Caveolin-1 level and Carotid Intima Media Thickness in Children with Type One Diabetes Mellitus

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ABSTRACT

Background: Renal disease and endothelial dysfunction are common complications in children with diabetes mellitus. This is usually associated with an increase in the carotid intima media thickness (CIMT). These events relative timing is important to avoid progression of vascular complications and atherosclerosis in these patients. Caveolin-1 protein has an important role in transduction of signals and acts as a crucial regulator of migration and cellular adhesion. It was proved that caveolin-1 is implicated in vascular function and atherosclerosis, however studies detecting its levels in relation to CIMT in pediatric type one diabetes populations are lacking.

Aim: Detect the level of caveolin in children with type one diabetes and point out the relation between urinary albumin excretion rate (UAER), caveolin level and subclinical atherosclerosis risk.

Methodology: This was a cross-sectional comparative study that included fifty patients with type one diabetes who had diabetes at least for 5 years. They were recruited from pediatric diabetes clinic at children's Hospital, Ain Shams University from January 2022 to July 2022. They were compared to twenty-five age and sex matched controls. Patients with type one diabetes were equally divided into two sub-groups according to (UAER); a normoalbuminuric and a micro-albuminuria group more than 300mg/24 hours. Enzyme-linked immunoassay was used to measure Caveolin level. Carotid intima media thickness was measured using a high resolution ultra-sound machine. It was used as a surrogate marker of early diabetic vascular changes.

Results: Higher levels of caveolin were detected in patients with diabetes in comparison to healthy controls with a p-value less than 0.01. In the patients' group, caveolin levels were found to be higher significantly among diabetic nephropathy patients, according to increased UAER, in comparison to patients without diabetic nephropathy, p-value less than 0.001. Carotid intima media thickness was higher among patients with diabetic nephropathy (P value less than 0.04). Using ROC curve analysis, a cut off value of caveolin greater than six ng/ml was found to differentiate between patients with diabetic nephropathy from those without nephropathy, with 96% specificity. Moreover, we found that caveolin levels are correlated positively with HbA1c level and (UAER). A cut off value of CIMT more than 0.03cm is best to differentiate patients suffering from diabetic nephropathy from those without nephropathy, with a specificity of 84%. Univariate and multivariate logistic regression analysis showed that a caveolin level more than 17 ng/ml and CIMT more than 0.03 cm were best associated with diabetic nephropathy patients.

Conclusion: Levels of Caveolin are associated significantly with urinary albumin excretion as well as subclinical vascular changes in patients with type one diabetes. Accordingly, we can conclude that high levels of caveolin may be correlated with the degree of diabetic nephropathy and angiopathy. This can be used as a therapeutic target.

Keywords: Type one Diabetes in children, Caveolin-1 Level, Diabetic nephropathy, diabetic vascular affection.

INTRODUCTION

Caveolin-1 (cav-1) is an integral membrane protein needed for the synthesis of the cholesterol-rich membrane microdomains caveolae. It is an important regulator of cellular migration and adhesion. It was found to be closely associated with metabolic-related diseases as obesity**,** diabetes and cardiovascular disease (Haddad et al. 2020). Cav-1 expression increased in several renal diseases as diabetic nephropathy. This supports the concept that cav-1 is a crucial pathologic trigger *(Van Krieken and Krepinsky 2017)***.**

Diabetic nephropathy is a common microvascular complication in diabetic patients and considered as the most important cause of end-stage renal disease(Van Krieken and Krepinsky 2017). These changes are activated by a complex group of different factors as oxidative stress, chronic low-grade inflammation, pro-sclerotic growth factors and cytokines interaction *(Gosmanov et al. 2014)***.** Diabetic nephropathy is characterized by extra-cellular matrix (ECM) accumulation in the glomerulus, leading to glomerulosclerosis. Mesangial cells are important regulators for the turnover process of the surrounding extra-cellular matrix in the glomeruli (Schlöndorff and Banas 2009). Cav-1 was found to increase the ECM production and accumulation in the mesangial cells by improving the upregulation and the activation of various profibrotic pathways. Moreover, it is needed for the synthesis of ECM proteins in response to hyperglycemia in the mesangial cells (Zhang et al. 2017).

