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Research Article

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sICAM-1 levels in type 2 diabetic atherosclerotic patients

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ABSTRACT

Atherosclerosis is the main cause of cardiovascular disease (CVD) which is the major cause of morbidity and mortality for diabetic patients. Endothelial dysfunction, which occurs early in atherogenesis, is associated with endothelial expression of the cell-surface adhesion molecules such as ICAM-1 (intercellular adhesion molecule-1). A soluble form of ICAM-1 can be measured in serum. Our study is a prospective cross-sectional study which included 65 participants aged 45-72 years and divided into three groups: type 2 diabetic atherosclerotic patients (n=24), type 2 diabetic non-atherosclerotic patients (n=20) and control group (n=21). Levels of sICAM-1, fasting blood glucose (FBG), total cholesterol (TC), triglycerides(TG), LDL-C and HDL-C were measured. sICAM-1 levels were significantly higher in diabetic atherosclerotic patients compared to diabetic patients (P<0.001) and control group (P<0.001) [470.94±15.24 ng/ml, 336.18±28.32 n g/ml, 273.46±7.2 respectively]. sICAM-1 levels were also significantly higher in diabetic patients compared to control group. Levels of sICAM-1 correlated positively and significantly with FBG and BMI values in diabetic atherosclerotic patients and diabetic patients whereas the correlation was not significant between sICAM-1 levels and lipid parameters levels. Our results showed that type 2 diabetes and atherosclerosis induce significant increase in sICAM-1 levels as a marker of endothelial activation. The coexistence of diabetes and atherosclerosis induces higher levels of sICAM-1.

Keywords: diabetes, atherosclerosis, adhesion molecules, sICAM-1.

INTRODUCTION

Atherosclerosis is the dominant cause of cardiovascular disease (CVD)[1] which is the major cause of morbidity and mortality for individuals with diabetes [2].In recent years, numerous novel markers of atherosclerosis and methods of its early diagnosis have been defined. The latest research is aimed at endothelium activity and defining its dysfunction[3].Current evidence suggests that endothelial dysfunction occurs early in the process of atherogenesis[4,5]. Endothelial dysfunction comprises a specific state of endothelial activation [5]which is defined by the endothelial expression of the cell-surface adhesion molecules such as ICAM-1 (intercellular adhesion molecule-1) in response to proinflammatory cytokines such as TNF-α and IL-6 [6].ICAM-1 is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily [7].It serves as a counter-receptor for the leukocyte integrin, lymphocyte function-associated antigen (LFA-1). Interaction between ICAM-1, present on endothelial cells, and LFA-1 facilitates leukocyte adhesion and migration across the endothelium[8]which is considered the first phase of atherosclerosis [9]. ICAM-1 is present in atherosclerotic lesions and is involved in the progression of these lesions [10].

A soluble form of ICAM-1 (sICAM-1) has been found in plasma[11].sICAM-1 generation can be explained by two mechanisms: ICAM-1 shedding from the cell membrane via proteolytic cleavage and the presence of messenger RNA transcripts coding for soluble ICAM-1 [8].sICAM-1levels are elevated in the serum of patients with cardiovascular disease and several studies have correlated serum levels of sICAM-1 with the severity of the disease [11].

Circulating levels of sICAM-1 are elevated in diabetic patients, and the increased lipoprotein oxidation in diabetes may be responsible for this increase which might contribute to the phenomenon of accelerated atherogenesis in patients with diabetes mellitus [12].

The purpose of the study was to evaluate sICAM-1 levels in type 2 diabetic patients with/without atherosclerosis and determine the relation between sICAM-1 levels and BMI, glucose, lipid parameters.

