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Soluble urokinase plasminogen activator receptor in type 1 diabetic children, relation to vascular complications

Eman Mounir Sherif, Abeer Ahmed Abd El Maksood, Omneya Ibrahim Youssef, Nouran Yousef Salah El-Din *, Ola Khaled Mohamed Khater

Pediatrics Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

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ABSTRACT

Background: Endothelial dysfunction caused by chronic inflammation is the cornerstone of vascular complications in type 1 Diabetes-Mellitus (T1DM). Soluble Urokinase Plasminogen Activator Receptor (SuPAR) is a novel marker of inflammation and endothelial dysfunction.
Aim: To evaluate SuPAR in T1DM children and correlate it to diabetic vascular complications.
Methods: Seventy T1DM children and 40 matched healthy controls were studied focusing on disease duration, insulin therapy and symptoms of diabetic complications. Blood-pressure, fundus and screening for peripheral-neuropathy were done. Fasting lipid profile, fraction-C of glycosylated hemoglobin (HbA1c%), Urinary albumin excretion (UAE), estimated-glomerular filtration rate (eGFR) and SuPAR were measured. Internal aortic diameter was measured with calculation of aortic distensibility and stiffness index.
Results: Sixteen T1DM patients(22.9%) had peripheral neuropathy, 12(17%) had nephropathy and none had retinopathy. SuPAR was significantly elevated in diabetic nephropathy ($p < 0.01$) and neuropathy ($p < 0.01$). Aortic stiffness index was significantly higher ($p < 0.01$) whereas, aortic strain and distensibility were significantly lower ($p < 0.01$) in T1DM than controls. SuPAR was significantly correlated to disease duration ($p < 0.01$), systolic blood pressure ($p < 0.01$), total cholesterol ($p < 0.01$), triglycerides ($p < 0.01$), UAER ($p < 0.01$) and aortic strain (0.013).
Conclusion: Increased SuPAR early in diabetes might become a useful indicator of developing vascular complications. Further prospective studies are needed to determine the cut-off level of SuPAR for detection of T1DM and its complications.

1. Introduction

Endothelial dysfunction caused by chronic inflammation is the key event responsible for the development of micro and macrovascular complications in type 1 diabetes mellitus (T1DM).[1]

Uncontrolled T1DM results in significant morbidity and mortality by causing microvascular complications including diabetic retinopathy, nephropathy and neuropathy. Macrovascular complications include cardiovascular, cerebrovascular and peripheral artery disease.[2]

Arterial stiffness is an early indicator of arteriosclerosis and predictor of cardiovascular events independently of classical cardiovascular risk factors.

Patients with T1DM especially those having micro and macrovascular complications have increased inflammatory activity expressed through elevated levels of inflammatory cytokines, mainly C reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[3,4]

Soluble urokinase plasminogen activator receptor (SuPAR) is the soluble form of urokinase plasminogen activator receptor (uPAR). SuPAR results from the cleavage and release of membrane-bound uPAR.[5] SuPAR, a marker of inflammation and endothelial dysfunction released from inflammatory cells has a role in inflammation, thrombosis and cell proliferation.[6] Under physiological conditions uPAR, the membrane bound form of SuPAR, maintains tissue function through regulation of cell proliferation, adhesion, migration and proteolysis. However during inflammation, recruitment and expression of uPAR/suPAR are upregulated in endothelial cells, fibroblasts, macrophages and glomerular cells.

Recently, SuPAR has been associated with podocytopathies, FSGS, and various forms of diabetic nephropathy in patients with Type 2 DM (T2DM).[7] Furthermore, elevated SuPAR in patients with T2DM precedes microalbuminuria, an established early sign of diabetic nephropathy by several years.[8]

Conflicts of interest disclosure: The authors declare that they have no conflict of interest.

* Corresponding author at: 25 korash street, Cairo, Egypt.
E-mail address: niron85@hotmail.com (N.Y. Salah El-Din).

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Extra-renal production of SuPAR from immune cells may also contribute to the plasma level of SuPAR and represent inflammation in other tissues. Inflammation is the cornerstone in the development of cardiovascular disease, and as SuPAR seems to be a good marker of the immune activation and inflammatory status of the individual, it can be used as a marker not only for cardiovascular disease but also for several infectious diseases, autoimmune diseases and cancers.[6]

The aim of this work was to evaluate SuPAR as a marker of inflammation and endothelial dysfunction in T1DM children and to correlate it to various clinical and biochemical markers of T1DM as well as to diabetic vascular complications.

