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Original Article

Correlation of plasma D-dimer concentration with severity of patients systemic sclerosis

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Abstract

Objective To find out the relationship between the level of plasma D-dimer concentration and severity of systemic sclerosis.

Methods This cross-sectional study was conducted in the department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from September, 2015 to August, 2017. Forty four patients of systemic sclerosis were included in this study through consecutive sampling. All of the patients were diagnosed by the dermatologist as systemic sclerosis on the basis of American College of Rheumatology (ACR) criteria. Using modified Rodnan Skin Scoring (mRSS) the patients were divided into three groups: mild, moderate and severe. All the patients in each group were tested for plasma D-dimer concentration and then plasma D-dimer concentration was correlated with the severity of disease. Statistical analysis was done by using Windows based computer software devised with statistical package for social sciences (SPSS-22, inc Chicago IL, USA). The results were obtained by using t-test, Chi-square test, ANOVA and Pearson's Correlation Coefficient test.

Results Among 44 patients, 21 (47.7%) had Diffuse Cutaneous Systemic Sclerosis (dcSSc) and 23 (52.3%) had Limited Cutaneous Systemic Sclerosis (lcSSc). According to mRSS 23 (52.3%) patients had mild, 15 (34.1%) had moderate and 6 (13.6%) had severe disease. Female patients were predominant in this study. D-dimer concentrations were increased in parallel with severity of the disease. Significant positive correlation was observed between D-dimer concentration and mRSS (p=0.009). Mean plasma D-dimer concentrations found to be significantly increased in patients with dcSSc in comparison with lcSSc (1.31±0.95 vs. 0.78±0.37, p=0.018).

Conclusion Plasma D-dimer concentration is directly related to the severity of the systemic sclerosis and it might be a helpful additional test to identify patients with systemic sclerosis at risk of developing thrombotic complications.

Key words
Plasma D-dimer, Systemic Sclerosis.

Introduction

Systemic Sclerosis (SSc) is a rare connective tissue disease, depends on autoimmunity, characterized by vascular endothelial cell injury and an extensive activation of fibroblasts. Though the skin, esophagus, lung, heart and kidneys are the most frequently affected organs, the extent of skin and organ involvement, disease progression and prognosis have gross individual variations. The disease has a female predominance with a female to male ratio of 3 to 14:1. The average age at onset of disease ranges between 30 and 50 years.[1]

The various mechanisms that play an important

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role in the pathogenesis are complex which depends on their microenvironment and key mediators. Multiple cell types like endothelial cells, epithelial cells, fibroblasts, and lymphocytic cells are also involved in this interaction through a variety of mechanisms. Distinct pathogenic process involved in different subsets and patients and different stages of SSc that result in clinical heterogeneity. Environmental and chemical factors act as triggers for the disease in a genetically susceptible person.[1]

Systemic Sclerosis (SSc) is a multisystem disorder in which endothelial dysfunction and haemorrheological abnormalities develop due to microcirculatory abnormalities. Similar abnormalities are seen in patients with macrovascular disease secondary to atherosclerosis. An inception cohort study demonstrated a fourfold increase in mortality in patients with SSc compared with their unaffected counterparts. Twenty nine per cent of deaths were attributable to cardiovascular causes.[2]

In SSc, vasospasm is responsible for frequent episodes of reperfusion injury and free radical mediated endothelial dysfunction, which might finally influence the onset of local thrombotic complications. The characteristic vascular involvement affects primarily small arteries and capillaries, causing reduced blood flow and tissue ischemia and supporting the typical clinical manifestations of this unique autoimmune disorder.[3] Mechanisms involved in the endothelial injury are as yet elusive and most biochemical evidences are often inconclusive or controversial. Some previous investigations suggested that SSc patient might be characterized by a procoagulant state, some reported depressed basal fibrinolytic activity and some reported stimulated fibrinolytic activity, while others studies have reported normal plasma fibrinolytic activity and normal skin and plasma tissue plasminogen activator (tPA) levels.[4] It has been also reported that the lack of a consistent and homogenous increase of some fibrinolytic markers, in the presence of normal levels of antithrombin, might indirectly highlight an impairment of the heparan sulphate-antithrombin system, which would finally promote thrombin generation. Cerinic and colleagues[5] provided evidence that fibrinolysis might be impaired in SSc. So, SSc patients display a hypercoagulable state which might finally predispose this peculiar subset of patients to the development of thrombotic complications.

