ORIGINAL RESEARCH

Serum Pentosidine is Associated with Cardiac Dysfunction and Atherosclerosis in T2DM

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Aim: The purpose of this paper is to investigate the relationship between serum pentosidine levels and cardiac function and vascular disease in diabetic patients, and to provide a new reference indicator for the early detection of diabetic cardiovascular complications.

Materials and Methods: This was a cross-sectional study. One hundred and twenty-two patients with type 2 diabetes were grouped by LVEF quartiles to compare the differences between their clinical data and serum pentosidine levels. Also, the correlation between serum pentosidine and clinical indicators was assessed. The effect of serum pentosidine on cardiac function and vascular stiffness was analyzed by multiple stepwise regression.

Results: Serum pentosidine levels were higher in patients with LVEF ≤57%. Serum pentosidine levels were positively correlated with waist-to-hip ratio, hemoglobin, AIP, baPWV, LVESD, and ARD, and negatively correlated with LVEF. Low serum pentosidine was associated with increased LVESD; high pentosidine was significantly associated with increased ARD, high AIP and high baPWV.

Conclusion: The results suggest that serum pentosidine, a member of AGEs, may reflect cardiac remodeling and dysfunction as well as atherosclerosis.

Keywords: pentosidine, T2DM, cardiac dysfunction, atherosclerosis

Introduction

According to the 10th edition of IDF Diabetes Atlas released in 2021, it is not difficult to see that the overall number of diabetics is predicted to rise to 643 million (11.3%) by 2030 and 783 million (12.2%) by 2045.[1] The clinical guidelines for the prevention and treatment of diabetes in the elderly in China released in January 2022 disclosed that there are approximately 260.4 million elderly people in China who are 60 years of age or older, with 78.13 million of them having diabetes.[2] The active prevention and treatment of various complications in elderly diabetic patients and the improvement of their long-term survival quality are currently the focus of various studies. As one of the chronic complications of diabetes, the incidence rate of cardiovascular diseases (CVD) has increased significantly in recent years,[3] but there are not many reliable markers to help with early detection.

Advanced glycation end-products (AGEs) are stable covalent adducts formed by the reaction of macromolecules such as proteins, lipids, nucleic acids with glucose, or other reducing monosaccharides under the action of non-enzymatic glycation reaction.[4] In patients with diabetes, the accumulation of AGEs accelerates and participates in the occurrence of chronic complications of diabetes.[5,6] It has also been shown that AGEs can contribute to cardiac and vascular dysfunction through a variety of pathways. However, because of the high heterogeneity of AGEs, there is no specific test for AGEs. Serum pentosidine, a member of AGEs, is significantly associated with AGEs in vivo and serum pentosidine levels can reflect AGEs levels.[7] Therefore, we hypothesized that serum pentosidine concentrations may reflect the degree of cardiovascular disease in patients with Type 2 diabetes. In this study, we investigated the relationship between serum pentosidine and cardiac function and vascular disease in diabetic individuals, with the aim to provide a new reference indicator for the early detection of diabetic cardiovascular complications.

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Materials and Methods
Subjects
Patients with Type 2 Diabetes Mellitus treated in the Department of Endocrinology of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University from December 2020 to December 2021 were enrolled. These participants were hospitalized for complication screening and glucose-lowering regimen adjustment due to poor glycemic control. And finally, 122 patients were included according to the inclusion and exclusion criteria.

Inclusion Criteria
Patients meeting the diagnostic criteria for type 2 diabetes in the 2016 ADA guidelines; patients aging 45–65 years old.

Exclusion Criteria
Patients having a history of cardiovascular organic diseases such as heart valve disease; patients having previous macrovascular or microvascular complications of diabetes, including retinopathy, nephropathy, neuropathy, peripheral vascular disease, and stroke; pregnant women; patients suffering from malignant tumors, thyroid dysfunction, liver and kidney dysfunction, rheumatic immune diseases or major mental diseases and other serious complications.