2. Patients and methods

This cross sectional study included 70 type 1 diabetic children recruited from the Pediatric Diabetes Clinic, Ain-Shams University and 40 age and sex matched healthy controls.

Sample size was calculated using STATA program, setting alpha error at 5% and power at 80%. Given the results of a previous study[9] that showed that SUPAR median (range) among controls was 2.3 (1.1–3.6) and among patients with diabetes mellitus was 3.5 (1.1–15.1). Median (range) values were transformed to mean ± SD according to Hozo et al.[10] to be 2.32 ± 0.62 versus 3.5 ± 2.3. Based on these data, the needed sample was 35 cases and 35 controls.

T1DM was defined according to the criteria of International Society of Pediatric and Adolescent Diabetes.[11] Exclusion criteria included patients with other types of diabetes e.g. type 2 and MODY, patients with clinical evidence of infection, patients with overt or known cardiovascular disease, hematological diseases, tumors, liver dysfunction and patients with connective tissue disease or other autoimmune disorders.

An informed consent was obtained from each patient and their legal guardians before enrollment in the study. This study was approved from the local ethical committee of Ain-Shams University. The study was done in the period from October 2016 to September 2017.

All included children were subjected to detailed medical history with special emphasis on age at onset of diabetes, disease duration, insulin therapy and chronic diabetic complications (retinopathy, neuropathy, nephropathy, or cardiovascular ischemic events); thorough clinical examination laying stress on anthropometric measures with calculation of standard deviation score and body mass index (BMI) measured as kg/m^2, measurement of vital data including blood pressure, fundus examination by direct ophthalmoscope through dilated pupils for assessment of diabetic retinopathy, neurological examination for evidence of any diabetic complications.

The simple rapid bedside neuropathy disability score (NDS) was adopted as a screening tool for diabetic peripheral neuropathy. The sensory modalities were scored; a score above two was defined as clinical diabetic peripheral neuropathy.[12]

- Laboratory investigations included measurement of mean random blood glucose levels in the last 3 months prior to the study, fasting lipid profile (10–12 h fast), kidney function tests, mean HbA1c%, serum level of SuPAR and urinary albumin excretion ratio. Serum triglycerides (TG) and total cholesterol (TC) were assessed by quantitative enzymatic colorimetric technique using a commercial kit purchased from Bio Merieux (Diagnostic Chemicals Ltd., Charlottetown, CA). Serum high density lipoproteins (HDL) were measured by the phosphotungstate precipitation method using a Bio Merieux kit (Marcy-l'Etoile, Craponne, France). Results were clinically interpreted according to recommendations of the European Atherosclerosis Society.[13] The mean HbA1C was calculated using 3–4 HbA1c% results per year in the last year prior to the study using D-10 (BioRad, France).[14] Urinary albumin excretion (UAE) in an early morning fasting urine sample was measured as albumin-to-creatinine ratio by an immuno-turbidimetric method (Cobas Integra 800; Roche Diagnostics, Mannheim, Germany). Urinary albumin excretion (UAE) in three early morning urine samples was calculated as albumin-to-creatinine ratio by an immuno-turbidimetric method (Cobas Integra 800; Roche Diagnostics, Mannheim, Germany). Patients were classified according to UAE in at least 2 out of 3 consecutive urine samples into normoalbuminuria group (UAER ≪30 mg/g creatinine), microalbuminuria group (UAER 30–299 mg/g creatinine) and macroalbuminuria group (UAER ≥300 mg/g creatinine). Nephropathy was defined as having micro or macro-albuminuria.[15] Estimated glomerular filtration rate (eGFR) was calculated using Creatinine Based Bedside Schwartz equation (eGFR = 41.13 × [Height (meter) ÷ S creatinine (mg/dL)]). [16]

Serum levels of SuPAR were assessed by enzyme linked immunosorbent assay (ELISA) using SuPAR ELISA kits in pg/mL. The detection range of the kit is 12 pg/mL-360 pg/mL (Glory Science CO., LTD, Del Rio, USA).