D-dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. It is so named because it contains two cross linked D fragments of the fibrin protein. Normal cut off value of plasma D-dimer is 0.55 mg/L. It is an important test for patients with suspected thrombotic disorders. A negative result practically rules out thrombosis and a positive result can indicate thrombosis but does not rule out other potential causes. A high plasma D-dimer concentration is a reliable marker of a systemic prothrombotic state, likely superior to alternative fibrinolytic markers, and its measurement might be helpful in predicting or preventing thrombotic events.[6] It also appears a strong, consistent predictor of cardiovascular events in the general population, in patients with cardiovascular disease and in other pathologies characterized by an increased risk of thrombosis. SSc patients are characterized by increased plasma D-dimer values reflecting a potential activation of both the coagulation and fibrinolytic pathways, which might finally predispose these patients to thrombotic complications. So this test thus aids to minimize thrombotic complications by adding antithrombotic agents at prothrombotic stage of systemic sclerosis.

The present study was conducted to measure the plasma D-dimer and to correlate it with the severity of the disease in patients with SSc with the aim that it would be able to establish the relationship between plasma D dimer concentration and severity of systemic sclerosis which would make a scientific background to modify existing treatment by adding anti platelet agent such as aspirin, clopidogrel along the conventional treatment of systemic sclerosis to arrest progression of prothrombotic stage to thrombosis.

Materials and methods

This cross sectional analytical study was conducted in the Department of Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from September 2015 to August 2017. Approval of the institutional review board of BSMMU was obtained. Patients who visited indoor and/ or outdoor of the above mentioned department of BSMMU were interviewed and systemic sclerosis was diagnosed by dermatologist on the basis of ACR criteria. Forty four patients irrespective of sex and aged over 20 years who gave written consent were enrolled by consecutive sampling technique. Patients with history of bleeding, thrombotic disorder, stroke, myocardial infraction, atrial fibrillation, heart failure, peripheral arterial disease, renal and liver diseases, malignancies, patients who were pregnant and were taking antithrombotic agents at the time of study were excluded. Modified Rodnan Skin Scoring (mRSS) of each and every patient was scored and the patients were labeled as mild, moderate and severe on the basis of mRSS. Each and every patient was tested for ANA, Anti Scl-70, Anti centromere antibody and plasma D-dimer. Data including age in years, sex, duration of disease, ANA, Anti Scl-70, Anti centromere Antibody and plasma D-dimer levels were recorded in a predesigned structured questionnaire. All the data were entered into a computer and statistical analysis of the data were done by using statistical package for social science version 22.0 for windows (SPSS-22, inc Chicago IL, USA). Appropriate tests like t-test, Chi-square test, ANOVA Test and Pearson's Correlation Coefficient test were done. Quantitative data were expressed as mean±standard deviation and qualitative data were expressed as frequency distribution and percentage. P values <0.05 was accepted as statistically significant.

Results

Age of the patients ranges range 20-65 years with a mean of 46.04±9.56 years. Majority (86.4%) of patients were female with a male female ratio of 1: 6.3 (**Table 1**). There was no significant difference in mean plasma D-dimer concentrations between male and female patients (p=0.550) (**Table 2**). Out of the 44 patients 52.3% had mild mRSS, 34.1% had moderate and 13.6% had severe mRSS (**Table 3**).

Table 1 Distribution of the study patients by age and sex (n=44).