All participants gave written informed consent in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of Changzhou Second People's Hospital Affiliated with Nanjing Medical University (Approval date of Registry and the Registration No. of the study/trial: 1 July 2020, MR-32-21-013406).

Collection of Demographic and Laboratory Data
On the morning of the next day after admission, fasting peripheral blood samples were collected from each patient. The sex, age, body mass index, waist-hip ratio, and duration of diabetes were collected. We also collected the laboratory examination results of selected patients, including glucose 0 minutes (FBG), insulin 0 minutes (0 "INS), C-peptide 0 minutes (0" C-P), glycosylated hemoglobin (HbA1c), hemoglobin (HB), platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) γ- Glutamyl transpeptidase (γ- GT), serum albumin (ALB), serum urea nitrogen (BUN), serum creatinine (CR), serum uric acid (UA), serum triglyceride (TG), serum total cholesterol (TC), serum high-density lipoprotein (HDL-C), serum low-density lipoprotein (LDL-C), urine microalbumin/creatinine ratio (UA/CR), etc. Except for 2hPBG, all other indicators were obtained from blood samples collected after fasting for 8 hours and before taking hypoglycemic drugs.

The triglyceride-glucose (TyG) index=Ln(TG×FPG/2).[8]

Atherogenic index of plasma (AIP)=Lg(TG/HDL-C).[9]

HOMA-IR=(FINS×FPG)/22.5.

Detection of Serum Pentosidine Levels
We collected 2–3mL of patients' fasting venous blood with a 5mL coagulation-promoting tube, centrifuged at 3000rpm at 4°C for 10 minutes, separated the upper serum, and stored it in the refrigerator at −80°C. The serum pentosidine level was measured with the ELISA Kit purchased by the Shanghai Tongwei company.

Evaluation of Cardiac Structure and Function
On the second day of admission, an experienced associate sonographer used the Y-video E9 system to perform an echocardiogram with the participants in the left lateral position and breathing quietly. The sonographer knew nothing else about the patient's data. The observed parameters mainly include aortic root dimension (ARD), left atrial diameter (LAD), ventricular septal thickness (IVST), left ventricular end diastolic diameter (LVDD), left ventricular posterior wall thickness (LVPWT), left ventricular ejection fraction (LVEF) Left ventricular end systolic dimension (LVESD), etc.

Assessment of baPWV and ABI
After the subject was instructed to rest for 15 minutes, the examiner measured the blood pressure of the extremities using a fully automatic atherosclerometer (OMRON BP-203RPEIII). The instrument recorded the waveforms of the brachial

and anterior tibial arteries and automatically calculated baPWV based on the transmission time and transmission distance and ABI based on the ratio of systolic pressure in the posterior tibial artery to that in the brachial artery.

Statistical Analysis

Patients were divided into four groups according to the quartile of the LVEF index. The measurement data are expressed by mean ± standard deviation; One-way analysis of variance (ANOVA) was used for comparison between groups; the Chi-square test was used to compare the count data between groups; Spearman correlation analysis was used to analyze the correlation between serum pentosidine and other clinical parameters. Multiple stepwise linear regression analysis was used to identify factors associated with echocardiographic parameters and arterial disease (AIP and baPWV). SPSS version 22.0 was used for statistical analysis. If the p-value <0.05, the difference is considered significant.

Results

Comparison of Clinical Characteristics in the Four Groups

One hundred and twenty-two participants were recruited and divided into four groups according to the quartile of the LVEF index, with 30, 30, 30, and 32 participants in each group. Table 1 shows the comparison of clinical characteristics between the study groups. The cut-off values of the quartile of LVEF index are LVEF > 63%, 61% < LVEF ≤ 63%, 57% < LVEF ≤ 61%, and LVEF ≤ 57%. The mean ± standard deviation of the LVEF index in the four groups are 65.80 ± 1.69, 62.23 ± 0.43, 59.30 ± 1.12, and 55.53 ± 1.67, respectively. Compared to quartiles 1 and 2, patients in quartile 4 had a greater waist-to-hip ratio, more visceral fat, higher triglyceride levels, higher Atherogenic index of plasma (AIP), higher triglyceride-glucose (TyG) index, and, of course, lower serum pentosidine levels. There were no differences in age, diabetes duration, medication, hepatic enzymes, creatinine, serum urea nitrogen, UA/CR, fT3, fT4, sTSH, and frequency of hypertension and hyperlipidemia among groups (Supplement Tables 1 and 2).