2.1. Samples collection

Peripheral blood samples were collected on ethylene diamine tetraacetic acid (EDTA) (1.2 mg/mL) for analysis of HbA1c. For chemical analysis, clotted samples were obtained and serum was separated by centrifugation for 15 min at 1000 ×*g* then stored at −80 °C until analysis. Urine samples were collected for assessment of urinary albumin excretion.

2.2. Radiological investigation

Internal aortic systolic and diastolic diameters by M-mode echocardiography were measured 3 cm above the aortic valve. Aortic distensibility and aortic stiffness index were calculated using accepted formulae. All aortic echocardiography scans were done using Vivid E9, GE Vingmed Cardiovascular Ultrasound A/S Strandpromenaden 45, N = 3191 Horten, Norway to evaluate aortic stiffness index, aortic strain and distensibility. The Doppler study results were obtained at maximum velocity.[17]

$$\text{Aortic stiffness index} = \frac{\frac{\text{SBP}}{\text{DBP}}}{\frac{AOS-AOD}{AOD}}$$

$$\text{Aortic strain} = \frac{100 \times (\text{AOS}-\text{AOD})}{\text{AOD}}\%$$

$$\text{Aortic distensiblity} = \frac{2 \times (\text{AOS}-\text{AOD})}{\text{PP} \times \text{AOD}}$$

AOD: Aortic Internal Diameter during Diastole, AOS: Aortic Internal Diameter during Systole, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PP: pulse pressure.

2.3. Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when parametric and median with interquartile range with non-parametric data. The comparison between two groups with qualitative data were done by using Chi-square test and/or Fisher exact test was used instead of Chi-square test when the expected count in any cell was found ≪5. The comparison between two groups regarding quantitative data with parametric distribution was done by using Independent *t*-test and also data with non-parametric distribution was done by using Mann-Whitney test. The comparison between more than two independent groups regarding quantitative data with parametric distribution was

done by using One Way Analysis of Variance (ANOVA). Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group.

3. Results

Twenty four males (34.3%) and 46 females (65.7%) with T1DM were studied. Their mean age was (11.86 ± 3.72), range (4–18). Their mean disease duration was (5.47 ± 3.22) years, range (1–15 years). They were compared to 40 age and sex matched healthy individuals who served as controls. The control group included 14 (35%) males and 26 (65%) females, their mean age was (10.6 ± 2.95), range (5–16) years. All T1DM patients were on basal bolus SC insulin regimen with a mean total daily dose of 1.2 ± 0.5 U/kg/day.

Upon comparison of the clinical data between patients and controls no significant difference was found as regards age, sex and BMI between both groups ($p \gg 0.05$). However, diastolic blood pressure was significantly higher in the type 1 diabetic group ($p = 0.008$) (Table 1).

As regards the frequency of micro-vascular complications in T1DM children (Table 2), it was observed that 12 (17.1%) out of 70 had nephropathy, 11 (15.7%) had microalbuminuria and one (1.4%) patient had macroalbuminuria. The mean eGFR of the studied T1DM group was 112.50 ± 47.27 (mL/min/1.73 m2). Sixteen (22.9%) patients had peripheral neuropathy and none of them had retinopathy. Thus, the most common micro-vascular complications encountered in T1DM children were peripheral neuropathy (22.9%) and nephropathy (17.1%).

SuPAR level was significantly elevated in T1DM patients compared to controls ($p \ll 0.01$) (Fig. 1) and in those with diabetic nephropathy ($p \ll 0.01$) and peripheral neuropathy ($p \ll 0.01$) compared to those without these complications. Upon performing ROC curve analyses, it was found that SuPAR could significantly detect the occurrence of nephropathy and peripheral neuropathy among T1DM. The cut-off value of SuPAR at 100 pg/mL could differentiate patients with and without nephropathy with a sensitivity of 100% and specificity of 91.38%, area under the curve (AUC) 0.978 ($p \ll 0.001$) (Fig. 2).While the cut-off value of suPAR at 105 pg/mL could differentiate patients with and without neuropathy with a sensitivity of 100% and specificity of 100%, area under the curve (AUC) 100 ($p \ll 0.001$) (Fig. 3).

Regarding the macrovascular complications, aortic stiffness index was significantly increased in T1DM patients compared to controls ($p \ll 0.01$), whereas aortic strain and distensibility were significantly decreased among T1DM group ($p \ll 0.01$) (Table 3).