	Number of patients (%age)	
Age (yrs.)		
20-29	11 (25.0%)	
30-39	15 (34.1%)	Mean±SD
40-49	5 (11.4%)	46.04±9.56;
50-59	9 (20.5%)	range 20-65
> 60	4 (9.1%)	yrs.
Sex		
Male	6 (13.6%)	Male to female
Female	38 (86.4%)	ratio 1:6.3
Total	44 (100%)	

Table 2 Comparison of mean Plasma D-dimer concentration (mg/L) between male and female systemic sclerosis patients (n=44).

Sex	*Plasma D-dimer concentration (mg/L) (mean±SD)*		
Male (n=6)	0.86±0.45	t value	P value
Female (n=38)	1.06±0.79	0.603	0.550^{ns}

Table 3 Distribution of the study subjects on the basis of Modified Rodnan Skin Score (mRSS) score (n=44).

Severity of mRSS scoring	*Frequency (%)*
Mild (score 1-14)	23 (52.3)
Moderate (score 15-29)	15 (34.1)
Sever (score > 30)	6 (13.6)
Total	44 (100)

Table 4 Severity with patients of systemic sclerosis compared with or without high plasma D-dimer concentration (n=44).

Severity of mRSS scoring	*No. of Patients*	*D-dimer (mg/L) n (%)*	
		>0.55	*< 0.55*
Mild (1-14)	23	15 (65.2%)	8 (34.8%)
Moderate (15-29)	15	12 (80.0%)	3 (20.0%)
Severe (> 30)	6	5 (83.3%)	1 (16.7%)
Total	44	32 (76.7%)	12 (27.3%)

Table 5 Comparison of mean Plasma D-dimer concentration (mg/L) among mild, moderate, severe form of modified Rodnan Skin Scoring in systemic sclerosis patients.

Modified Rodnan Skin Scoring	*Plasma D-dimer concentration in mg/L (Mean±SD)*	*P value*
Mild (n=23)	0.78±0.37	
Moderate (n=15)	1.02±0.45	<0.001*
Severe (n=6)	2.04±1.46	

*significant

Normal cut off value of plasma D-dimer is 0.55 mg/L. D-dimer concentrations were increased in parallel with severity of the disease. 65.2% of the mild, 80% of the moderate and 83.3% of the severe patients had above normal plasma D-dimer level (**Table 4**). There were significant differences in plasma D-dimer concentration in patients with mild, moderate and severe form of systemic sclerosis (**Table 5**). Mean plasma D-dimer concentrations were significantly increased in patients with diffuse cutaneous systemic sclerosis in comparison with limited cutaneous systemic sclerosis (1.31±0.95 vs. 0.78±0.37, p=0.018) (**Table 6**). We found a significant positive correlation between D-dimer with mRSS score ('r' = 0.389, p<0.009) (**Figure 1**). ANA test was positive in 100% cases having both high and normal level of D-dimer concentration; Anti Scl-70 Antibody test was positive in 18.8% cases with high D-dimer concentration and 33.3% cases with normal D-dimer concentration; Anti-Centromere antibody test was positive in 6.3% cases with high D-dimer concentration (**Table 7**). 37 (84.1%) patients had duration of disease from 1-5 years whereas only 7(15.9%) patients had duration <1 year. Mean D-dimer concentration in 1-5 years group was 1.04±0.79 and <1 year group was 0.99±0.44. 32 (72.7%) patients had duration of treatment 1-5 years and 12 (27.3%) patients had duration of treatment <1 year. Mean D-dimer concentration in 1-5 years group was 1.07±0.81 and in < 1 year group was 0.95±0.57. There was no significant difference between mean D-dimer with duration of illness and treatment (**Table 8**).

Discussion

Systemic sclerosis is an autoimmune disorder characterized by widespread vascular involvement. Macrovascular involvement is considered rare, although increased prevalence of macrovascular disease has been reported as well. This cross-sectional study was carried out with the aim to assess the correlation between plasma D-dimer concentration and severity of patients with systemic sclerosis.