EXPERIMENTAL SECTION

This is a prospective cross-sectional study conducted at vascular surgery department and endocrine clinic at Al-Assad University Hospital, Damascus University, Damascus, Syria. Subjects were enrolled between June and December 2014. All participants gave written informed consent. Ethical approval was obtained from the ethical committee of Damascus University. The study included 65 participant saged 45-72 years and divided into three groups: type 2 diabetic atherosclerotic patients (24 patients: 16 males, 8 females), type 2 diabetic non-atherosclerotic patients (20 patients: 14 males, 6 females) and control group (21 subjects: 14 males, 7 females).Inclusion criteria were patients with diagnosed type 2 diabetes without atherosclerosis and patients with diagnosed type 2 diabetes and atherosclerosis. Exclusion criteria were thyroid disorders, cancers, autoimmune diseases, using glucocorticoids. All subjects underwent Doppler ultrasonography of carotid and lower limbs arteries to detect thickness or plaques in the intima-media layers. Venous blood samples were obtained from subjects between 8-10 AM after fasting for 12 hours, then centrifuged at 4000 rpm (1789×g) for 5 minutes at 4°C to isolate serum. Biochemical analysis was performed at Children's Hospital of Damascus within two hours of sampling. sICAM-1 levels were measured by sandwich ELISA method using a commercial kit (Sun Red, China).Glucose, total cholesterol, TG, LDL and HDL were measured by enzymatic colorimetric method using an automatic analyzer (Hitachi 911, Japan) and commercial assay kits (Audit diagnostics, Ireland). Statistical analysis was performed using SPSS 20.0 (IBM Inc., USA).All data are expressed as mean ± SD. Data was analyzed using One Way Analysis of variance (ANOVA) followed by Bonferroni testing to compare the results between groups. Pearson correlation was used to study the correlation between studied parameters. $p<0.05$ was considered significant.

RESULTS

Mean ± SD values of sICAM-1 were: 470.94±15.24 ng/ml for diabetic atherosclerotic patients, 336.18±28.32 ng/ml for diabetic patients and 273.46±7.2 ng/ml for control group.

sICAM-1 levels were significantly higher in diabetic atherosclerotic patients compared to diabetic patients ($P<0.001$) and control group ($P<0.001$). sICAM-1 levels were also significantly higher in diabetic patients compared to control group ($P<0.001$).

Table 1.subjects' characteristics and levels of studied parameters

		Mean	SD	Minimum	Maximum
Type 2 diabetic atherosclerotic patients (n=24)	**Age (years)**	59.17	5.01	49	67
	BMI (kg/m^2)	27.97	1.89	25.39	31.74
	FBG (mg/dl)	162.88	6.61	148	175
	sICAM-1 (ng/ml)	470.94	15.24	447.63	497.25
	TC (mg/dl)	213.08	24.49	175	265
	LDL-C (mg/dl)	147.63	21.15	114	188
	HDL-C (mg/dl)	30	9.05	16	50
	TG (mg/dl)	180.67	13.87	164	210
Type 2 diabetic patients (n=20)	**Age (years)**	55.6	5.31	47	65
	BMI (kg/m^2)	26.41	1.24	24.22	28.68
	FBG (mg/dl)	150.2	8.92	138	167
	sICAM-1 (ng/ml)	336.18	28.32	288.25	383.25
	TC (mg/dl)	198.8	17.7	170	229
	LDL-C (mg/dl)	128.86	19.97	98	173.2
	HDL-C (mg/dl)	37.33	4.51	30	45
	TG (mg/dl)	163.65	31.93	105	229
Control group (n=21)	**Age (years)**	57.95	6.48	45	68
	BMI (kg/m^2)	23.99	1.17	22.2	25.95
	FBG (mg/dl)	85	6.75	75	97
	sICAM-1 (ng/ml)	273.46	7.2	262.5	284.75
	TC (mg/dl)	182.86	15.37	152	205
	LDL-C (mg/dl)	106.06	18.6	66	135
	HDL-C (mg/dl)	57.01	9.92	42	75.4
	TG (mg/dl)	102.38	26.11	60	150

P values for comparison of studied parameters between groups are shown in table 2.

Mean, standard deviation (SD), minimum and maximum values of age, BMI, fasting blood glucose (FBG), sICAM-1, total cholesterol (TC), triglyceride (TG), LDL-C and HDL-C are shown in table 1.

Table 2. P values for comparison of studied parameters between groups.

	Diabetic atherosclerotic versus diabetic	Diabetic atherosclerotic versus control	Diabetic versus control
BMI	P<0.01	P<0.001	P<0.001
FBG	P<0.001	P<0.001	P<0.001
sICAM-1	P<0.001	P<0.001	P<0.001
TC	P=0.06 NS*	P<0.001	P<0.05
LDL-C	P<0.01	P<0.001	P<0.01
HDL-C	P<0.05	P<0.001	P<0.001
TG	P=0.07 NS*	P<0.001	P<0.001

**Not significant at 0.05 level*

Levels of BMI, fasting blood glucose and LDL-C were significantly higher in diabetic atherosclerotic patients compared to diabetic patients whereas levels of total cholesterol and triglyceride were not significantly higher in diabetic atherosclerotic patients compared to diabetic patients. Levels of HDL-C were significantly lower in diabetic atherosclerotic patients compared to diabetic patients.

