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A Study of the Circulating Biomarkers (MMP-9, Plasma Fibrinogen, d-dimer, IL-6 and CRP) in Arterial Aneurysms

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Abstract

Background: The role of circulating proteins as potential biomarkers of presence and progression of abdominal aortic aneurysms has been studied in several series; however, their role in the peripheral artery aneurysm has not been thoroughly investigated. No data is available from the Indian population regarding the biomarker levels. Based on the western data, analysis of five circulating biomarkers (MMP-9, Il-6, CRP, Fibrinogen and D-Dimer) was done to investigate their role as markers of disease presence in peripheral and abdominal aortic aneurysms and pseudoaneurysms.

Method: 22 cases of peripheral artery or abdominal aortic aneurysm and pseudoaneurysm were included in the study and the levels of MMP-9, Il-6, CRP, Fibrinogen and D-Dimer were estimated and compared with controls.

Results: The levels of circulating biomarkers were found to be significantly elevated in the cases as compared to controls. The circulating MMP-9 among cases was 3306.8 ± 622.91 ng/mL which was significantly elevated as compared to controls, 2442.1 ± 904.71 ng/mL ($p<0.001$). A significant elevation among the other variables was also noted for Il-6- median in cases was 66.25 pg/mL (IQR 31.78 to 145.46 pg/mL) as compared with control 13.1 pg/mL (9.85 to 16.10 pg/mL); CRP-median in cases was 5.44 mg/L (IQR 2.39-8.05 mg/L) against controls 0.45 mg/L (0.20-0.60 mg/L); mean Fibrinogen levels among cases was 440.64 ± 121.62 mg/dL vs. controls 311.95 ± 66.87 mg/dL and D-Dimer was also significantly elevated (1700.40 ± 864.49 mg/L in cases compared with controls 149.45 ± 83.45 mg/L).

Conclusion: The levels of circulating biomarkers tested in the current study (MMP-9, Il-6, Fibrinogen, D-Dimer and CRP) in patients with arterial aneurysm and pseudo-aneurysm are a marker of disease presence.

Key Words: Biomarkers; Matrix metallo proteinases; C reactive protein; Interleukins; Aorta; Peripheral arteries

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Introduction

Arterial aneurysm is a common source of morbidity and mortality in the western set-up, the most common aetiology has been degenerative, attributed to atherosclerosis and age related vessel changes. Arterial aneurysms have varied shape and size, the definition laid down by the Ad Hoc committee on reporting standards of the society of Vascular Surgery as "A permanent localized (i.e., focal) dilation of an artery having at least 50% increase in diameter of the artery in question" [1]. The dominant histological feature of any aneurysm is chronic medial and adventitial inflammation with medial degeneration including smooth muscle apoptosis and loss of extracellular

matrix. This entails the increased turnover and loss of type I and III fibrillar collagen as well as excessive elastolysis, as a result of increased activity of the enzymes collagenases, elastase and more importantly the expression of MMP, due to the underlying arterial dilation and rupture.

The average incidence of Abdominal Aortic Aneurysm in the US was about 62% (Lawrence and Gazak [2]), it was the most common aneurysm to be encountered outside the Cranial cavity and thorax. This was followed by lower extremity, thoracic, neck, axillary and Sub-clavian aneurysms. The popliteal artery aneurysm was most common among the peripheral arterial aneurysms in most series and bilateral aneurysm was noted in most cases [3-5].

The current understanding of the mechanism of degenerative aneurysm formation and rupture has the potential to create better protocols for the management of arterial aneurysms. The development of better imaging and availability of intensive care units have reduced the mortality associated with aneurysm rupture, especially that of the abdominal aorta.

With the recent studies on circulating biomarkers, their role in predicting rupture can become more practical in future. The present study attempts to confirm the findings of circulating biomarkers in the Indian population for peripheral and abdominal aortic aneurysms.