As shown in Table 4, multiple regression analysis for predictors of increased aortic stiffness showed that decreased aortic strain and distensibility, were independently related to increased aortic stiffness in T1DM patients.

Upon reviewing the correlations between SuPAR levels and clinical and laboratory parameters of T1DM, significant positive correlations were found between SuPAR and each of disease duration ($p \ll 0.01$), systolic blood pressure ($p \ll 0.01$), total cholesterol ($p \ll 0.01$), triglycerides, LDL ($p = 0.013$), UAER ($p \ll 0.01$) and aortic strain (0.013) (Table 5).

Table 1
Clinical characteristics of type 1 diabetic patients and control group.

		Control group	Patients group	Independent *t*-test	
		No. = 40	No. = 70	t/X^{2a}	*p*-Value
Age (years)	Mean ± SD	10.6 ± 2.95	11.86 ± 3.72	1.836	0.069
	Range	5–16	4–18		
Sex	Females	26 (65.0%)	46 (65.7%)	0.006[a]	0.938
	Males	14 (35.0%)	24 (34.3%)		
Weight (%)	≪5th	0 (0.0%)	4 (5.7%)	4.272[a]	0.118
	5th–95th	40 (100.0%)	63 (90.0%)		
	≫95th	0 (0.0%)	3 (4.3%)		
Height (%)	≪5th	0 (0.0%)	14 (20.0%)	5.560[a]	0.062
	5th–95th	40 (100.0%)	54 (77.1%)		
	≫95th	0 (0.0%)	2 (2.9%)		
BMI (%)	≪5th	0 (0.0%)	2 (2.9%)	3.626[a]	0.163
	5th–95th	40 (100.0%)	64 (91.4%)		
	≫95th	0 (0.0%)	4 (5.7%)		
Systolic blood pressure (%)	5th–≪90th	40 (100.0%)	60 (85.7%)	0.01[a]	0.920
	≥90th–95th	0 (0.0%)	10 (14.3%)		
Diastolic blood pressure (%)	5th–≪90th	40 (100.0%)	59 (84.3%)	6.984[a]	0.008
	≥90th–95th	0 (0.0%)	11 (15.7%)		

BMI: Body Mass Index. Data were expressed as mean and standard deviation where Student *t*-test was used for comparisons or as median (IQR) using Mann-Whitney test for comparison unless specified as number (percentage) using Chi-square (X^2) test for comparison.

[a] X^2: Chi-square test; t: independent *t*-test; Z: Mann Whitney.

Table 2
Laboratory characteristics among type 1 diabetic patients:

		Patients group
		No. = 70
HbA1c (%)	Mean ± SD	9.20 ± 2.26
	Range	6–15.8
Blood cholesterol (mg/dl)	Median (IQR)	169 (138–189)
	Range	92–250
Blood cholesterol level	High	12 (17.1%)
Triglycerides (mg/dl)	Median (IQR)	77.5 (52–112)
	Range	36–142
Triglycerides level	High	19 (27.1%)
HDL (mg/dl)	Median (IQR)	46 (37–55)
	Range	26–80
HDL level	≪40	22 (31.4%)
LDL (mg/dl)	Median (IQR)	106 (92–128)
	Range	41–160
LDL level	High	14 (20.0%)
UAER (mg/g creatinine)	Median (IQR)	13.67 (8–26.6)
	Range	3–388.85
	30–300	11 (15.70%)
	≫ 300	1 (1.40%)
eGFR (mL/min/1.73 m2)	Mean ± SD	112.50 ± 47.27
Nephropathy	Positive	12 (17.1%)
Peripheral neuropathy	Positive	16 (22.9%)
Retinopathy	Positive	0 (0.0%)

HbA1c: hemoglobinA1c; HDL: high density lipoproteins; LDL: low density lipoproteins; UAER: Urinary albumin excretion rate. Data were expressed as mean and standard deviation where Student *t*-test was used for comparisons or as median (IQR) using Mann-Whitney test for comparison unless specified as number (percentage) using Chi-square (X^2) test for comparison.

