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The Evaluation of SCUBE-1 and sCD40L Levels in Diabetic Nephropathy

Diyabetik Nefropatide SCUBE-1 ve sCD40L Seviyelerinin İncelenmesi

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ABSTRACT

Aim: There is a close link between diabetic nephropathy and atherosclerotic heart disease. We aimed to evaluate the changes of SCUBE-1 and sCD40L, which play role in the course of atherosclerosis, with the progression of nephropathy in patients with type 2 diabetes.
Material and Methods: Thirty healthy subjects (group 1) and 74 patients with type 2 diabetes (divided into 3 groups as normal albuminuria group (group 2, n=33), moderately increased albuminuria group (group 3, n=22) and severely increased albuminuria group (group 4, n=19)) were enrolled in the study. Plasma SCUBE-1 and sCD40L levels were measured using the enzyme-linked immunosorbent assay technique.
Results: Mean SCUBE-1 levels were significantly higher in group 4 compared to group 1 and group 2 (p=0.005 and p=0.014, respectively) and in group 3 compared to group 1 and group 2 (p=0.011 and p=0.028, respectively). Mean sCD40L levels were significantly higher in group 4 than in other three groups (all p<0.001), and in group 3 than in group 1 and group 2 (p=0.001 and p=0.016, respectively). Furthermore, SCUBE-1 level was positively correlated with total cholesterol level (r=0.212, p=0.031) and triglyceride (r=0.194, p=0.049). Likewise, sCD40L level was positively correlated with only creatinine level (r=0.297, p=0.002).
Conclusion: SCUBE-1 and sCD40L levels increased with the progression of nephropathy in type 2 diabetes. This increment suggested that SCUBE-1 and sCD40L may play key role in the course of atherosclerosis due to diabetic nephropathy and, diabetic nephropathy may affect the levels of these parameters.
Keywords: SCUBE-1; sCD40L; atherosclerosis; diabetic nephropathy.

ÖZ

Amaç: Diyabetik nefropati ve aterosklerorik kalp hastalıkları arasında yakın bir ilişki mevcuttur. Biz de, ateroskleroz sürecinde rol oynadığı bilinen SCUBE-1 ve sCD40L'ın tip 2 diyabeti olan hastalarda, nefropatinin ilerlemesi ile birlikte nasıl değiştiğini araştırmayı amaçladık.
Gereç ve Yöntemler: Otuz sağlıklı kişi (grup 1) ve 74 tip 2 diyabeti olan hasta (normal albuminüri grubu (grup 2, n=33), orta derece artmış albuminüri grubu (grup 3, n=22) ve şiddetli derecede artmış albuminüri grubu (grup 4, n=19) olarak üç gruba ayrıldı) çalışmaya dahil edildi. Plazma SCUBE-1 ve sCD40L seviyeleri, enzim-bağlı immunosorbent analiz tekniği kullanılarak ölçüldü.
Bulgular: Ortalama SCUBE-1 seviyeleri grup 1 ve grup 2 ile karşılaştırıldığında, grup 4'te (sırasıyla p=0,005 ve p=0,014) ve grup 1 ve grup 2 ile karşılaştırıldığında grup 3'te (sırasıyla p=0,011 ve p=0,028) anlamlı olarak yüksekti. Ortalama sCD40L seviyeleri grup 4'te diğer üç gruptan (tüm p<0,001) ve grup 3'te ise grup 1 ve grup 2'den (sırasıyla p=0,001 ve p=0,016) anlamlı olarak yüksekti. Ayrıca SCUBE-1 seviyeleri total kolesterol seviyesi (r=0,220; p=0,025) ve trigliserit (r=0,194; p=0,049) ile pozitif yönlü koreleydi. Yanı sıra, sCD40L seviyesi ise sadece kreatinin seviyesi (r=0,297; p=0,002) ile pozitif yönlü koreleydi.
Sonuç: SCUBE-1 ve sCD40L seviyeleri tip 2 diyabette nefropatinin progresyonu ile artmaktadır. Bu artış SCUBE-1 ve sCD40L'ın diyabetik nefropatiye bağlı ateroskleroz sürecinde anahtar rol oynuyor olabileceğini ve diyabetik nefropatinin bu parametrelerin seviyelerini etkiliyor olabileceğini düşündürmektedir.
Anahtar kelimeler: SCUBE-1; sCD40L;ateroskleroz; diyabetik nefropati.