Methods

Study population

Patients of peripheral and abdominal aortic aneurysm were included in the study, presenting in our surgical unit and in the cardiothoracic and vascular surgery department of the Sir Sunderlal Hospital, BHU. Patients already on anticoagulants were excluded from the study; patients of intra-cranial and thoracic vascular aneurysm were not included. Clinical assessment of each case including a thorough history and physical examination, followed by investigations including haematological and biochemical tests (Complete blood counts, renal profile, liver function tests, lipid profile, random blood glucose levels) and special investigations for diagnosis and planning of management (Duplex Scanning, CT Angiography/MR Angiography, ECG, Echocardiography and Chest X-ray).

Collection of samples

Blood samples of the patients were collected pre-operatively; serum samples (4 mL) and plasma samples (2.6 mL) were separated for testing serum MMP-9, Il-6, CRP and Fibrinogen, D-Dimer, respectively.

Biomarkers assessment

Levels of circulating MMP-9 was determined using ELISA, serum Il-6 was done using Il-6-EASIA, Turbidimetric immunoassay was used for determining circulating CRP levels, FIBRI-PREST kit using the Claus principle was used for determination of circulating Fibrinogen levels and D-Dimer was estimated using NycoCard READER II based on immunometric flow through principle.

Ethics

The study was carried out on patients with written informed consent that was approved by the ethical committee of the university and conforms to the ethical guidelines of the "World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008.

Statistics

Data was analysed using the SPSS software for Windows, 16th edition. Total of 22 cases (12 males and 10 females) were studies and to compare, 20 healthy controls were taken. Mean values were considered for MMP-9, Fibrinogen and D-Dimer, test for significance using the Student's t-test; Median value of Il-6 and CRP were analysed using Mann-Whitney and Wilcoxon tests to determine significance. Correlation between individual variables and the variables with age, sex and maximum transverse diameter were done using the Pearson's product moment coefficient and Spearman's rank correlation analysis. Strength of association was determined for each variable to determine the validity of the result. All the variables were significantly elevated, so that a multivariate analysis was not applicable to the data. The sample size was small due to limited number of cases presenting to the centre and can be considered a limitation for the study.

Results

Total 22 (12 male and 10 female) patients with extra-cranial, extra-thoracic arterial aneurysms were included in the study. Among the cases only a single case of 1 year child with brachial artery aneurysm was found, maximum number of cases belonged to the young age group (10-20 yrs) and had a traumatic pseudoaneurysm, followed by older age group patients with atherosclerotic and traumatic aetiologies. The arteries of the trunk and lower limb accounted for maximum number of cases, with the Saccular morphology of aneurysm being the most common. Two cases of diffuse arterial dilation involving the axillary artery and abdominal aorta were present. There was presence of intra-arterial thrombus in 14 cases with complete thrombosis in one case (SMA Jejunal branch pseudo-aneurysm). Four cases presented with associated AV malformation, 2 cases of huge AVM involving the entire upper extremity and had to undergo amputation and major resection with skin grafting respectively; the other 2 were those in the popliteal fossa and were formed after orthopaedic procedures for fracture tibia. Pain and swelling remain the two most common complaints at presentation. A major group among cases had pseudoaneurysms while true aneurysms were encountered in only 4 cases. The male to female ratio in the study group was 1.2:1 showing a nearly equal distribution in both sexes. No significant difference was noted between the two groups, the presentation of Abdominal Aortic Aneurysm was in 2 male and 1 female patients. The current data as seen in 2 major studies demonstrated a significant increase in atherosclerosis and mean aortic diameter among males more than females [6,7], however, due to the small sample size, significance of greater male patients with AAA cannot be justified. With other

aneurysms, the incidence is variable among both sexes, although a tendency towards higher incidence in males has been noted in few series [7] for Popliteal and Femoral aneurysms. In the current series, a high incidence of male patients with Femoral and Popliteal artery aneurysms was encountered, with only one case of popliteal aneurysm in female patients recorded. Splanchnic artery aneurysms were exclusively seen in female patients save one case of chronic pancreatitis in a young male in his 30s who had a pseudoaneurysm of splenic artery.