4. Discussion

Chronic hyperglycemia plays an important role in the initiation of diabetic vascular complications through metabolic derangement and chronic inflammation. This include the production of advanced glycation end products (AGE), abnormal activation of signaling cascades (such as protein kinase C), elevated production of reactive oxygen species (ROS) that can interact with other biomolecules and result in tissue damage and abnormal stimulation of hemodynamic regulation systems (such as the renin-angiotensin system).[3]

SuPAR originates from cleavage and release of the membrane-bound uPAR and is present in plasma, urine, blood, serum and cerebrospinal fluid.[18] It's concentration in various body fluids varies depending on the “activation” level of the immune system. In this study, SuPAR was significantly elevated in type 1 diabetic children compared to controls. This goes in concordance Theilade et al. who found that SuPAR was higher among diabetics than controls.[19]

Significantly high level of SuPAR was found among T1D children with nephropathy (macro and microalbuminuria). Similarly Theilade et al. found that there was a stepwise increase in the median SuPAR levels in patients with normo-, micro- and macro-albuminuria. SuPAR levels were higher in patients with albuminuria compared to those with normo-albuminuria.[19] In a study conducted by, Wu et al., serum SuPAR was significantly elevated in most kidney diseases (except

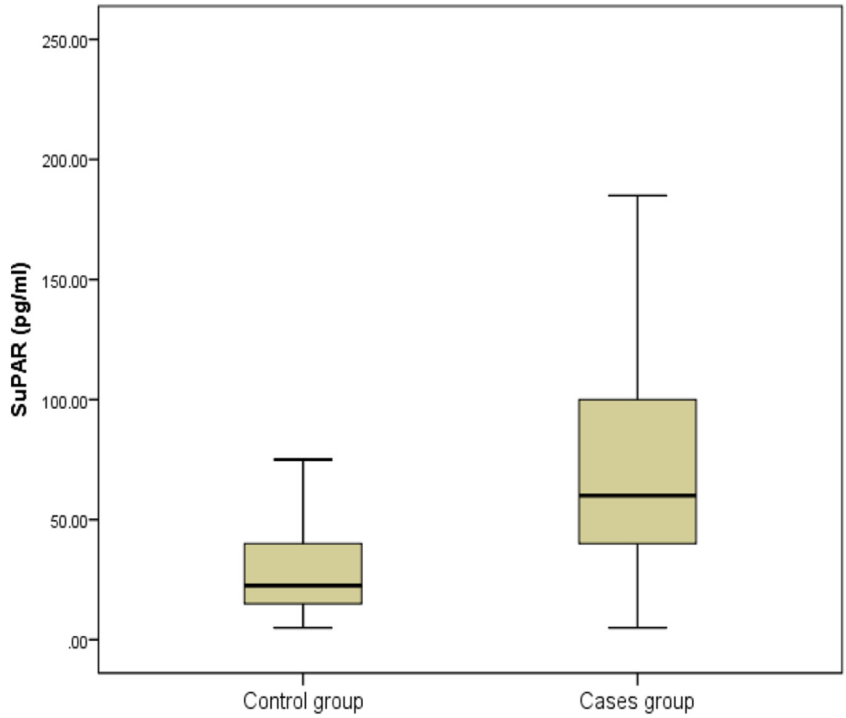


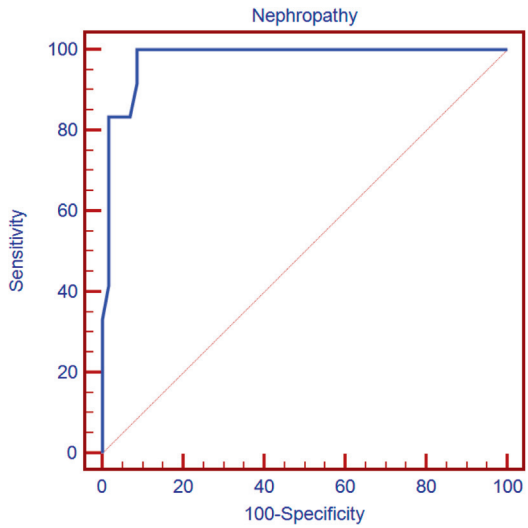
Fig. 1. SuPAR levels among type 1 diabetic patients and controls.

minimal change disease) and was highest in diabetic nephropathy and progressively increased with staging of diabetic nephropathy.[20]

In concordance with these results, Rhanadeer et al. studied patients with manifest T2DM and they found that higher SuPAR level is correlated with high urinary albumin. This shows that SuPAR might be involved in the pathogenesis and progression of diabetic nephropathy.[21]