INTRODUCTION

Diabetic nephropathy (DN) is a leading complication of diabetes mellitus progressing to end-stage renal disease (ESRD) (1). Patients with DN have exceptionally high risk of cardiovascular morbidity and mortality (2). It has been considered a close link between atherosclerotic heart disease and DN and they shared common predisposing factors such as hyperglycemia, dyslipidemia, hypertension, obesity and genetic background (3). Furthermore, atherosclerosis was more frequent in ESRD of DN (4).

Signal peptide-CUB (complement C1r/C1s, Uegf and Bmp1) epidermal growth factor-alanine-containing protein-1 (SCUBE-1) is a member of the SCUBE gene family and a cell surface protein (5). SCUBE-1 is secreted in the vascular endothelium and platelets (5-7). It has been shown that SCUBE-1 level was elevated in atherosclerosis related diseases such as coronary artery disease, hypertension and stroke (8-10).

CD40 Ligand (CD40L) produced by variety of cells as a proinflammatory mediator. Soluble form of CD40L (sCD40L) may be secreted by activated platelets (11). It has been shown that sCD40L has a role in the course of atherosclerosis and it was an independent prognostic marker for cardiovascular diseases among healthy individuals (12-16).

Both SCUBE-1 and sCD40L levels has been shown to be increased in ESRD (17-20). To the best of our knowledge, there are no studies evaluating SCUBE-1 or sCD40L levels with diabetes mellitus of type DN 2 at an early stage (T2DM). Herein, we aimed to the evaluate changes of SCUBE-1 and sCD40L with the progression of nephropathy in patients with T2DM.

MATERIAL AND METHODS

Participants

Randomly selected 74 outpatients diagnosed as T2DM who admitted to Harran University Education and Research Hospital Endocrinology Department were enrolled. The study protocol was approved by the Harran University School of Medicine Ethics Committee with number 17/02/06 in 09.02.2017. All subjects approved the written consent. The study was performed in accordance to the Declaration of Helsinki. Patients with severe organ failure, systemic inflammatory disease, malignancy, pregnancy and any renal disease other than DN were not included. Microalbumin to creatinine ratio was measured in early morning spot urine samples. The mean of two measurements was evaluated. Age and gender matched 30 healthy subjects were accepted as control group (group 1). T2DM patients were divided into three groups considering the level of proteinuria; the groups of normal albuminuria (albumin/creatinine <30 mg/g, group 2, n=33), moderately increased albuminuria (albumin/creatinine =30-300 mg/g, group 3, n=22) and severely increased albuminuria (albumin/creatinine >300 mg/g, group 4, n=19).

Biochemical Measurement

Blood samples were drawn from antecubital vein after an overnight fasting, centrifuged at 2000× g for 15 min, and stored at -80°C until analysis. A commercial kit following the manufacturer's instructions (Elabscience Biotechnology Co., Ltd., China, Catalog no: E-EL-H5405, Lot: AK0015NOV30024) using the enzyme-linked immunosorbent assay technique were performed to measure plasma SCUBE-1 and sCD40L levels.

Statistical Analysis

The data were analyzed using SPSS v.20. Chi-square test was performed to compare categorical data. Distribution of variable was controlled with Kolmogorov-Smirnov test. For continuous variables with normal distribution, One-way ANOVA was used to compare data between groups. LSD, as a post-hoc test, was performed to evaluate significance of the groups. Kruskal-Wallis test was used for non-normal data, and Mann-Whitney U test for separately each two groups in case of need. Spearman correlation analysis was used to determine correlations. A value of $p<0.05$ was considered to be statistically significant. All data were expressed as mean±standard deviation and median (minimum-maximum).

RESULTS

The groups were similar in terms of age and gender ($p=0.402$ and $p=0.397$, respectively, Table 1). There was a significant difference between groups in terms of mean plasma glucose levels ($p<0.001$) and it were significantly higher in diabetic groups according to the control group (all $p<0.001$). There was a significant difference between groups in terms of A1c levels ($p=0.031$). According to the post hoc test results, mean A1c levels of groups 3 and 4 were significantly higher than those of group 2 ($p=0.041$ and $p=0.020$, respectively). Mean blood urea and creatinine levels were significantly different between groups (all $p<0.001$). Mean blood urea and creatinine levels were significantly higher in group 4 than in the other groups in post hoc tests (all $p<0.001$). Moreover, there was a significant difference between groups in terms of mean total cholesterol level ($p=0.039$) and it was significantly higher in group 4 compared to group 1 ($p=0.011$).

Furthermore, SCUBE-1 and sCD40L levels were found to be significantly different between groups ($p=0.006$ for SCUBE-1 and $p<0.001$ for sCD40L). According to the post hoc test results, mean SCUBE-1 levels were significantly higher in group 4 than in group 1 and group 2 ($p=0.005$ and $p=0.014$, respectively), and in group 3 compared to group 1 and group 2 ($p=0.011$ and $p=0.028$, respectively). Moreover, mean sCD40L levels were significantly higher in group 4 than in other 3 groups (all $p<0.001$), and in group 3 than in group 1 and group 2 ($p=0.001$ and $p=0.016$, respectively).