The results showed significant elevations in MMP-9, IL-6, CRP, Fibrinogen and D-Dimer as compared to the healthy controls **(Table 1)**. There was no correlation noted between age and the circulating biomarker levels, however, there was a positive correlation between circulating MMP-9 and D-Dimer, MMP-9 , D-Dimer and vessel diameter **(Table 2)**. Correlation analysis using Pearson's product moment correlation Coefficient demonstrated statistical correlation between MMP-9, D-Dimer and Sac Size, MMP-9 vs. Fibrinogen, Il-6, D-dimer, CRP among cases only and in the total study group (cases+controls) was done to judge the linearity of the findings and a strength of association with the compounded variables (**Table 3** demonstrating the association between circulating biomarkers) **Figure 1** shows a linear correlation between D Dimer and MMP-9. **Figure 2** and **Figure 3** demonstrate a linear correlation between circulating D-Dimer and MMP-9 and the vessel diameter.

Discussion

The key mechanisms of inflammation and the resultant immune response generated by the body which ultimately results in the formation of aneurysm can be understood by the model proposed by Shimizu et al [8]. In their model, the pathogenesis of development of aortic aneurysm occurs in 2 steps each having its own triggers; the first is the activation of the inflammatory cascade that results in IFN-γ increase and in turn the activation of Th1 mediated cytokines that results in development of the athero-occlusive aorta. This is followed by the second trigger which is the result of free radical and auto-immune triggers which then block the IFN-γ signal and activate the Th2 mediated cytokines. It is essentially the second trigger that is responsible for the development of the atherosclerotic aortic aneurysm. The degenerative aetiology that has been found most commonly in AAA is primarily the end result of age related atherosclerotic changes as have been hypothesized. It was due to the development of this and similar models that the role of biomarkers came to limelight and are being investigated for the development of arterial aneurysms, with the future use of serving as the markers of presence and progression. Data from previous studies have shown mixed reports of biomarker positivity in Abdominal Aortic Aneurysms and even fewer studies remain for peripheral arterial aneurysms [7-9].

The hallmark of arterial aneurysm has been the degradation of extracellular matrix and its pathogenesis is characterized by the raised levels of circulating enzymes of matrix degradation including the MMPs (Matrix Metallo-Proteinases) and Cathepsin family The earliest studies conducted by Lindholt et al [9] in 1994 on 122 male patients in 65 to 73 year age group with aortic aneurysm diameters between 3 to 5 cm to screen them for the concentrations of serum elastase complexes, plasma α1-Anti-trypsin, MMPs and elastin peptides, Procollagen III-N-terminal pro-peptides over a four year period to correlate the increase

Table 1 Circulating Markers mean and median values as observed.

Group	MMP-9 (Mean ± SD)	Fibrinogen (Mean ± SD)	IL6 Median (IQR)	CRP Median (IQR)	D-dimer (Mean ± SD)
Case N=22	3306.8 ± 622.91	440.64 ± 121.62	66.25 (31.78-145.46)	5.44 (2.39-8.05)	1700.40 ± 864.49
Control N=20	2442.1 ± 904.71	311.95 ± 66.87	13.10 (9.85-16.10)	0.45 (0.20-0.60)	149.45 ± 83.45
P value	<0.001	<0.001	<0.001	<0.001	<0.001

Table 2 Correlation of MMP-9, Fibrinogen, D-Dimer, Il6, CRP and Sac size.

		MMP9	Fibrinogen	D-Dimer	Il6	CRP	Sac Size
MMP-9	R	1	0.219	0.833	0.240	0.132	0.741
	P		0.327	**0.000**	0.282	0.560	**.000**
Fibrinogen	R	0.219	1	0.275	-0.436	0.110	0.372
	P	0.327		0.215	0.042	0.627	0.088
D-Dimer	R	0.833	0.275	1	0.111	0.236	0.962
	P	**0.000**	0.215		0.624	0.290	**0.000**
Il6	R	0.240	-0.436	0.111	1	-0.140	-0.026
	P	0.282	0.042	0.624		0.534	0.908
CRP	R	0.132	0.110	0.236	-0.140	1	0.312
	P	0.560	0.627	0.290	0.534		0.158
Sac Size	R	0.741	0.372	0.962	-0.026	0.312	1
	P	**0.000**	0.088	**0.000**	0.908	0.158	

Table displays the correlational analysis of MMP-9, Il-6, CRP, D-Dimer, and Fibrinogen with the size of aneurysm (sack size) using the Pearson's product moment correlation coefficient. The Pearson's product moment correlation coefficient gave statistically significant correlation between MMP-9, D-Dimer; MMP-9 sac size and D-Dimer and sac size, with direct linear correlation.