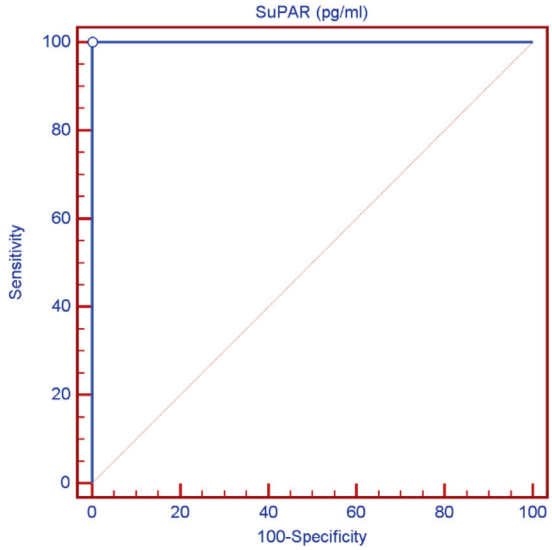
Atherosclerosis is regarded as a combination of atherosis and sclerosis. Sclerosis depends on deterioration of aortic elastic properties.[22] Arterial stiffness predicts cardiovascular events independently of classical cardiovascular risk factors in several populations.[23] Assessment of subclinical target organ damage, including arterial stiffness, has been considered essential for the evaluation of cardiovascular risk, the choice of treatment and the follow up in different clinical settings.[22]

A number of studies have identified abnormalities of arterial stiffness in subjects with T2DM and it has been recognized that aortic stiffness is highly predictive of cardiovascular mortality in subjects with T2DM.[24]



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>100	0.978	100.00	91.38	70.6	100.0

Fig. 2. Receiver Operating Characteristic (ROC) curve analysis of suPAR levels for detection of diabetic patients with nephropathy.



Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
>105	100.00	100.00	100.0	100.0	100.0

Fig. 3. Receiver Operating Characteristic (ROC) curve analysis of SuPAR levels for detection of diabetic patients with neuropathy.

In this study, aortic stiffness index was significantly higher among T1DM compared with healthy controls while aortic strain and distensibility were significantly decreased. In agreement with these results, Llauradó et al. showed that T1DM patients had higher arterial stiffness compared to healthy controls.[25] Similarly, Prince et al. reported more pronounced arterial stiffness in patients with diabetic complications such as microalbuminuria, retinopathy and neuropathy.[26] This might be explained by the presence of subclinical atherosclerosis in young patients with T1DM which may enable the recognition of preclinical cardiac impairment and proactive modifications of treatment strategies.

In the current study, significant correlations were found between SuPAR level and each of disease duration, systolic blood pressure, total cholesterol, triglycerides, LDL cholesterol and UAER. In line with these results, Theilade et al. investigated the associations between SuPAR and diabetes, including diabetes duration and complications in patients with T1DM. SuPAR levels were lower in controls versus diabetics. They found that in unadjusted analysis including all participants, SuPAR was correlated with diabetes duration ($r = 0.47$), UAER ($r = 0.46$), Pulse Wave Velocity (PWV) ($r = 0.42$), age ($r = 0.39$), CRP ($r = 0.24$), HbA1c ($r = 0.23$) and systolic blood pressure ($r = 0.20$) ($p \ll 0.001$ for all) and was weakly associated with total cholesterol ($r = 0.09$, $p = 0.021$).[19] Thus SuPAR might be considered as a potential marker for the development of diabetes complications.

5. Conclusion

SuPAR levels are elevated in children with T1DM. The increase in SuPAR levels is more evident in diabetics with vascular complications than those without suggesting its possible role as an early marker of vascular complications. Thus increased SuPAR levels in children with T1DM might become an early indicator to the development of vascular complications later in life. This might help in the development of a timely and appropriate intervention even before complications are clinically apparent. Further prospective studies are needed to determine the cut off level of SuPAR for detection of T1DM and its complications.

6. Study limitations

The reference range of the used kit is different from that of the kits used in other studies. Thus the values of SuPAR in our study shouldn't be compared to that of the references cited.

Funding sources

No funding sources.