In correlation analyze, SCUBE-1 level was positively correlated with total cholesterol ($r=0.220$, $p=0.025$) and triglyceride ($r=0.194$, $p=0.049$) levels. sCD40L level was positively correlated with only creatinine ($r=0.297$, $p=0.002$) level (Table 2).

DISCUSSION

In our study, we found following issues: i) SCUBE-1 and sCD40L levels were increased depending on the degree of DN, ii) SCUBE-1 was correlated with total cholesterol and triglyceride, and iii) sCD40L was correlated with creatinine.

SCUBE-1 is a platelet-endothelial adhesion molecule that plays pathological roles in atherothrombosis (9). It has been showed that SCUBE-1 level increased in acute thrombotic and ischemic events; e.g., acute coronary syndrome, ischemic stroke and mesenteric ischemia (8,10,21,22). Furthermore, as a chronic atherosclerotic process, Ozkan et al. (23) found that SCUBE-1 level increased in

Table 1. Comparison of clinical and laboratory parameters between groups

	Group 1 (n=30)	Group 2 (n=33)	Group 3 (n=22)	Group 4 (n=19)	p
Gender					
Male	16 (53.3%)	17 (51.5%)	14 (63.6%)	7 (36.8%)	0.397
Female	14 (46.7)	16 (48.5%)	8 (36.5%)	12 (63.2%)	
Age (year)	48.9±10.1	49.7±10.0	52.3±10.4	52.9±8.1	0.402
	49.0 (34.0-65.0)	51.0 (33.0-65.0)	54.5 (32.0-65.0)	55.0 (35.0-64.0)	
Glucose (mg/dL)	88.4±7.4[a]	180.3±78.3[b]	209.5±99.5[b]	220.9±96.8[b]	**<0.001**
	89.0 (67.0-99.0)	160.0 (94.0-398.0)	179.5 (109.0-480.0)	207.0 (106.0-425.0)	
A1c (%)	-	7.9±1.9[a]	9.2±2.0[b]	9.4±2.6[b]	**0.031**
		7.4 (5.2-11.8)	9.2 (5.9-12.7)	9.0 (6.7-14.6)	
Urea (mg/dL)	30.6±9.8[a]	31.2±7.0[a]	29.6±7.6[a]	50.9±31.3[b]	**<0.001**
	30.3 (12.5-49.0)	30.0 (18.4-46.1)	29.5 (15.3-43.8)	42.0 (19.8-138.0)	
Creatinine (mg/dL)	0.8±0.1[a]	0.8±0.1[a]	0.9±0.2[a]	1.2±0.5[b]	**<0.001**
	0.7 (0.4-1.2)	0.8 (0.6-1.2)	0.9 (0.6-1.2)	1.1 (0.6-2.0)	
Total-C (mg/dL)	170.6±39.3[a]	174.3±38.2[ab]	194.9±45.3[ab]	202.5±47.7[b]	**0.039**
	163.0 (105.0-258.0)	178.0 (113.0-273.0)	200.0 (124.0-301.0)	202.0 (122.0-323.0)	
Triglyceride (mg/dL)	153.2±68.1.2	184.8±92.0	236.0±192.0	210.4±82.7	0.069
	155.0 (60.0-348.0)	150.0 (65.0-408.0)	164.5 (63.0-821.0)	213.0 (88.0-345.0)	
HDL-C (mg/dL)	45.3±9.7	40.5±8.9	40.8±10.7	43.2±8.4	0.187
	44.8 (29.2-68.8)	40.2 (23.7-59.7)	42.1 (23.4-66.7)	45.0 (30.4-58.7)	
LDL-C (mg/dL)	96.8±36.8	97.9±32.5	108.9±29.7	117.2±39.6	0.147
	87.2 (34.7-178.8)	92.9 (36.8-176.0)	103.1 (64.7-169.0)	108.4 (71.2-227-7)	
SCUBE-1 (ng/ml)	1.6±0.6[a]	1.8±0.9[a]	2.8±2.2[b]	2.9±2.8[b]	**0.006**
	1.5 (0.8-2.9)	1.6 (0.8-4.2)	2.5 (0.8-10.8)	1.6 (0.8-11.6)	
sCD40L (pg/ml)	108.9±68.5[a]	385.4±237.9[a]	950.8±918.1[b]	2053.2±1669.5[c]	**<0.001**
	100.2 (37.9-302.3)	388.5 (48.1-973.4)	540.8 (176.4-3652.4)	1419.8 (294.4-5069.1)	