Table 3 Spearman's correlation between the circulating variables.

			MMP9	Fibrinogen	D-dimer	IL6	CRP
Spearman's rho N=42 **CASE+CONTROL**	MMP9	Correlation Coefficient	1.000	0.176	0.600	0.473	0.340
	Fibrinogen	Correlation Coefficient	0.176	1.000	0.515	0.362	0.282
	D-dimer	Correlation Coefficient	0.600	0.515	1.000	0.727	0.649
	IL6	Correlation Coefficient	0.473	0.362	0.727	1.000	0.572
	CRP	Correlation Coefficient	0.340	0.282	0.649	0.572	1.000

Correlation analysis using Pearson's product moment correlation Coefficient had previously demonstrated statistical correlation between MMP-9, D-Dimer and Sac Size, a Spearman's Rank correlation analysis for MMP-9 vs. Fibrinogen, Il-6, D-dimer, CRP among cases only and in the total study group (cases+controls) was done to judge the linearity of the findings a nd a strength of association with the compounded variables.

R Square value of association between MMP-9 and other variables was 0.316 or ~ 32%; between D-Dimer and MMP-9 was 26%, strongest correlation between MMP-9 and D-Dimer among the studied biomarkers.

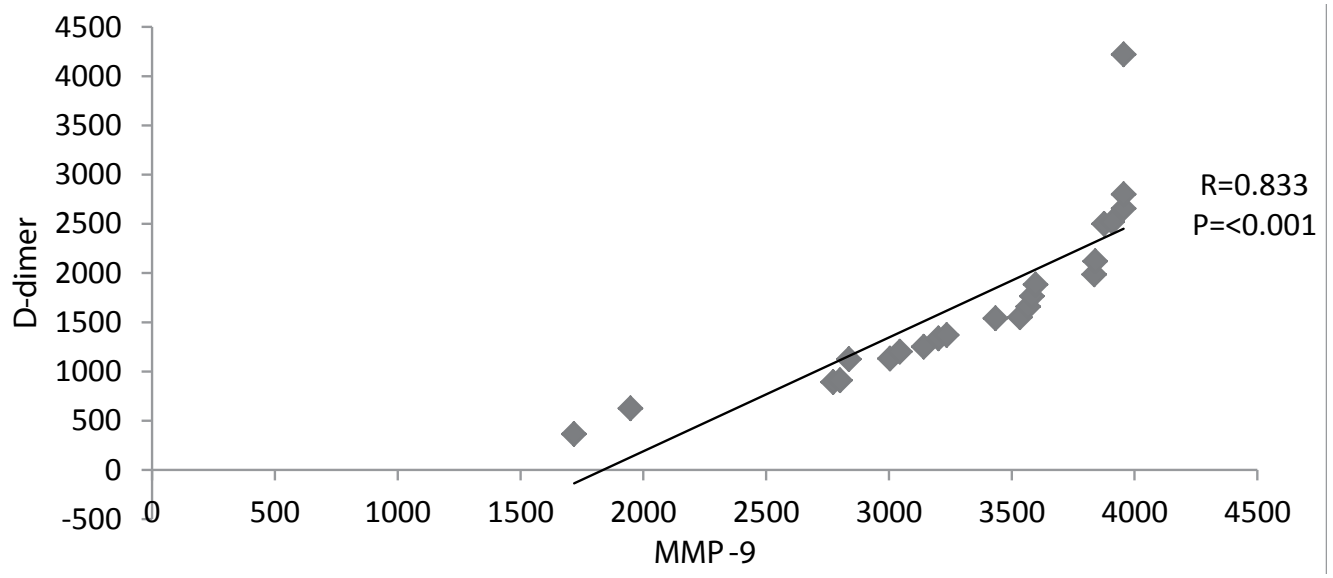

Figure 1 Demonstrating linear positive correlation between circulating D-Dimer and MMP-9 levels.

