRS derived from ESC was suitable for early screening of CAN in patients with diabetes (24). Similarly, in a study involving 90 patients with T2D, the

combination of ESC and heart rate variability was capable of accurately diagnosing and assessing CAN (25). However, no association between ESC and CAN was observed in patients with T1D (26). This discrepancy may be attributed to the different populations enrolled and the different pathogenesis of T1D and T2D. In a word, it is plausible that the CANRS and CVDRS calculated based on the ESC results reflect the risks of developing CAN and CVD in patients with T2D. In this study, we found that serum SDF-1 levels were independently associated with the EZSCAN score, CANRS and CVDRS.

CVD with atherosclerosis as the main pathological feature is the primary cause of mortality among patients with diabetes (3). SDF-1 is not expressed in normal vessels but is abundantly expressed in smooth muscle cells, endothelial cells and macrophages at human atherosclerotic plaques (27). The key to atherosclerotic plaque formation is that macrophages phagocytose oxidized low-density lipoprotein (oxLDL) to form foam cells, and SDF-1 can accelerate this process (28). As an inflammatory chemokine, SDF-1 can induce the expression of tumor necrosis factor-α (TNF-α), leading to the apoptosis of cardiomyocytes (29). In addition, SDF-1 can aggravate cardiac remodeling and worsen cardiac function by enhancing the proliferation of cardiac fibroblasts and collagen production (30). Correspondingly, plasma SDF-1 levels can serve as a predictor of myocardial infarction (MI) in patients with chronic kidney disease (CKD) (31). Thus, increased SDF-1 in serum may be closely related to CVD in patients with T2D.

SDF-1 is constitutively expressed in astrocytes, microglia and neurons (32), which proposes a basis for

Table 2 Multiple linear regression models displaying adjusted estimates for SDF-1 for EZSCAN score, CANRS and CVDRS adjusted for the other clinical covariates in each model in patients with T2D. Model 0: unadjusted model; Model 1: adjusted for age, male, diabetic duration, BMI, smoking history, drinking history; Model 2: additionally adjusted for SBP, DBP, TG, TC, HDL-c, LDL-c, UA, eGFR; Model 3: additionally adjusted for HbA1c, antidiabetic treatments, statins medications.

Models	B (95% CI)	β	t	P	R^2 for model
EZSCAN score					
Model 0	−3.366 (−4.362 to −2.370)	−0.391	−6.657	<0.001	0.153
Model 1	−2.187 (−3.258 to −1.116)	−0.254	−4.022	<0.001	0.226
Model 2	−2.305 (−3.494 to −1.117)	−0.262	−3.824	<0.001	0.254
Model 3	−2.437 (−3.743 to −1.131)	−0.273	−3.679	<0.001	0.268
CANRS					
Model 0	8.227 (6.435 to 10.018)	0.496	9.044	<0.001	0.246
Model 1	5.034 (3.221 to 6.847)	0.301	5.470	<0.001	0.400
Model 2	5.692 (3.678 to 7.707)	0.330	5.569	<0.001	0.432
Model 3	5.770 (3.544 to 7.996)	0.334	5.110	<0.001	0.439
CVDRS					
Model 0	5.294 (4.185 to 6.402)	0.510	9.403	<0.001	0.260
Model 1	3.695 (2.617 to 4.773)	0.355	6.753	<0.001	0.454
Model 2	4.449 (3.320 to 5.579)	0.416	7.762	<0.001	0.530
Model 3	2.040 (1.233 to 2.846)	0.191	4.983	0.003	0.810

the close correlation between serum SDF-1 levels and CANRS in patients with T2D. SDF-1 may contribute to diabetes-induced pain by resulting in the activation of microglia, which in turn derives pronociceptive cytokines (33). Additionally, SDF-1 can induce the apoptosis of astrocytes and neurons by inducing the production of TNF-α and aggravating neurologic impairment in patients with T2D (34). In addition, SDF-1 can act as a regulatory neuropeptide that regulates both central cholinergic and dopaminergic systems in the brains of adult rats (35). Under pathological conditions, increased SDF-1 can activate the sympathetic nervous system, possibly contributing to autonomic dysfunction in patients with T2D (36). Hence, serum SDF-1 levels may be closely associated with CAN in patients with T2D.

However, SDF-1 also promotes the mobilization and migration of endothelial progenitor cells (EPCs), so a number of studies have reported that elevated SDF-1 levels may have a protective effect *in vivo*. There are several possible explanations for the discrepancies between these studies and our study. First, EPCs isolated from patients with diabetes are deficient in migration function in response to SDF-1, so elevated SDF-1 levels under diabetic conditions may fail to play a protective role by attracting EPCs (37). Second, due to the rapid degradation of SDF-1, serum SDF-1 levels do not reflect the local concentration of SDF-1 (27). Third, different concentrations of SDF-1 may have completely opposite effects (27).

Some limitations to our study should be addressed. First, as a cross-sectional study, the present study cannot reach a cause-effect relationship between serum SDF-1 levels and the risk indices of CAN and CVD in patients with T2D. Secondly, the EZSCAN test is not the gold standard for screening and evaluating CAN and CVD. However, the accuracy of the EZSCAN test has been well validated, so this is not a major concern. Thirdly, the present study was conducted in a Chinese population with T2D, which might limit the generalizability of our study. Therefore, further research should be conducted to validate the results of our study and to address the above limitations.

Conclusions

In summary, serum SDF-1 levels were independently related to EZSCAN score, CANRS and CVDRS evaluated by EZSCAN test in patients with T2D.

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