A1c: Glycosylated Hemoglobin, Total-C: Total Cholesterol, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, SCUBE-1: Signal peptide-CUB (complement C1r/C1s, Uegf and Bmp1) Epidermal growth factor-alanine-containing protein-1, sCD40L: Soluble form of CD40 Ligand, [a,b,c]: Different superscript letters denote significant differences between the groups, Descriptive statistics given as mean±standart deviation and median (minimum-maximum)

Table 2. Correlation analyses of sCD40L and SCUBE-1 with other parameters

	SCUBE-1		sCD40L	
	r	**p**	**r**	**p**
Age	-0.087	0.379	0.092	0.354
Glucose	0.189	0.055	0.576	**<0.001**
A1c	0.222	0.057	0.005	0.968
Urea	0.190	0.051	0.130	0.189
Creatinine	0.120	0.223	0.297	**0.002**
Total-C	0.220	**0.025**	0.128	0.197
Tri-glyceride	0.194	**0.049**	0.130	0.189
HDL-C	-0.186	0.058	-0.129	0.192
LDL-C	0.152	0.124	0.120	0.225

A1c: Glycosylated Hemoglobin, Total-C: Total Cholesterol, HDL-C: High Density Lipoprotein Cholesterol, LDL-C: Low Density Lipoprotein Cholesterol, SCUBE-1: Signal peptide-CUB (complement C1r/C1s, Uegf and Bmp1) Epidermal growth factor-alanine-containing protein-1, sCD40L: Soluble form of CD40 Ligand

hypertensive patients. Moreover, Ulusoy et al. (17) found that hemodialysis patients had high level than healthy subjects. More recently, Icel et al. (24) showed that SCUBE-1 was increased with the presence and progression of diabetic retinopathy. However, SCUBE-1 has not been studied in DN until now. We showed that SCUBE-1 level increased with the progression of nephropathy in T2DM at first time.

It is believed that, CD40L has a key role in the course of progressive atherosclerosis in healthy and diabetic subjects (25). Varo et al. (26) showed that sCD40L plasma levels were higher in T2DM patients according to healthy subjects. Lajer et al. (27) found that plasma sCD40L levels were elevated nephropathy of type 1 diabetes. Furthermore, Chiarelli et al. (25) showed that type 1 diabetic patients with persistently increased sCD40L levels had increased risk of nephropathy. On the other hand, Desideri et al. (19) indicated prognostic value of sCD40L for cardiovascular prognosis in patients with ESRD. To the best of our knowledge, the level of sCD40L in DN of T2DM is not known. We firstly showed that sCD40L level increased with the degree of nephropathy in T2DM.

Increased albuminuria has been accepted to be a principle risk factor of cardiovascular and renal diseases in T2DM (28). Barrios et al. (29) found that, patient with any stages of DN had higher risk of atherosclerosis compared to non-diabetic chronic kidney disease. Momeni et al. (30) showed that proteinuria was associated with atherosclerosis in T2DM. Platelets contribute to the onset and continuity of atherosclerosis as well as acute atherosclerotic events (31). Tarnow et al. (32) showed that DN due to T1DM was associated with increased circulating activated platelets and platelet hyper reactivity. SCUBE-1 mediates platelet-platelet or platelet-matrix interactions and is considered a biologically important molecule in the vascular system (6). The important role of sCD40L has been found in the bridge between inflammation, atherosclerosis, and thrombosis (33). Our

results suggested that increased SCUBE-1 and sCD40L might be the result of DN or might contribute to the progression of DN. Our study design could not distinguish this dilemma. So that, further studies with follow-up design are need to detect exact role of SCUBE-1 and sCD40L in DN and atherosclerosis. This situation is the most important limitation of our study.

Interestingly, we found that sCD40L level was correlated with renal function (i.e. creatinine level), but SCUBE-1 level with the lipid parameters (i.e. total cholesterol and triglyceride). Thus, we thought that increased atherosclerosis in DN may be related with different mechanisms. As discussed previously, risk of nephropathy is increased in type 1 diabetic patients with persistently increased sCD40L (24). The same predictor role of sCD40L in T2DM to estimate nephropathy risk should be explored in further studies.

CONCLUSION

We showed that SCUBE-1 and sCD40L levels increased with the progression of nephropathy in T2DM. This increment may be one of the pathological pathways causing to atherosclerosis or subclinical atherosclerosis may be the reason of this increment. Extensive studies are needed to confirm the results of the present study.

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