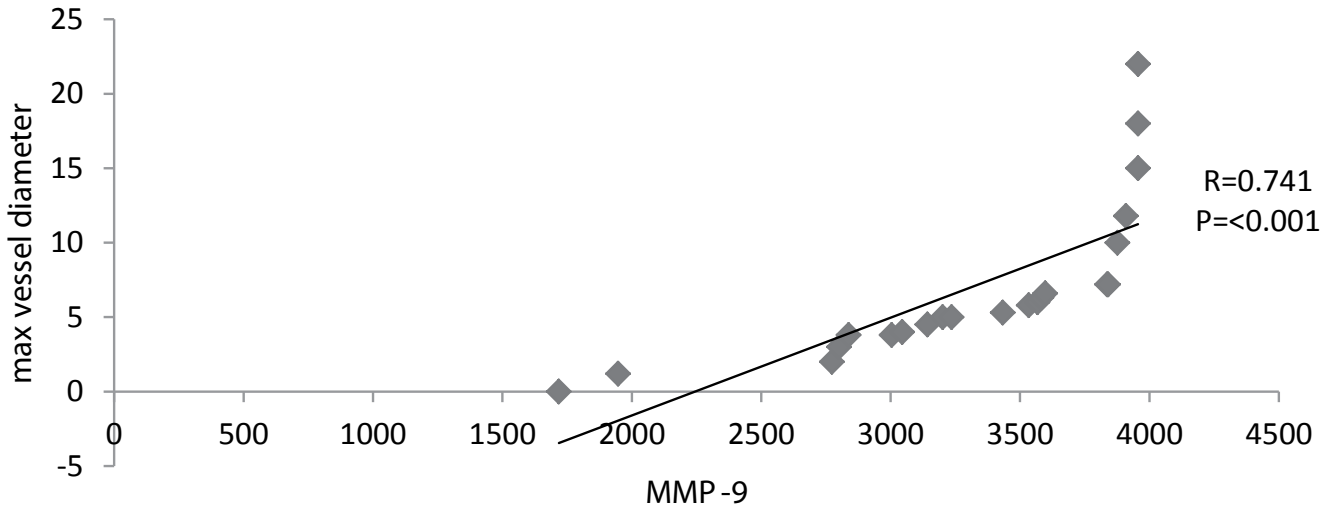

Figure 2 Demonstrating a linear positive correlation between circulating MMP-9 levels and vessel diameter.