Analysis of Serum Pentosidine and Related Clinical Parameters in Patients with T2DM

Serum pentosidine level was positively correlated with waist-hip ratio, hemoglobin, AIP, baPWV, LVESD, and ARD, and negatively correlated with LVEF (Table 2).

Table 1 Comparison of Baseline Characteristics According to LVEF Quartiles

	Q1 (n=30) LVEF>63%	Q2 (n=30) 61% <LVEF≤63%	Q3 (n=30) 57% <LVEF≤61%	Q4 (n=32) LVEF≤57%	p
Age (years)	50.63±10.54	53.27±8.92	48.80±10.49	48.94±11.24	0.304
BMI (kg/m^2)	25.83±4.12	25.20±5.12	25.55±2.93	26.97±4.78	0.404
Waist-hip ratio	0.91±0.05	0.91±0.05	0.94±0.05[b]	0.94±0.07[ab]	0.029
Visceral fat area (cm^2)	87.90±31.61	83.28±34.15	95.24±24.78	115.15±48.02[abc]	0.006
Duration of diabetes (years)	8.01±6.68	6.73±5.14	4.84±5.78	6.98±6.16	0.225
FBG (mmol/L)	7.74±2.31	7.98±2.30	8.40±3.11	8.06±2.45	0.794
0'INS (pmol/L)	46.98±43.86	52.41±53.71	48.63±42.00	54.68±41.16	0.907
0'C-P (pmol/L)	619.60±335.78	708.71±447.76	698.10±404.50	719.26±364.64	0.746
HbA1c (%)	8.86±2.10	9.18±2.18	9.42±2.17	8.23±2.01[c]	0.138
Hb (g/L)	141.76±13.39	146.83±14.79	150.62±14.51[a]	152.03±13.23[a]	0.028
UA (umol/L)	300.74±82.84	286.90±87.88	304.11±57.41	310.06±111.88	0.770
TG (mmol/L)	1.59±0.91	1.81±0.91	2.81±2.88[ab]	2.48±1.65[b]	0.034
TC (mmol/L)	4.10±1.09	4.61±1.16	4.72±1.28	4.57±1.18	0.206
HDL-c (mmol/L)	0.99±0.20	1.05±0.23	1.00±0.30	1.07±0.39	0.651
LDL-c (mmol/L)	2.49±0.81	2.83±0.95	2.77±0.89	2.73±0.88	0.460
AIP	0.15±0.27	0.20±0.26	0.32±0.39[a]	0.32±0.37[a]	0.105
TyG	9.00±0.67	9.20±0.63	9.45±0.98[a]	9.45±0.64[a]	0.063

(*Continued*)

Table 1 (Continued).

