

Original Articles

D-dimer levels in patients with thromboangiitis obliterans

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ABSTRACT

Background. Thromboangiitis obliterans (TAO) or Buerger disease is a recurring progressive segmental vasculopathy that presents with inflammation and thrombosis of small and medium arteries and veins of the hands and feet. The exact cause remains unknown, with tobacco use (primarily smoking but also smokeless tobacco) being highly associated with the disease. The diagnosis is clinical and the lack of a diagnostic gold standard is a deterrent to diagnosing it in patients with atypical presentations. Obliterative endarteritis occurs perhaps due to a mixture of thrombosis and inflammation. The diagnostic sensitivity and specificity of D-dimer as a biomarker for thrombosis is well reported from its use in other areas such as deep vein thrombosis. Identification of a biomarker linked to the causation yields a diagnostic adjunct with a role in therapeutic decision-making, aiding diagnosis in atypical presentation, monitoring disease activity and gauging response to therapy.

Methods. Between April 2014 and May 2015, we studied serum D-dimer (a marker of thrombosis) in 62 patients with TAO and compared this to 330 normal age- and sex-matched controls. We included all patients with peripheral arterial disease clinically diagnosed to have TAO according to the Shionoya criteria. There was no history of thrombosis or arterial disease in the control group. The control group was matched for baseline characteristics such as age and sex. All patients underwent a standard diagnostic protocol including blood tests (haemoglobin and creatinine), electrocardiogram, chest X-ray and ankle brachial pressure index. Blood was collected using an evacuated tube system into a citrate anti-coagulant tube for testing D-dimer.

Results. All the 62 patients diagnosed to have TAO were men with an average age of 40 years (range 18–65 years). They all had a history of tobacco use and did not have other atherogenic risk factors (part of the diagnostic criteria).

Medium-vessel involvement was present in 53 patients (85%) and the rest presented with additional involvement of the popliteal and femoral vessels. Upper limb involvement or superficial thrombophlebitis was present in 95% of patients. Laboratory and imaging studies were consistent with TAO. The groups were well matched for age ($p=0.3$). The median and interquartile range for D-dimer values were 61 ng/ml and 41–88 ng/ml in controls ($n=330$) and 247 ng/ml and 126–478 ng/ml in patients ($n=62$), respectively ($p<0.001$).

Conclusions. D-dimer levels are considerably elevated in patients with TAO. This indicates an underlying thrombotic process and suggests its potential role as a diagnostic adjunct. It also leads us to hypothesize a potential therapeutic benefit of anticoagulants in this disease.

Natl Med J India 2019;32:134–6

INTRODUCTION

Thromboangiitis obliterans (TAO) or Buerger disease is a recurring progressive segmental vasculopathy, which presents with inflammation and thrombosis of small and medium arteries and veins of the hands and feet.¹ Its exact cause is not known but tobacco use (primarily smoking but also smokeless tobacco) is highly associated with the disease.² TAO is common in India,³ and its diagnosis is based on the Shionoya criteria. However, not all patients present with these classical features. The diagnosis may be missed when patients have an atypical clinical presentation. Hence, a diagnostic adjunct such as a laboratory test would help in detecting atypical presentations of TAO.

Obliterative endarteritis is thought to occur due to an admixture of thrombosis and inflammation.¹ Identification of a biomarker linked to the causation could have a role in therapeutic decision-making. D-dimer is a small protein fragment present in the blood after a clot is degraded by fibrinolysis.^{4,5} We studied the levels of D-dimer as a biomarker for the presence of an ongoing thrombotic process in patients with TAO.

METHODS

In this prospective case–control study, we compared D-dimer levels in patients with TAO to those in normal controls. The study was done from April 2014 to May 2015 in the department of vascular surgery. The clearance from our institutional review board was taken as well as informed consent obtained from all patients.

We included all patients with peripheral arterial disease

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diagnosed clinically to have TAO according to the Shionoya criteria.⁶ The inclusion criteria were: onset of symptoms at <50 years of age, history of considerable tobacco use/smoking, absence of other atherogenic risk factors, involvement of medium-sized blood vessels (infrapopliteal/brachial) with upper limb involvement or superficial thrombophlebitis. The first three of these criteria were essential for diagnosis. We followed the diagnostic and management protocols, as per the current clinical practice, for patients with peripheral arterial disease.

The diagnostic protocol included blood tests (haemoglobin and creatinine), electrocardiogram, chest X-ray and ankle-brachial pressure index. Echocardiogram, vasculitis work-up or other tests (e.g. antiphospholipid antibody and homocysteine) were done if clinically indicated and were not included as a part of the study.

Controls

Healthy blood donors, who had no history of thrombosis or arterial disease, were randomly selected as controls and matched for age.

Exclusion criteria

We excluded patients with a peripheral arterial disease attributable to another cause such as atherosclerosis, embolic vascular occlusion, dyslipidaemia, vasculitis, trauma and radiation arteritis or procoagulant states.