On the other hand, the function of endothelium is impaired in patients with diabetes for the first decade after its onset. It is characterized by impaired vasodilatation in main and resistance arteries, which leads to atherosclerosis, hypertension and coronary arteries disease(Zimnicka et al. 2016). This is associated with an increase in the carotid intima media thickness (CMIT). The onset of these events is a major determinant different policies evaluation to prevent the development of different vascular complications as atherosclerosis in these patients (Singh et al. 2003)**.** Cav-1 is abundant in the endothelium of blood vessels (Wang et al. 2009). Studies in mice with deficient caveolin showed that caveolin can down regulate eNOS (endothelial nitric oxide synthase), which is mainly responsible for the generation of nitric oxide in the endothelium of blood vessels, and hence promoting paracellular permeability (Liu and Liu 2019).

This work aimed to measure the level of caveolin among children with type one diabetes and detect the relation between the level of caveolin, urinary albumin excretion rate (UAER) and carotid intima media thickness (CIMT) which was used as a surrogate marker of atherosclerosis.

Subjects And Methods

Ethical Considerations:

1. An informed consent was obtained from the caregivers or their legal guardians. The aim of the study was explained to them. They had the right to withdraw from the study at any time.
2. The aim of the study was explained to the parents before the study onset. They had the right to withdraw from the study at any time.
3. The patients' personal information, data and the study results are confidential and the patient has the right to keep them.
4. The study was approved by the ethics committee of Ain Shams University (approval number: FAMSU MS 459/ 2021).
5. The contributing authors stated there was no potential conflicts of interest regarding to the authorship, research, or publication in connection with the reported study.
6. Authors declare that there was no funding provided to this study

Sample size: Using PASS 11 program for sample size calculation, setting power at 80% alpha error at 5%, reviewing results from previous study ***(Moriyama et al., 2011)*** showed that the expression of cav-1 was significantly increased in the glomeruli of patients with glomerular disease, and it was related to urinary albumin excretion, assuming an effect size difference =0.8 regarding the mean Caveolin-1 level between cases and control group, a total sample of at least 70 participants (24 Type1 diabetic patients without diabetic nephropathy, 24 Type1 diabetic patients with diabetic nephropathy) and 22 controls were needed. For dropout, sample size increased to 25 per each group.

Inclusion criteria: Our study included children of both sexes who had type one diabetes mellites for five or more years, whose age is from six to 18 years old.

Exclusion criteria: Patients who suffered from thyroid disease or familial dyslipidemia

Study population:

This was a comparative cross-sectional study that included a total of 50 patients following up at the pediatric diabetes clinic, at children's hospital, Ain-Shams University. The study was carried out in the period from January 2022 to July 2022 at pediatric diabetes clinic and pediatric cardiology unit at children's hospital, Ain-Shams University, Cairo, Egypt. The enrolled patients were further sub-divided into two equal categories; 25 patients with Type one diabetes without diabetic nephropathy, 25 patients with Type one diabetes and diabetic nephropathy, and compared to 25 healthy controls.

Study Procedures:

Data were collected from the patients' files, including age of onset, disease duration, insulin type and total daily dose, associated comorbidities, and diabetes related complications.

All included children were subjected to the following:

I. Complete General examination including:

1- Anthropometric assessment including weight, height and plotted against body centiles.

2- Vital data including systolic and diastolic blood pressure were measured in a quiet room using a conventional oscillatory system placed at the right upper arm.

3- Thorough clinical examination of the chest, heart and abdomen.

II. Laboratory investigations:

All studied patients underwent the following investigations:

- Hemoglobin Al C measurement using cation exchange high performance liquid chromatography (CE-I-IPLC).
- Fasting lipid profile and kidney function tests measurement using Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany).
- Microalbumin in urine was used as a marker of nephropathy. It was assessed in an early morning urine sample using immunonephelometric method. Microalbuminuria was diagnosed if the urinary albumin excretion in at least 2 out of 3 consecutive urine samples over a period of three to six months was 30-299mg/g creatinine and >300 mg/g creatinine respectively (Molitch et al., 2004) .
- Caveolin-1 level was assessed using ELISA technique. This is based on the Biotin double antibody sandwich technology to assay the Human Caveolin-(Cav-1). Caveolin-l (Cav-l) was added to the wells, which are pre-coated with Caveolin-l(Cav-1) monoclonal antibody and then incubated. After that, anti Cav-1 antibodies labeled with biotin were added to unite with streptavidin. This leads to the formation of an immune complex. Unbound enzymes were removed after incubation and washed. Substrate A and B were added. The solution color changes into yellow with the acid effect. The solution shades and the human Caveolin-1 (Cav-1) concentration were positively correlated .