Table 3
Aortic stiffness index and aortic strain among type 1 diabetic patients and controls:

		Control group	Patients group	Independent *t*-test	
		No. = 40	No. = 70	t/Z[a]	*p*-Value
Aortic stiffness index	Mean ± SD	5.51 ± 1.55	11.36 ± 2.82	12.102	≪0.001
	Range	3.4–9.1	7.9–16.2		
Aortic strain (%)	Mean ± SD	20.17 ± 5.35	10.50 ± 3.03	12.121	≪0.001
	Range	9.5–33.2	5.3–19		
Aortic distensibility (cm^2/dynes 10^{-6})	Mean ± SD	0.03 ± 0.06	0.01 ± 0.00	8.974	≪0.001
	Range	0.03–0.06	0–0.01		

[a] : Mann Whitney test. Data were expressed as mean and standard deviation where Student *t*-test was used for comparisons or as median (IQR) using Mann-Whitney test for comparison.

Table 4
Multiregression analysis for predictors of increase aortic stiffness.

	Unstandardized coefficients		Standardized coefficients	*t*	Sig.
	B	Std. Error	Beta		
(Constant)	18.574	1.657		11.212	0.000
Age of onset (years)	.088	0.090	0.118	0.983	0.332
Aortic strain (%)	−0.304	0.116	−0.328	−2.629	0.013
Aortic distensibility (cm2/dynes 10–6)	−568.088	150.692	−0.484	−3.770	0.001

Table 5
Correlation between SuPAR levels and clinical and laboratory parameters of T1DM.

	SuPAR (pg/mL)	
	r	*p*-Value
Age (years)	0.140	0.249
Age of onset (years)	−0.223	0.063
Disease duration (years)	0.461	≪0.001
Weight (%)	0.017	0.888
Height (%)	−0.171	0.157
BMI (%)	−0.030	0.805
Systolic blood pressure (%)	0.383**	0.001
Diastolic blood pressure (%)	0.115	0.343
HbA1C (%)	0.220	0.068
Total. cholesterol (mg/dl)	0.465**	≪0.001
Triglycerides (mg/dl)	0.466**	≪0.001
HDL (mg/dl)	−0.022	0.859
LDL (mg/dl)	0.295*	0.013
UAER (mg/g creat)	0.673**	≪0.001
eGFR (mL/min/1.73 m2)	−0.236*	0.049
Aortic stiffness index	−0.097	0.553
Aortic strain (%)	0.389*	0.013
Aortic distensibility (cm^2/dynes 10–6)	0.104	0.525

Statement of human and animal rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Statement of informed consent

Informed consent was obtained from all patients for being included in the study.

Role of authors

Eman Mounir Sherif: Reviewing and supervising the results and the manuscript.

Abeer Ahmed Abd El Maksood: Finding the idea and reviewing the results.

Omneya Ibrahim Youssef: Data collection and performance of the cardiac imaging.

Nouran Yousef Salah El-Din: Data collection, paper writing and submission.

Ola Khaled Mohamed Khater: Data collection and investigations performance.