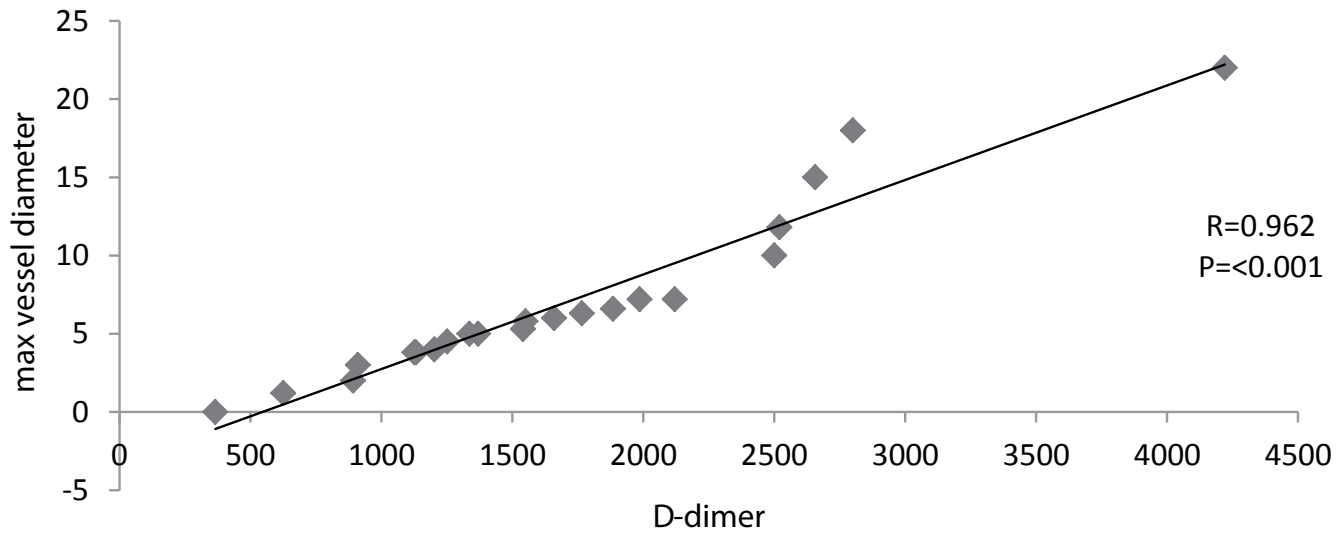

Figure 3 Demonstrating a linear positive correlation between circulating D-dimer levels and vessel diameter.

in their levels with aneurysm expansion. The average MMP-9 concentration in their series was 60 ng/mL with an increase in value that correlated with the abdominal aortic diameter increase in the evaluated patients. Hovsepian et al [10] published data comparing the mean values of MMP-9 in patients with Abdominal Occlusive Disease and Abdominal Aortic Aneurysms and the comparison with tissue and plasma level of MMP-9. They found statistically significant elevations in plasma MMP-9 levels in AAA cases (99.4 ± 17.4 ng/mL) as compared to the patients with AOD (54.7 ± 10.5 ng/mL) and healthy controls (36.1 ± 7.7 ng/mL) and also a positive correlation between tissue and plasma elevations in MMP-9 suggesting that the production of MMP-9 is increased in aortic aneurysms. MMP-9 plasma levels did not correlate significantly with age, gender, or aneurysm diameter, although there was a trend toward the highest values in male patients with large AAAs. More studies revealed similar data and the levels of circulating MMP-9 have been found to be significantly elevated in patients with abdominal aortic aneurysms. Data from meta-analysis by Takagi et al [11] and Speelman et al [12] have shown positive confirmation towards the association of circulating MMP-9 levels and presence and progression of Abdominal Aortic Aneurysms. Two studies were found which aimed to investigate the levels of MMP-9 in peripheral arteries. The first of these was by Francis et al [13], found significant elevations in circulating plasma MMP-9 in patients with multiple peripheral arterial aneurysms and AAA. The second by Serra et al [14], demonstrated significant elevations in circulating MMP-9 levels in patients with extremity aneurysms.

The data presented from the above studies provided a basis for the current research. In this study, the serum MMP-9 levels were assessed in patients with peripheral artery aneurysms and pseudo aneurysms. The mean value of serum MMP-9 in the cases was 3306.8 ± 622.91 ng/mL, as opposed to the control value of 2442.1 ± 904.71 ng/mL which was found to be significant ($P<0.001$). A positive correlation was also noted between the size of sac and serum MMP-9 values. This supports the finding of significant elevations in circulating MMP-9 levels in peripheral arterial aneurysms and pseudo aneurysms as well as Abdominal Aortic aneurysms, suggesting that matrix degradation is a key element in the pathogenesis of the disease and the large sac aneurysms with more extensive matrix degradation will present with higher levels of circulating MMP-9.

Thrombosis is frequently seen in the lumen of an arterial; aneurysm and pseudo-aneurysm. Most AAA have a significant amount of thrombus and the presence of pseudo-aneurysm causes the activation of coagulation cascade, thereby causing an increase in the circulating levels of markers of thrombosis including fibrinogen, D-dimer, homocysteine, tissue plasminogen activator, von Willebrand factor, soluble thrombomodulin, plasminogen activator inhibitor-1, activated protein C–protein C inhibitor complexes, plasmin-antiplasmin complexes, P-selectin, thrombin–antithrombin III complex, and fibrinogen degradation products [15].