III. Cardiac imaging

Carotid intima media thickness assessment was done using a high-resolution Philips Ultrasonography machine with a linear 5 MHz probe. The probe was placed over the patients hyperextended neck in the antero-lateral position. The measurement place was standardized to be 1 cm from the common carotid artery bulb in each study. Measurements were done in the longitudinal plane of the common carotid artery. The CIMT was defined as the distance from the blood-intima interface to the junction between the media and adventitia. Three separate readings were taken during the diastole in centimeters. The mean value was used for the statistical purposes.

Statistical Analysis

Data were collected, coded, and entered into the statistical package for social science (IBM SPSS) version 23 (IBM Corp, Armonk, NY, USA). The quantitative data were presented as standard deviations, mean, median and ranges. The qualitative variables were presented as percentages and numbers. Spearman correlation coefficients were used to determine the correlation between two quantitative parameters in the same group. The comparison between two independent groups with quantitative data and parametric distribution was carried out using an independent t-test. In cases with non-parametric distribution, Mann-Whitney test was used. The comparison between different groups regarding the qualitative data was performed using the chi-square test and/or Fisher exact test when the expected count in any cell was less than five. The confidence interval was set to 95% with an accepted error margin set to be 5%. The p value was considered significant if p value was < 0.05.

RESULTS

Our results will be demonstrated in the following tables:

Table 1: Comparison between patients with diabetic nephropathy and without nephropathy regarding clinical and demographic data

		DM without nephropathy	DM with nephropathy	Test value	P-value	Sig.
		No. = 25	No. = 25			
Weight (kg)	Mean ± SD Range	45.64±11.88 27 – 65	49.64±13.45 24 – 70	0.835•	0.438	NS
Weight centile	<3rd (3rd – 25th) (25 – 75th) (75 – 90th)	4 (16.0%) 9 (36.0%) 11 (44.0%) 1 (4.0%)	6 (24.0%) 4 (16.0%) 10 (40.0%) 5 (20.0%)	5.037*	0.169	NS
Height (cm)	Mean ± SD Range	150.88 ± 11.29 135 – 176	150.12 ± 11.98 123 – 166	0.726•	0.487	NS
Height centile	<3rd (3rd – 25th) (25 – 75th) (75 – 90th)	3 (12.0%) 4 (16.0%) 15 (60.0%) 3 (12.0%)	6 (24.0%) 9 (36.0%) 5 (20.0%) 5 (20.0%)	8.423*	0.038	S
Systolic BP (mmHg)	Mean ± SD Range	111.60 ± 8.98 90 – 130	116.04 ± 10.45 100 – 140	1.529•	0.224	NS
Diastolic BP (mmHg)	Mean ± SD Range	75.20 ± 6.53 60 – 80	75.48 ± 6.55 60 – 90	0.065•	0.937	NS
Blood pressure	Normal High for age	24 (96.0%) 1 (4.0%)	21 (84.0%) 4 (16.0%)	2.000*	0.157	NS

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant *: Chi-square test; •: One Way ANOVA test*

Upon comparing the anthropometric parameters between the two diabetic groups, there was a statistically significant difference was found in the height centile (p= 0.038). About six diabetic patients with nephropathy (24%) and three diabetic patients without nephropathy (12%) had stunted growth as they were uncontrolled

and had elevated HbA1C. Almost all diabetic patients had normal blood pressure except five patients who were non-compliant.