Levels of BMI, FBG, TC, LDL-C and TG were significantly higher in diabetic atherosclerotic patients compared to control group and in diabetic patients compared to control group whereas levels of HDL-C were significantly lower in diabetic atherosclerotic patients compared to control group and in diabetic patients compared to control group.

Levels of sICAM-1 correlated positively and significantly with FBG and BMI values in diabetic atherosclerotic patients [(r=0.88, p<0.001), (r=0.57, p<0.01) respectively] and in diabetic patients [(r=0.95, p<0.001), (r=0.56, p<0.05) respectively]whereas the correlation was not significant between sICAM-1 levels and lipid parameters in diabetic atherosclerotic patients and diabetic patients as shown in table 3.

Table 3.correlation between sICAM-1 levels and BMI, FBG, lipid parameters in diabetic atherosclerotic group and diabetic group

		FBG	BMI	TC	LDL-C	HDL-C	TG
Diabetic atherosclerotic group	sICAM-1	r=0.88 p<0.001	r=0.57 p<0.01	r=0.04 p=0.85*	r=0.1 p=0.64*	r=-0.16 p=0.47*	r=0.12 p=0.59*
Diabetic group	sICAM-1	r=0.95 p<0.001	r=0.56 p<0.05	r=0.12 p=0.62*	r=0.14 p=0.56*	r=-0.43 p=0.06*	r=0.19 p=0.42*

**Not significant at 0.05 level*

DISCUSSION

Atherosclerosis is a chronic immunoinflammatory disease of large and medium sized arteries fuelled by lipids [13].endothelial dysfunction represents a key early step in the development of atherosclerosis and is also involved in plaque progression and the occurrence of atherosclerotic complications[5].Activated endothelium has an increased expression of adhesion molecules such as ICAM-1[6]which participates in leukocyte adhesion and facilitates leukocyte transendothelial migration[14].sICAM-1 is a soluble form of ICAM-1 found in plasma[11].Increased levels of sICAM-1 have been linked to progression of atherosclerotic lesions in apoE -/- mice [15].

Our results showed that sICAM-1 levels were significantly higher in diabetic atherosclerotic patients compared to control group (P<0.001) and diabetic patients (P<0.001), so the coexistence of diabetes and atherosclerosis induces higher levels of sICAM-1 as a marker for endothelial dysfunction and atherosclerosis. These findings are in agreement with previous studies by Kawamura *et al.*[16] which found elevated sICAM-1 levels in diabetic atherosclerotic patients compared to diabetic patients. Rubio-Guerra *et al.* found a correlation between sICAM-1 levels and the degree of atherosclerosis in type-2 diabetic patients. [17] In Edinburgh Artery Study[18], Tzoulaki*et al.* found an association between sICAM-1 levels and peripheral atherosclerosis progression assessed by the ankle-brachial index (ABI), but only 6% of participants were diabetic. A study by Matsumoto *et al.* [19]found higher sICAM-1 levels in diabetic patients with microangiopathy not macroangiopathy; this difference might be due to the relatively small number of participants in our study and due to the classification of diabetic patients into 3 groups: microangiopathy (retinopathy), macroangiopathy and no complication group in that study, but in our study we did not take microangiopathy in concern.

Previous studies have suggested that lipoprotein oxidation and protein glycation may contribute to the increased monocyte binding to the diabetic vasculature. There is increasing evidence that acute and chronic hyperglycemia induce activation of endothelial cells by upregulating levels of adhesion molecules such as ICAM-1[12],also insulin inhibits the expression of ICAM-1 through stimulation of nitric oxide and thereby suppresses monocyte adhesion to

endothelial cells[20].The chronic hyperglycemia in diabetic subjects leads to the development of advanced glycation end products (AGEs). AGEs together with inflammatory stimuli led to a higher expression of VCAM-1, ICAM-1, and E-selectin on cultured human endothelial cells[12].

Our study results showed that sICAM-1 levels were significantly higher in diabetic patients compared to control group ($P<0.001$). This result is in agreement with other studies[21-24].

sICAM-1 levels in our study correlated positively and significantly with FBG and BMI values in diabetic atherosclerotic patients and in diabetic patients, and this agrees with other studies[25-27],whereas the correlation was not significant between sICAM-1 levels and lipid parameters which agrees with other studies[26,28].

CONCLUSION

Our results showed that type 2 diabetes and atherosclerosis induce significant increase in sICAM-1 levels as a marker of endothelial activation. The coexistence of diabetes and atherosclerosis induces higher levels of sICAM-1. sICAM-1 levels correlated positively and significantly with Fasting glucose levels and BMI values.