	Q1 (n=30) LVEF>63%	Q2 (n=30) 61% <LVEF≤63%	Q3 (n=30) 57% <LVEF≤61%	Q4 (n=32) LVEF≤57%	*p*
ABI	1.08±0.11	1.07±0.12	1.10±0.09	1.10±0.09	0.737
baPWV (cm/s)	1493.19±283.02	1418.28±247.39	1535.35±293.60	1630.28±400.75[b]	0.081
LAD(mm)	37.23±3.69	35.83±3.10	36.40±3.94	36.97±3.81	0.453
IVST(mm)	9.47±1.20	9.13±0.97	9.20±1.03	9.31±1.03	0.637
LVDD(mm)	49.10±3.52	45.87±8.65	49.60±4.22[b]	50.63±4.00[b]	0.006
LVPWT(mm)	9.23±0.97	9.20±0.92	9.03±0.61	9.22±0.87	0.785
LVEF(%)	65.80±1.69	62.23±0.43	59.30±1.12	55.53±1.67	0.000
LVESD (mm)	31.53±2.29	31.50±2.01	33.97±2.99[ab]	35.97±2.92[ab]	0.000
ARD(mm)	29.17±2.34	29.27±2.24	30.53±2.85	31.41±3.60[ab]	0.005
LVM(g)	742.06±166.75	644.67±174.13	731.74±183.85	768.07±171.27	0.039
LVI	416.11±80.47	365.70±76.63[a]	410.11±82.15[b]	420.01±72.71[b]	0.027
Serum pentosidine (pmol/mL)	605.66±219.20	607.36±194.20	741.26±233.52[ab]	901.08±353.45[ab]	0.000
Smoking(%)	26.1%	17.4%	17.4%	39.1%	0.049

Notes: Continuous values consistent with normal distribution are shown as mean ± standard deviation. Categorical values are shown as frequency. [a]$p < 0.05$ compared with Quartile 1;[b]$p < 0.05$ compared with Quartile 2;[c]$p < 0.05$ compared with Quartile 3.
Abbreviations: BMI, body mass index; FPG, fasting plasma glucose;0 "INS, insulin 0 minutes; 0" C-P, C-peptide 0 minutes; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; UA, uric acid; TyG, The triglyceride-glucose index; AIP, Atherogenic index of plasma;ARD, aortic root dimension; LAD, left atrial diameter; IVST, ventricular septal thickness; LVDD, left ventricular end diastolic diameter; LVPWT, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction; LVESD, Left ventricular end systolic dimension; LVM, left ventricular mass; LVI, left ventricular mass index.

Table 2 Correlation Analysis of Serum Pentosidine and Clinical Test Results

	r	*p*
Waist-hip ratio	0.222	0.014
Hb	0.209	0.023
AIP	0.192	0.035
baPWV	0.229	0.016
LVEF	−0.356	0.000
LVESD	0.295	0.001
ARD	0.345	0.000

Influencing Factors of Echocardiographic Results in T2DM Patients

Table 3 summarizes the determinants of LVEF, LVESD, and ARD among the subjects. Stepwise regression analysis of age, BMI, waist-hip ratio, HOMA-IR, course of diabetes, fasting blood glucose, fasting insulin, serum pentosidine, Hb, PLT, ALT, AST, ALP, γ-GT, ALB, BUN, Cr, UA, TG, TC, HDL-C, LDL-C on cardiac ultrasound related parameters. Multivariable stepwise linear regression analysis showed that low serum pentosidine (p = 0.001), low BUN (p = 0.008), and low ALT (p = 0.038) were significantly correlated with high LVEF. High body weight (p = 0.000), high serum pentosidine (p = 0.000), low waist-hip ratio (p = 0.001), low triglycerides (p = 0.008) and low hemoglobin (p = 0.033) were associated with increased LVESD. High pentosidine (p = 0.009) and low 0'C-P (p = 0.047) were significantly correlated with the increase in ARD.

Influencing Factors of Atherosclerotic Indexes in Patients with T2DM

Table 4 lists the risk factors for atherosclerosis. In multiple stepwise linear regression analysis, high uric acid (p = 0.000), high FBG (p = 0.018), high serum pentosidine (p = 0.026), and high waist-hip ratio (p = 0.013) were significantly correlated with

Table 3 Determinants for Echocardiographic Parameters Using Multivariable Stepwise Linear Regression Analysis