Table 2: Comparison between patients with diabetic nephropathy and without nephropathy regarding laboratory data

		DM without nephropathy	DM with nephropathy	Test value	P-value	Sig.
		No. = 25	No. = 25			
HbA1c	Mean ± SD Range	11.56 ± 2.28 6.5 – 15.3	11.47 ± 2.17 7.5 – 15	0.133•	0.894	NS
Creatinine (mg/dl)	Mean ± SD Range	0.65 ± 0.19 0.3 – 1	0.71 ± 0.14 0.5 – 0.95	-1.350•	0.183	NS
Creatinine	Normal for age High for age	22 (88.0%) 3 (12.0%)	22 (88.0%) 3 (12.0%)	0.000*	1.000	NS
Total cholesterol (mg /dl)	Median (IQR) Range	166 (139 – 203) 35 – 256	182 (156 – 200) 138 – 252	-0.747≠	0.455	NS
Total cholesterol	Normal High	23 (92.0%) 2 (8.0%)	24 (96.0%) 1 (4.0%)	0.355*	0.552	NS
Triglycerides (mg /dl)	Median (IQR) Range	101 (77 – 199) 25 – 447	145 (100 – 167) 46 – 456	-0.912≠	0.362	NS
Triglycerides	Normal High	19 (76.0%) 6 (24.0%)	20 (80.0%) 5 (20.0%)	0.117*	0.733	NS
LDL (mg/dl)	Median (IQR) Range	80 (59 – 99.2) 22 – 126	92 (80 – 99) 33 – 147	-1.415≠	0.157	NS
LDL	Normal High	25 (100.0%) 0 (0.0%)	25 (100.0%) 0 (0.0%)	–	–	–
HDL (mg /dl)	Median (IQR) Range	56 (50 – 64) 8 – 90	51 (45 – 63) 32 – 93	-0.360≠	0.719	NS
HDL	Normal	25 (100.0%)	25 (100.0%)	0.368*	0.544	NS

*P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant *: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test*

There was no significant difference between diabetic patients with nephropathy and those without nephropathy regarding the HbA1c level, kidney function tests and lipid profile markers

Table 3: Comparison between control and patient groups regarding Caveolin levels and Carotid intima media thickness

		Control group	DM without nephropathy	DM with nephropathy	Test value	P-value	Sig.
		No. = 25	No. = 25	No. = 25			
Caveolin level (ng/ml)	Median (IQR) Range	4 (3 – 6) 2 – 7	9 (7 – 14) 4 – 18	20 (12 – 27) 5 – 35	47.228≠	0.000	HS
Carotid intima media thickness (cm)	Mean ± SD Range	0.025 ± 0.006 0.01 – 0.04	0.036 ± 0.012 0.02 – 0.06	0.045 ± 0.014 0.03 – 0.09	20.527•	0.000	HS
Post Hoc analysis							
		Control Vs DM without nephropathy		**Control Vs DM with nephropathy**		**DM without nephropathy Vs DM with nephropathy**	
Caveolin level (ng/ml)		0.000		0.000		0.000	
Carotid intima media thickness (cm)		0.001		0.000		0.005	

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant •: One Way ANOVA test; ≠: Kruskal-Wallis test

Diabetic patients had higher Caveolin levels in comparison to the control group. Moreover, significantly higher caveolin levels were found in diabetic nephropathy patients in comparison to patients without diabetic nephropathy ($p<0.001$). To add, CIMT had higher values among patients with type one diabetes and

especially those with diabetic nephropathy in comparison to the other groups with p value less than 0.005 and 0.04 respectively

Table 4: Correlation between caveolin level, CIMT and other studied parameters among DM cases without nephropathy

	DM without nephropathy				DM with nephropathy			
	Caveolin level		Carotid intima media thickness		Caveolin level		Carotid intima media thickness	
	r	P-value	R	P-value	r	P-value	R	P-value
Caveolin level (ng/ml)	–	–	**0.520****	**0.008**	–	–	**0.786****	**0.000**
Carotid intima media thickness (cm)	**0.520****	**0.008**	–	–	**0.786****	**0.000**	–	–
Age (years)	-0.037	0.861	0.116	0.582	0.150	0.475	0.180	0.389
Duration of diabetes (years)	-0.178	0.395	-0.233	0.263	0.324	0.115	0.396	0.050
Total daily dose (unit/kg/day)	0.365	0.073	0.139	0.508	0.366	0.072	**0.417***	**0.038**
HbA1c	0.455	0.231	0.129	0.601	**0.746****	**0.000**	**0.513****	**0.009**
Microalbumin in urine					**0.859****	**0.000**	**0.762****	**0.000**

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant, Spearman correlation coefficient

There was a significantly positive correlation between caveolin levels and CIMT in patients with diabetic nephropathy R=0.78, P=0.00). Additionally, levels of caveolin are positively correlated with urinary albumin excretion rate (UAER) and HbA1c in patients with diabetic nephropathy with (R=0.85, P=0.00) and (R=0.74, P=0.00) respectively