Lee et al [16], in 1996, by a nested case controlled study, showed a significant correlation between increased Fibrinogen and D-Dimer to the presence of AAA. Milne et al [17] however gave conflicting results in their analysis of Fibrinogen and D-Dimer levels in circulation for patients with asymptomatic infra-renal aortic aneurysms. A 10% less platelet count was also noted in their study attributed to the presence of generalized vascular disease. Fowkes et al [18] while investigating into the co-existence of COPD in AAA patients in association with smoking, cardiovascular disease and increased inflammatory and haemostatic activity, found that while several patients of AAA had COPD with worse lung functions (as measured by FEV1 and FVC), but were also associated with increased levels of circulating markers of inflammation and haemostasis such as Plasma Fibrinogen, Plasmin-antiplasmin complexes, Il-6 and D-dimer and this effect was not accounted for by the presence of smoking and cardiovascular diseases. Yamazumi et al [15], in their study

correlating the sac morphology with blood coagulation and fibrinolysis noted a positive correlation between tortuosity and vessel diameter with the blood levels of fibrinolytic factors like D-dimer, fibrinogen/fibrin degradation products and plasmin-antiplasmin complexes.

A large population based analysis by Golledge et al [19], the odds of having an AAA with D-Dimer levels >400 ng/mL and >900 ng/mL was 12.1 and 24.7; a significant correlation was also noted between the annual growth rate and progressive increase in D-Dimer levels. Al-Barjas et al [20] obtained plasma samples from a group of 110 patients with AAA and also demonstrated positive correlation between the AAA size and fibrinogen concentration (r=0.323). Meta-analysis by Sidloff et al [21], revealed significant elevations in both Fibrinogen and D-Dimer in patients with AAA (Mean Difference for Fibrinogen 0.43 g/l with 95% CI; 0.28-0.58 g/l; P<0.00001 and that for D-Dimer 325.82 ng/mL 95% CI, 199.74-451.89 ng/mL; P<0.00001). Positive correlation between Abdominal Aorta Diameter and D-Dimer concentrations was also noted. Similar reports by Takagi et al [22], in another meta-analysis were also seen.

While investigating into significance of D-Dimer levels in post-catheterisation Superficial Femoral Artery Pseudoaneurysms, Matthias et al [23], found significant elevations in circulating plasma D-Dimer in patients developing pseudo-aneurysms after cannulation as compared to healthy controls (1.9 µg/ml vs 0.8 µg/ml; P<0.0001). The current study supports the positive results of the previous studies, in the Indian population. Presence of thrombus was noted in about 64% cases and in all cases with AAA. Significant elevations were noted in the circulating Fibrinogen and D-Dimer levels in our study. These results signify a positive correlation between presence of aneurysm and thrombosis and fibrinolytic by-products.

The basic pathology behind the matrix degradation phenomenon as stated by Shimizu [10] was the inflammatory cascade. Most studies, to assess the presence of these inflammatory biomarkers, have been carried out for AAA in small population series. Fowkes et al [18] in their study on association between haemostatic and inflammatory markers in association with AAA and COPD found significant elevations in the levels of Il-6 in cases 2.8 pg/ml (2.0-4.2) as compared to controls 1.8 pg/ml (1.3-2.7) [p <0.001]. Junoven et al [24], found elevations in Il-6 levels in both male and female patients with AAA (males-6.40 pg/mL, female-7.99 pg/mL; p<0.05), however, the circulating cytokines did not correlate with the aneurysm size and the presence of intraluminal thrombus, suggesting that the degree of inflammation is not correlated with the thrombotic process or the matrix degradation rate. Dawson et al [25] tested the hypothesis: "AAA secretes Il-6" and found a significant raised level of Il-6 (4.9 ± 0.5 pg/ml; P=0.002) in AAA group as compared to control (2.7 ± 0.5). There was also a positive correlation between Il-6 level and aneurysm surface area (TAA avg 0.07 m^2 vs. AAA avg 0.03 m^2). Meta-analysis of 13 case controlled studies by Takagi et al [26], Concluded that the circulating levels of Il-6 was elevated in AAA patients than without. In the current study, the level of Il-6 was found raised significantly in the patients with peripheral artery and abdominal aortic aneurysm as compared to the controls [median (IQR) - 66.25 pg/mL (31.78-145.46) in cases vs. 13.10 (9.85-16.10) for controls; P<0.001]; no correlation was found with the sac size.