	β	S$\bar{X}$	β'	T	p	VIF	R^2	F	p
LVEF							0.822	12.343	0.002
Pentosidine	−0.006	0.001	−0.779	−4.914	0.001	1.131			
BUN	−1.895	0.535	−0.528	−3.538	0.008	1.001			
ALT	−0.105	0.042	−0.393	−2.481	0.038	1.132			
LVESD							0.983	67.734	0.000
Weight	0.263	0.021	1.016	12.380	0.000	2.322			
Pentosidine	0.005	0.001	0.634	9.189	0.000	1.642			
Waist-hip ratio	−36.265	5.789	−0.454	−6.265	0.001	1.808			
TG	0.300	0.078	0.218	3.853	0.008	1.104			
Hb	−0.052	0.019	−0.215	−2.765	0.033	2.079			
ARD							0.633	7.775	0.011
Pentosidine	0.006	0.002	0.663	3.285	0.009	1.001			
0'C-P	−0.009	0.004	−0.465	−2.303	0.047	1.001			

Table 4 Determinants for AIP, baPWV Using Multivariable Stepwise Linear Regression Analysis

	β	S$\bar{X}$	β'	T	p	VIF	R^2	F	p
AIP							0.383	13.031	0.000
UA	0.002	0.000	0.425	4.870	0.000	1.038			
Waist-hip ratio	1.289	0.510	0.227	2.526	0.013	1.102			
FBG	0.028	0.011	0.207	2.414	0.018	1.006			
Pentosidine	0.000	0.000	0.200	2.266	0.026	1.065			
baPWV							0.563	24.198	0.000
Age	18.137	2.314	0.579	7.839	0.000	1.175			
DBP	13.393	2.156	0.444	6.212	0.000	1.100			
Pentosidine	0.273	0.081	0.236	3.394	0.001	1.038			
UA	0.843	0.281	0.221	3.005	0.003	1.160			
ALT	−2.875	1.310	−0.167	−2.195	0.031	1.242			

high AIP. High baPWV was significantly correlated with old age (p = 0.000), high diastolic blood pressure (p = 0.000), high pentosidine (p = 0.001), high uric acid (p = 0.003) and low alanine aminotransferase (p = 0.031).

Conclusion

At present, heart failure (HF) has been considered a common complication of diabetes.[10] The prevalence and incidence of diabetes is increasing. The data also show that diabetes patients without other basic diseases will also have heart failure, and heart failure may be the first manifestation of cardiovascular disease in many diabetes patients.[11] The UK Prospective Diabetes Study (UKPDS) showed that during the 10-year follow-up period, the annual incidence rate was as high as 11.9/1000.[12] So far, the evaluation of cardiac function in patients with type 2 diabetes mainly depends on echocardiography, and there is a lack of meaningful serological biomarkers. Therefore, starting with LVEF, which reflects cardiac function,[13] this study found that serum pentosidine was significantly negatively correlated with LVEF, and proposed that serum pentosidine may become a serological indicator of early cardiac insufficiency in patients with diabetes, so as to further explore the correlation between serum pentosidine and cardiac function and arteriosclerosis in patients with type 2 diabetes.

AGEs are a kind of heterogeneous biological macromolecules produced by glucose, protein, lipid, and even nucleic acid through a series of non-enzymatic glycosylation reactions (ie, Maillard reaction).[14,15] There are two sources of AGEs in human body: exogenous AGEs come from a daily high-calorie diet[16] and endogenous AGEs

come from Maillard reaction in the body.[17] Diabetes patients with hyperglycemia are particularly prone to the formation of endogenous AGEs.[18] After the generation of AGEs, it will damage the metabolism of lipids and proteins in cells.[19] At the same time, AGEs interfere with cell signal transduction by promoting oxidative stress and producing pro-inflammatory factors and inflammatory mediators,[20] which significantly affect the normal function of the body, especially insulin-mediated metabolic response.[21] Serum pentosidine, a common glycosylation end-product, is positively correlated with AGEs and may represent serum accumulation of AGEs in vivo.