The present study showed that there were 6 (13.6%) men and 38 (86.4%) women. Female patients were predominant in this study. Such differences have been explained by genetic and hormonal factors and lifestyle. Age range of the patient was 20 to 65 years. The mean age of the patients was 46.04±9.56 years. Maximum patients 34.1% patients belong to age range 30-39 years followed by 25.0% patients were in 20-29 years and 20.5% patients were 50-59 years (**Table 1**). Marie *et al*. reported in a study of one

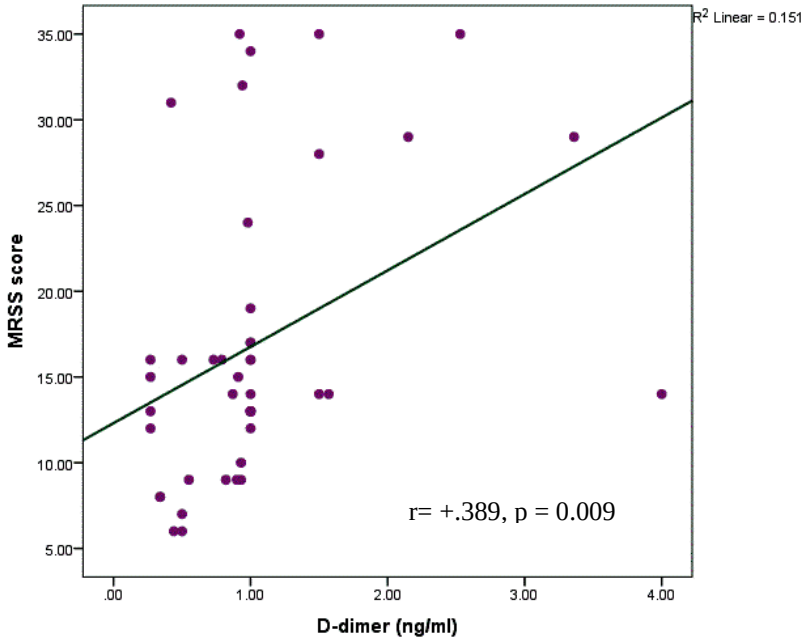

Figure 1 In Pearson's correlation test, scatter diagram showing the correlation of mRSS score with D-dimer of the systemic sclerosis patients.

Table 6 Comparison of mean Plasma D-dimer concentration (mg/L) with the subset of patients of systemic sclerosis (n=44).

Subset of systemic sclerosis patients	*Level of Plasma D-dimer in mg/L (mean±SD)*	*t value*	*P value*
Limited Cutaneous SSc (n=23)	0.78±0.37	2.468	0.018*
Diffuse Cutaneous SSc (n=21)	1.31±0.95		

*significant

Table 7 Association of serological marker of patients with systemic sclerosis (SSc) with or without high plasma level of D-dimer concentration (n=44).

Serological markers	*Patients*		*P value*
	D-dimer >0.55 mg/L (N=32) n (%)	*D-dimer < 0.55 mg/L (N=12) n (%)*	
ANA Test (positive)	32 (100.0)	12 (100.0)	1.000^{ns}
Anti Scl-70 Antibody Test (positive)	6 (18.8)	4 (33.3)	0.304^{ns}
Anti-Centromere Antibody Test (positive)	2 (6.3)	0 (0.0)	0.375^{ns}

ns= not significant

Table 8 Distribution of the study subjects according to duration of illness treatment (n=44).