C-reactive protein (CRP) is a non-specific acute phase reactant mainly produced in the liver stimulated by various cytokines believed to be involved in the pathogenesis of degenerative aneurysms. The biomarker is more commonly employed for cardiovascular diseases and chronic infections. Wanhainen et al [27] in their study found significant correlation between raised CRP levels and AAA presence (mean 4.8 mg/L (2.2-7.3) in cases compared to 2.4 mg/L (1.8-3.0) in controls; P=0.003). Vainas et al [28] studied the relation between serum CRP levels and diameter of aneurysm in asymptomatic AAA patients. The mean hsCRP level in serum was 3.23 mg/l (SD=2.96). CRP mRNA was detected in 4 of 16 tissue samples (25%). When patients were divided in 3 equally-sized groups according to hsCRP level (hsCRP<1.13, 1.13 ≤ hsCRP<4.15, and hsCRP ≥ 4.15), aortic diameter increased from lowest to upper tertile (49 mm, 61 mm, and 67 mm, respectively; P<0.05 for 3rd versus 1st tertile), suggesting that serum hsCRP is associated with aneurysm size in patients with asymptomatic AAA. Speelman et al [12], found that while there was a weak relation between wall stress and rise in biomarker levels, the high stress group had significant rise in hs-CRP (>3 mg/l), suggesting that even though not statistically proven in their study. Golledge et al [29], found elevations in CRP (avg 4.7 mg/L in >3 cm AAA and >4.6 for >40 mm AAA) in patients with small asymptomatic as well as large diameter aneurysms. Similar findings were reported in more series [30,31]. In the current series, the median CRP among cases was 5.44 mg/L (IQR 2.39-8.05) which was significantly raised as compared to the controls 0.45 mg/L (IQR 0.20-0.60); P<0.001. The data supports the observations of previous studies and raised CRP levels were correlated with presence of peripheral artery aneurysms and pseudoaneurysm apart from the Abdominal Aortic Aneurysm.

A novel cardiovascular marker soluble ST2 is being explored for myocardial ischemia and may be earliest detectable in blood once there is ischemia in vascular system [32]. Shear stress and 3 dimensional structures may lead to vascular aneurysm formation [33].

To sum up, in our case controlled study, there was significant elevations noted in the circulating levels of biomarkers MMP-9, Il-6, CRP, Fibrinogen and D-Dimer in patients with abdominal aortic and peripheral artery aneurysms. A positive correlation was also found between elevations of plasma D-Dimer and serum MMP-9 levels, suggesting that the matrix degradation and thrombolysis go hand in hand in the aneurysm. Positive correlation was also obtained between levels of circulating D-Dimer and MMP-9 with aneurysm sac size suggesting that the degradation process and thrombosis have direct relation to the increased sac size.

Limitation

Small sample size was main limiting factor of this study. Considering rare incidence in population and under reporting, both mask the true epidemiological profile of extra-cranial, extra-thoracic vascular aneurysms. Clinical manifestations are just tip of

iceberg and screening the population with either colour Doppler or CT angiogram or MR angiogram in selected group may provide some true picture of the problem and a more elaborate study and conclusion when sample size of study population expands.

Conclusion

The levels of circulating biomarkers tested in the current study (MMP-9, Il-6, Fibrinogen, D-Dimer and CRP) in patients with arterial aneurysm and pseudo-aneurysm are a marker of disease presence. The study findings need to be tested on larger population for gaining greater significance of the results obtained in this study.

Declaration

There is no conflict of interest.

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