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REFERENCES

[1] J Frostegard. *BMC Med*,**2013**, 11, 117.
[2] American Diabetes Association. *Diabetes Care*, **2015**, 38(Suppl 1), S49-S57.
[3] B Glowmska-Olszewska; JTotwinska; MUrban. *J PediatrEndocrinolMetab*, **2007**, 20(10), 1125-1136.
[4] S Sitia; L Tomasoni;F Atzeni; G Ambrosio; C Cordiano; A Catapano; S Tramontana;F Perticone; P Naccarato;P Camici; E Picano;L Cortigiani;M Bevilacqua;L Milazzo; D Cusi;C Barlassina;P Sarzi-Puttini; MTuriel.*Autoimmun Rev*, **2010**, 9, 830–834.
[5] N Chhabra. *Internet Journal of Medical Update*, **2009**, 4(1), 33-41.
[6] JK Liao. *J Clin Invest*, **2013**, 123(2), 540-541.
[7] L Fotis;D Giannakopoulos;L Stamogiannou;M Xatzipsalti. *Hormones*, **2012**, 11(2), 140-146.
[8] AM Witkowska;MH Borawska.*Eur Cytokine Netw*, **2004**, 15(2), 91-98.
[9] V Lubrano; S Balzan. *World J Exp Med*, **2015**, 5(1), 21-32.
[10] SI Wolf;C Lawson. *Coronary Artery Disease - New Insights and Novel Approaches*, InTech, Croatia, **2012**,65-90.
[11] C Lawson;S Wolf. *Pharmacol Rep*, **2009**, 61, 22–32.
[12] T Peschel;J Niebauer.*Cytometry Part B (Clin. Cytometry)*, **2003**, 53B, 78–85.
[13] E Falk. *J Am CollCardiol*, **2006**,47(8)Suppl C, C7-C12.
[14] W Tang;JS Pankow; JJ Carr; RPTracy; SJBielinski; KE North; PNHopkins; ATKraja;DK Arnett. *BMC CardiovascDisord*,**2007**, 7, 30.
[15]K Kitagawa; M Matsumoto; TSasaki; H Hashimoto;K Kuwabara; T Ohtsuki;M Hori. *Atherosclerosis*, **2002**,160(2), 305-310.
[16] T Kawamura; TUmemura; A Kanai; MNagashima; NNakamura; T Uno; M Nakayama;T Sano;Y Hamada; J Nakamura; NHotta. *Metabolism Clinical and Experimental*, **2006**, 55, 461–466.
[17] AF Rubio-Guerra; H Vargas-Robles; AM Serrano; JJLozano-Nuevo; BA Escalante-Acosta.*Cell AdhMigr*, **2009**, 3(4), 369-372.
[18]I Tzoulaki; GD Murray; AJ Lee; A Rumley;GD Lowe; FGRFowkes. *Circulation*, **2005**, 112,976-983.
[19]K Matsumoto; Y Sera; Y Ueki; G Inukai; E Niiro; SMiyake. *Diabet Med*, **2002**,19,822 - 826.
[20] SY Jin;EK Kim; JM Ha; DH Lee; JS Kim; IY Kim; SH Song; HK Shin; CD Kim;SS Bae.*BiochimBiophysActa*, **2014**, 1842, 1539–1548.
[21] L Raynor;JS Pankow; BBDuncan; MISchmidt; RCHoogeveen; MAPereira; J Hunter Young;CM Ballantyne. *Diabetes Care*,**2013**, 36, 70–76.
[22] MS Boulbou; GN Koukoulis; EDMakri; EA Petinaki; KI Gourgoulianis; AE Germenis. *Int J Cardiol*, **2005**, 98, 39-44.
[23] N Moussavi; G Renier; A Roussin; JC Mamputu; J Buithieu; O Serri. *Diabetes, ObesMetab*, **2004**,6, 69–77.
[24] S Kado; N Nagata. *Diabetes Res ClinPract*, **1999**, 46, 143–148.
[25] M Blüher; R Unger; F Rassoul; V Richter; R Paschke. *Diabetologia*,**2002**, 45, 210-216.
[26]K Matsumoto; Y Sera; H Nakamura; Y Ueki; S Miyake. *Diabetes Res ClinPract*,**2002**, 55, 131-138.

[27]E Leinonen; E Hurt-Camejo; O Wiklund; LM Hultén; A Hiukka; M Taskinen. *Atherosclerosis,* **2003**, 166, 387-394.
[28] G Targher; RCBonadonna; MAlberiche; MBZenere; M Muggeo; EBonora. *Diabetes Care,***2001**, 24(11), 1961-1966.