Table 5: ROC curve for caveolin level, CIMT and to detect DM cases

Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
Caveolin level (ng/ml)	>6	0.953	90.00	92.00	95.7	82.1
Carotid intima media thickness (cm)	>0.03	0.850	70.00	92.00	94.6	60.5

Table 6: ROC curve for caveolin level, CIMT to detect DM cases with nephropathy

Variables	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
Caveolin level	>17	0.793	56.00	96.00	93.3	68.6
Carotid intima media thickness	>0.03	0.692	84.00	44.00	60.0	73.3

Using ROC curve analysis, a cut off value of caveolin more than 6 ng/ml can differentiate patients suffering from type one diabetes from healthy controls, with a specificity of 92%. Moreover, a cut off value of caveolin more than 17 ng/ml can differentiate patients suffering from diabetic nephropathy from those without nephropathy, with a specificity of 96%. While a cutoff value of CIMT more than 0.03cm is best to differentiate patients suffering from diabetic nephropathy from those without nephropathy, with a specificity of 84%.

Table 7: Univariate and Multivariate logistic regression analysis for factors associated with DM with nephropathy

	Univariate				Multivariate			
	P-value	Odds ratio (OR)	95% C.I. for OR		P-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
Caveolin level >17 ng/ml	**0.002**	30.545	3.556	262.389	**0.011**	28.657	2.147	382.512
Carotid intima media thickness >0.03 cm	**0.018**	13.500	1.556	117.137	**0.037**	19.992	1.206	331.282

Using Univariate and multivariate logistic regression analysis, a caveolin level more than 17 ng/ml and CIMT>0.03 cm were best associated with diabetic nephropathy patients

DISCUSSION

Diabetic nephropathy is a common microvascular complication in diabetic patients and is considered as the main cause of end-stage renal disease (Van Krieken and Krepinsky 2017). On the other hand, the function of endothelium is impaired in patients with diabetes leading to atherosclerosis, hypertension and coronary arteries disease (Zimnicka et al. 2016). The onset of these events is a major determinant different policies evaluation to prevent the development of atherosclerosis and other vascular complications in these patients (Singh et al. 2003). It was proved that caveolin-1 is implicated in vascular function and atherosclerosis (Ramirez et al. 2019). However, to our knowledge, studies detecting its levels in relation to CIMT in pediatric type one diabetes populations are lacking.

In our study, we focused on detecting the level of caveolin in children with type one diabetes and point out the relation between urinary albumin excretion rate (UAER), caveolin level and subclinical early diabetic vascular changes using carotid intima media thickness.

We found that caveolin levels were significantly higher among patients with diabetic nephropathy patients in comparison to patients without diabetic nephropathy and healthy controls ($p<0.001$). These findings are consistent with an earlier study carried by Moriyama et al. His study showed that Cav-1 expression was noticed in patients with glomerular disease, being secreted from the capillary loops, mesangial area and the Bowman's capsule parietal cells. Cav-1 expression was increased significantly in patients with glomerular disease. Cav-1 expression was detected on the capillary loops in the glomeruli, together with other endothelial markers (Moriyama et al. 2011). Also, a study carried out on animal models showed that caveolae were expressed in the glomeruli of rats and that Cav-1 played an important role in the development mesangial proliferative glomerular disease (Tamai et al. 2001).

Data from our study reported that caveolin levels were positively correlated with urinary albumin excretion rate (UAER) in patients with diabetic nephropathy. Our results agree with the results of previous studies showing that the Cav-1 expression correlated positively with UAER. Some reports proved that caveolae are necessary for the albumin uptake and transport from the blood stream to the interstitium in the lung vascular endothelial cells (Wang et al. 2009) (Moriyama et al. 2011). Accordingly, caveolae was proved to play a key role in albumin endocytosis into the cytoplasm of glomerular endothelial cells and serum albumin transport from the capillary lumen to bowman's space through glomerular endothelial cells (Moriyama et al. 2011).