Previous studies have shown that AGEs may cause cardiac and vascular dysfunction in two ways: vascular stiffness and cardiac fibrosis through the cross-linking of elastin and collagen; inflammation and oxidative stress through AGER.[22] Both in vivo and in vitro studies conducted by Zhong et al suggest that the endoplasmic reticulum stress induced by AGEs can mediate the activation of PERK/CaN/NFAT4c signal transduction in cardiac microvascular endothelial cells, and then trigger the transcription of targeted genes, leading to apoptosis, inflammation, and micro thrombosis, thereby exacerbating microvascular dysfunction in non-obstructive coronary artery disease.[23] Liang B et al also found that the AGEs-RAGE axis mediates myocardial fibrosis by activating autophagy-induced cardiac fibroblasts in heart failure.[24] Hoorn's study showed that there was an association between the higher serum pentosidine level and serum total AGEs level and poor systolic function.[25] A prospective study (community atherosclerosis risk study) explored the relationship between sRAGE and HF events, which concluded that lower levels of sRAGE were independently associated with the development of HF in the community population.[26]

It is reported that patients with metabolic syndrome without heart failure, myocardial infarction, and history of LVEF < 50% have subclinical left ventricular systolic dysfunction.[27] In this study, we found that serum pentosidine levels were significantly negatively correlated with LVEF, suggesting that serum pentosidine accumulation in the body can cause subclinical left ventricular systolic dysfunction. At the same time, our results show that there is a significant positive correlation between serum pentosidine and LVESD, which proves that the increase of serum pentosidine can lead to ventricular remodeling, but other indicators of echocardiography, such as left atrial diameter and left ventricular end diastolic diameter, can be seen that Q1 group has no significant difference compared with Q3 and Q4 groups, but higher than Q2 group, so we further analyzed the reasons that may lead to this result, such as hypertension, hyperlipidemia, and smoking, We found that the proportion of smoking in Q1 group was significantly higher than that in other groups, which explained the reason for this result.[28]

Another important finding of this study is that serum pentosidine is positively correlated with AIP and baPWV. Previous studies have proved that AIP is a powerful and reliable predictor of coronary artery disease in patients with type 2 diabetes. High AIP levels are independently associated with the increased risk of rapid plaque progression.[9,29,30] A 15-year cohort study shows that AIP is an independent factor in predicting cardiovascular events and related mortality.[31] Similarly, as a powerful indicator of arteriosclerosis,[32] baPWV has been proved to be closely related to the 10-year risk of atherosclerotic cardiovascular disease (ASCVD) in the middle-aged and elderly population.[33] Through multiple stepwise linear regression analysis, this study found that hemorrhagic pentosidine was significantly correlated with these two indicators. We speculated that the increase of serum pentosidine caused vascular inflammation and oxidative stress, affected the cross-linking of angioplasty protein and collagen, resulting in vascular sclerosis, and then caused cardiac insufficiency. This may become the research direction to reduce the occurrence of cardiovascular events in patients with type 2 diabetes in the future.

At present, there are few studies on the serum markers of cardiac function and vascular disease in patients with type 2 diabetes in the early stage. Therefore, we include patients with type 2 diabetes who have not undergone clinical changes in the early stage and introduce serum pentosidine, a member of AGEs, to explore its relationship with cardiac ultrasound parameters and indicators reflecting vascular hardness. However, this study is a single-center cross-sectional study, which may need to include more patients for prospective research in the future to further explore its relevance. At the same time, our current content is limited to clinical practice, and we have not yet discussed its in-depth mechanism, which will be our future research direction.

In conclusion, we proved the significant correlation between high serum pentosidine and high LVESD, low LVEF, high AIP, and high baPWV in this study. These results suggest that serum pentosidine, as a member of AGEs, may reflect cardiac remodeling, dysfunction, and atherosclerosis.

Data Sharing Statement

All datasets presented in this study are included in the article/Supplementary Material. Further enquiries can be directed to the corresponding author.

Ethics and Consent Statements

The study was approved by the ethics committee of Changzhou Second People's Hospital Affiliated with Nanjing Medical University. Written informed consent was obtained from all the participants after a full explanation of the study. Approval date of Registry and the Registration No. of the study/trial: 1 July 2020, MR-32-21-013406.

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Disclosure

Yuyan Cao and Xinhua Ye are co-first authors for this study. The authors declare that they have no conflicts of interest for this work.

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