Duration of illness	*Number (%)*	*D-dimer (mg/L) Mean±SD*	*p value*
< 1 year	7 (15.9)	0.99±0.44	0.867^{ns}
1 to 5 years	37 (84.1)	1.04±0.79	
Duration of treatment	*Number (%)*	*D-dimer (mg/L) Mean±SD*	*p value*
< 1 year	12 (27.3)	0.95±0.57	0.650^{ns}
1 to 5 yrs.	32 (72.7)	1.07±0.81	

ns = not significant.

hundred and thirty-three consecutive patients with a definite diagnosis of SSc, there were 18 men and 115 women with a median age of 58.5 years (range 25–84 years).[7]

Plasma D-dimer (a breakdown product of cross-linked fibrin) has been reported to be a marker of systemic prothrombotic state in patients with macrovascular complications with SSc.[8-12] Meta-

analyses of prospective studies have shown that plasma levels of D-dimer were independent predictors of increased risk of coronary heart disease, stroke, peripheral arterial disease as well as cardiovascular death.[9,10,13,14]

To date, only a few investigators have reported that D-dimer levels are higher in patients with SSc compared with healthy controls.[4,8,15,16] In a small series of 28 patients with SSc, Lippi G *et al*.[15] noted a higher plasma D-dimer concentration (362 vs. 229 ng mL^{-1}) in patients with SSc than in controls. Our study demonstrates that patients with SSc exhibit higher levels of D-dimer and increases in parallel with the severity of systemic sclerosis. We have observed that plasma concentration of D-dimer exceeded the upper limit of normal (>0.55mg/L) in a statistically significant number of patients (**Table 4**); as previous series have found that temporal variations of D-dimer levels are important sources of heterogeneity.[12] There is clear evidence of a significant activation of the coagulation cascade resulting in a procoagulant state that might finally raise the relative risk of thrombotic events in SSc patients.[5]

This study finds no significant difference in mean plasma D-dimer concentrations between male and female patients p = 0.550 (**Table 2**). Lippi *et al*. also found no correlation between plasma D-dimer concentration sex.[15] According to modified Rodnan skin scoring scale, in our study 52.3% patients had mild, while 34.1% patients had moderate and 13.6% patients had severe form of disease (**Table 3**). Plasma D-dimer concentration parallelly increased with severity of disease (**Table 4**). Mean plasma D-dimer concentrations appeared significantly increased in patients with diffuse cutaneous systemic sclerosis compared with limited cutaneous systemic sclerosis (1.31±0.95 vs. 0.78±0.37, p=0.018) (**Table 6**) which were consistent with the findings of Lippi G *et al*.[15] A high plasma D-dimer concentration, reflecting a potential activation of both the coagulation and fibrinolytic pathways. In present study showed significant positive correlation between D-dimer with mRSS score ('r'=0.389, p<0.009) (**Figure 1**). Finally, we observed significant difference of plasma D-dimer concentration in patients among mild, moderate and severe (modified Rodnan Skin scoring) form of systemic sclerosis (**Table 5**). Plasma D-dimer concentration significantly increased with the severity of systemic sclerosis patients. Similar findings were reported Lippi *et al*.[15] D-dimer concentration correlated significantly with the modified Rodnan total skin score.

In systemic sclerosis there was a loss of balance between fibrinolysis and coagulation process that might contribute to vessel engulfment with fibrin and break down of vessel patency, a tendency to the development of thrombotic complications.

This study did not find any statistical significant correlation with plasma D-dimer concentration and serological markers, duration of illness or duration of treatment of Systemic sclerosis (**Table 7, 8**).

The present study found that the plasma D-dimer concentration significantly increased with the severity of systemic sclerosis. Marie I *et al*. suggested an association between high levels of plasma D-dimer (≥.55mg/dl) and macrovascular involvement in patients with SSc. They mentioned that the D-dimer levels might be a helpful additional test to identify patients with SSc at risk of developing thrombotic arterial complications (peripheral arterial disease, stroke and coronary event); such patients with high levels of plasma D-dimer (≥.55 mg/dl) might require close monitoring of vascular parameters especially macrovascular impairment.[17]

Conclusion

Plasma D-dimer concentration is directly related to the severity of the systemic sclerosis. As advanced cases of systemic sclerosis are prone to develop thrombotic complications. So patients having plasma D-dimer concentration >0.55 mg/L may require close monitoring for macrovascular impairment.

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