References

1. Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: distinct or continuum? Indian J Endocrinol Metab 2016;20:546-51.
2. Mitrović M, Popović ĐS, Naglić DT, Paro JN, Ilić T, Zavišić BK. Markers of inflammation and microvascular complications in type 1 diabetes. Central European Journal of Medicine 2014;9:748-53.
3. Chase HP, Cooper S, Osberg I, Stene LC, Barriga K, Norris J, et al. Elevated C-reactive protein levels in the development of type 1 diabetes. Diabetes 2004;53:2569-73.
4. Devaraj S, Glaser N, Griffen S, Wang-Polagruto J, Miguelino E, Jialal I. Increased monocytic activity and biomarkers of inflammation in patients with type 1 diabetes. Diabetes 2006;55:774-9.
5. Thuno M, Macho B, Eugen-Olsen B. suPAR: the molecular crystal ball. Dis Markers 2009;27:157-72.
6. Eugen-Olsen J, Andersen O, Linneberg A, Ladelund S, Hansen TW, Langkilde A, et al. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. J Intern Med 2010;268:296-308.
7. Hayek S, Sever S, Ko Y, Trachtman H, Awad M, Wadhwani S, et al. Soluble urokinase receptor and chronic kidney disease. N Engl J Med 2015;373:1916-25.
8. Guthoff M, Wagner R, Randrianarisoa E, Hatziagelaki E, Peter A, Häring H, et al. Soluble urokinase receptor (suPAR) predicts microalbuminuria in patients at risk for type 2 diabetes mellitus. Sci Rep 2017;7, 40627.
9. Theilade S, Lyngbæk S, Hansen T, Eugen-Olsen J, Fenger M, Rossing P, et al. Soluble urokinase plasminogen activator receptor levels are elevated and associated with complications in patients with type 1 diabetes. J Intern Med 2015;277:362-71.
10. Hozo S, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5https://doi.org/10.1186/1471-2288-5-13.
11. Bratina N, Forsander G, Annan F, Wysocki T, Pierce J, Calliari L, Pacaud D, Adolfsson P, Dovč K, Middlehurst A, Goss J, Janson S, Acerini C. ISPAD Clinical Practice Consensus Guidelines 2018: management and support of children and adolescents with type 1 diabetes in school 2018; 19 (S27): 287–301.https://doi.org/10.1111/pedi.12743.
12. Yang Z, Chen R, Zhang Y, Huang Y, Hong T, Sun F, Ji L, Zhan S. Scoring systems to screen for diabetic peripheralneuropathy. Cochrane Database Syst Rev 2014(3), CD010974, https://doi.org/10.1002/14651858.CD010974.
13. Harley CR, Gandhi SK, Blasetto J, Heien H, Sasane R, Nelson SP. Lipid levels and low-density lipoprotein cholesterol goal attainment in diabetic patients: rosuvastatin compared with other statins in usual care. Expert Opin Pharmacother 2008;9:669-76.
14. Goldstein DE, Little RR, Wie-dmeyer HM, England JD, McKenzie EM. Glycated hemoglobin: methodologies and clinical applications. Clin Chem 1986;32:B64-70.
15. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1982;1:1430-2.
16. Levin A, Stevens P, Bilous R, Coresh J, De Francisco AL, De Jong P, et al. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1-150. (2013).
17. Gürel E, Tigen K, Karaahmet T, Gecmen C, Mutlu B, Bulut M, et al. Aortic elastic properties predict occult coronary artery disease: a multi detector row computed tomography study. Kardiol Pol 2015;73:101-8.
18. Theilade S, Lajer M, Persson F, Joergensen C, Rossing P. Arterial stiffness is associated with cardiovascular, renal, retinal, and autonomic disease in type 1 diabetes. Diabetes Care 2013;36:715-21.
19. Theilade S, Rossing P, Eugen-Olsen J, Jensen JS, Jensen MT. suPAR level is associated with myocardial impairment assessed with advanced echocardiography in patients with type 1 diabetes with normal ejection fraction and without known heart disease or end-stage renal disease. Eur J Endocrinol 2016;174:745-53.
20. Wu CZ, Chang LC, Lin YF, Hung YJ, Pei D, Chu NF, et al. Urokinase plasminogen activator receptor and its soluble form in common biopsy-proven kidney diseases and in staging of diabetic nephropathy. Clin Biochem 2015;48:1324-9.
21. Dande RR, Peev V, Altintas MM, Reiser J. Soluble urokinase receptor and the kidney response in diabetes mellitus. Journal of Diabetes Research 2017:3232848-57.
22. Zapolski T, Wysokiński A, Hajjar RJ. Left atrium volume index is influenced by aortic stiffness and central pulse pressure in type 2 diabetes mellitus patients: a hemodynamic and echocardiographic study. Med Sci Monit 2013;19:153-64.
23. Llauradó G, Ceperuelo-Mallafré V, Vilardell C, Simó R, Freixenet N, Vendrell J, et al. Arterial stiffness is increased in patients with type 1 diabetes without cardiovascular disease. A potential role of low-grade inflammation. Diabetes Care 2012;35:1083-9.
24. Woodman RJ, Watts GF. Measurement and application of arterial stiffness in clinical research: focus on new methodologies and diabetes mellitus. Med Sci Monit 2003;9:RA81-9.
25. Llauradó G, Ceperuelo-Mallafré V, Vilardell C, Simó R, Freixenet N, Vendrell J, et al. Arterial stiffness is increased in patients with type 1 diabetes without cardiovascular disease. Diabetes Care 2012;35:1083-9.
26. Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ. Cardiovascular autonomic neuropathy, HDL cholesterol, and smoking correlate with arterial stiffness markers determined 18 years later in type 1 diabetes. Diabetes Care 2010;33:652-7.