We noticed that the mean CIMT had significantly higher values in patients with type one diabetes and especially those with diabetic nephropathy in comparison to the other groups with p value less than 0.005 and 0.04 respectively. Our results are remarkably close to those reported in literature (Järvisalo et al. 2002) (Järvisalo et al. 2004). Many other groups demonstrated that type one diabetes patients have a higher mean CIMT values in comparison to matched control subjects. However, other authors reported differences in mean CIMT above or below the values we reported, varying from 0.01 mm (Parikh et al. 2000) to 0.20 mm (Abdelghaffar et al. 2006).

Additionally, data from the current we found that caveolin levels are positively correlated with HbA1c among patients with diabetic nephropathy. This agrees with the study carried by Zhang et al. which states that cav-1 and was found to increase the extra-cellular matrix (ECM) production and accumulation in the mesangial cells by improving the upregulation and the activation of various profibrotic pathways. Moreover, it is needed for the synthesis of ECM proteins in response to hyperglycemia in the mesangial cells (Zhang et al. 2017), where diabetic nephropathy hallmarks are glomerular hypertrophy, extracellular matrix (ECM) hypertrophy causing interstitial fibrosis and glomerulosclerosis. This ultimately leads to end-stage renal disease (Ziyadeh 2004).

Moreover, we found a significantly positive correlation between caveolin levels and CIMT thickness in patients with diabetic nephropathy (P=0.00).

The relationship between levels of caveolin-1 and carotid intima-media thickness (CIMT) in children with type 1 diabetes (T1D) is not well-established in the current literature. Although it was proved that caveolin-1 is implicated in vascular function and atherosclerosis, specific studies examining its levels in relation to CIMT in pediatric T1D populations are deficient. We found studies which explored the relationship between CIMT and other cardiovascular risk factors in children with T1D as the study carried out by Mona et al. which highlighted the correlation between increased CIMT and markers of oxidative stress, such as oxidized LDL, in children and adolescents with T1D, indicating that oxidative damage may contribute to vascular changes (El Samahy et al. 2013). Also, Robert et al., showed that impaired endothelial function, as evidenced by reduced flow-mediated dilation, is associated with increased CIMT in children with T1D, pointing to early vascular dysfunction in this group (Dalla Pozza et al. 2011).

Additionally, animal models revealed that endothelial cells lacking caveolin showed an increase in prostaglandinI2 expression. This proves that caveolin may be involved in PGI2 expression regulation. The main components of nitric oxide synthesis and gap junctions, nitric oxide synthetase and connexins, respectively, are found in caveolae and are physically associated with caveolin in human endothelial cells (Kuo et al. 2018). Studies in caveolin-deficient mice showed that caveolin is able to down regulate eNOS (endothelial nitric oxide synthase), which is responsible for the production of nitric oxide in the vascular endothelium, and hence promoting paracellular permeability (Ramirez et al. 2019).

Univariate and multivariate logistic regression analysis showed that a caveolin level more than 17 ng/ml and CIMT>0.03 cm were best associated with diabetic nephropathy patients. These results suggest that we can use caveolin and CIMT for early categorization of patients at risk and can be used as a therapeutic target to alleviate the pathology of diabetic nephropathy and angiopathy.

Our small sample size limited our conclusions, so we recommend that future studies include larger sample size.

CONCLUSION

Caveolin-1 plays an important role in the pathogenesis of diabetic nephropathy and angiopathy through facilitating a complex interplay of intracellular signal transduction involving pro-fibrotics and cytokines. Caveolin and CIMT can be used for early categorization of patients at risk and can be used as a therapeutic target to alleviate the pathology of diabetic nephropathy and angiopathy.

RECOMMENDATIONS

The presence of diabetic kidney disease in patients with type 1 diabetes requires prompt assessment of subclinical atherosclerotic risk. It is important now to move forward to early detection and prevention of disease complications. High levels of caveolin may be correlated with the degree of diabetic nephropathy and angiopathy. To add, it can be used as a therapeutic target and for early categorizing patients at risk of a diabetes related complications for better management of these patients.

LIMITATIONS

The study had some limitations as it was conducted on a small number of patients and some patients were missed during the study.

AUTHORS CONTRIBUTIONS

Abo El Asrar Formulation of the study idea, methodology and paper revision. Salem: Data collection and statistical analysis. ElHenawy: Formulation of the study idea, methodology, revising the results, data interpretation. Elsamman: CIMT assessment, revising the results, data interpretation, manuscript writing and revision.

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