The calculated sample size for this study was 62 patients and 330 controls (using test sensitivity 96% and specificity 71% as per the guidelines of the American College of Chest Physicians [ACCP]).⁷

Method of D-dimer assessment

Blood was collected using an evacuated tube system (Vacuttee, Greiner) into a citrate anticoagulant tube for testing D-dimer. An immunological test detected the presence of an antigen-antibody complex of D-dimer, with the machine reading the result and translating it to a numerical value.

Statistical methods

Demographic data, comorbid medical conditions, clinical presentation, diagnostic and laboratory test results, operative records and the treatment plan were recorded. The results of D-dimer levels in all patients and controls were analysed using the Mann-Whitney U test (rank sum test). Further, a case-control analysis was done with one-to-one matching in each age group and a crude odds ratio (OR) and 95% CI were estimated for the association between TAO and D-dimer level ≥ 250 ng/ml. Since all controls were negative, i.e. with level <250 ng/ml, the OR was calculated using a median unbiased estimator for binary data in the unconditional logistic regression model.^{8,9} This statistical approach is appropriate for zero cells and was applicable to our study, in which the sample size was small (62 cases and 62 controls) and data are sparse. The p value was fixed at 0.05 to indicate the level of significance. The analysis was done using STATA software version 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP, USA).

RESULTS

All 62 patients diagnosed to have TAO were men with an average age of 40 years (range 18–65 years). As per the diagnostic criteria, they all had a considerable history of tobacco use and did not have other atherogenic risk factors. Medium-vessel involvement was present in 85% of patients, and the rest presented with additional

involvement of the popliteal and femoral vessels. Upper limb involvement or superficial thrombophlebitis was present in 95% of cases. The controls were age-matched men with no other medical comorbid conditions (Table I).

The median and interquartile range for D-dimer values were 247 (126–478) ng/ml and 61 (41–88) ng/ml for the patient and control groups, respectively. The difference in the distribution was statistically significant between the two groups ($p < 0.001$). The D-dimer level was significantly elevated in patients with TAO.

Analysis of a matched subset (one-to-one) yielded a high OR of 84.4 (95% CI 14.2 to ∞) as none of the controls had a D-dimer value > 250 ng/ml (Table II). However, D-dimer being a non-specific test, the clinical relevance of a non-elevated D-dimer may have as a negative predictor rather than a diagnostic test in patients with TAO.

DISCUSSION

TAO, also known as Buerger disease or von Winiwarer-Buerger syndrome, is a chronic, non-atherosclerotic, segmental, inflammatory, obliterative, tobacco-associated vasculopathy involving primarily the infrapopliteal and infrabrachial medium-sized and small arteries of predominantly young male smokers.¹ TAO is a common disease in India comprising up to 40% of patients with peripheral arterial disease. This is different from the West where this disease is much less common, and is known as an 'orphan disease'.³ Despite considerable speculation as to the underlying mechanisms, the aetiology of TAO is unknown. Auto-immune mechanisms, genetic predisposition, hypercoagulable states and an oral infection-inflammatory pathway have all been suggested as potential factors. However, only tobacco use has been proven to have a direct causal relationship^{8–12} and in the absence of a definite aetiopathogenesis, TAO is diagnosed clinically and lacks a diagnostic gold standard test.

Our study showed that the D-dimer level is elevated in those presenting with symptomatic disease and hence it can be a potential diagnostic adjunct in these patients. It may also have a potential role in establishing diagnosis in those with atypical arterial involvement or in those who do not satisfy all the necessary clinical diagnostic criteria.

The coexistence of inflammation and thrombosis in the histopathology of this disease leads us to wonder how much each of these individual processes contribute to the disease.¹³ The blood content of D-dimer indirectly reflects the generation of

TABLE I. Age distribution of cases and controls

Age (years)	Controls, n (%)	Cases, n (%)
18–25	59 (17.9)	1 (1.6)
26–30	75 (22.8)	12 (19.4)
31–35	68 (20.7)	9 (14.5)
36–40	43 (13.1)	7 (11.3)
41–45	35 (10.6)	19 (30.7)
46–50	25 (7.6)	11 (17.7)
51–55	18 (5.5)	2 (3.2)
56–65	6 (1.8)	1 (1.6)

TABLE II. Relation between D-dimer levels and thromboangiitis obliterans (TAO)

D-dimer level (ng/ml)	Controls (n=62)	Patients with TAO (n=62)	OR (95% CI)
<250	62 (100)	31	84.4 (14.2– ∞)
≥ 250	0	31	

thrombin and plasmin, indicating the turnover or activation state of the coupled blood procoagulant and fibrinolytic mechanisms.^{6,13,14} A normal D-dimer result (≤ 250 ng/ml D-dimer unit and ≤ 0.50 $\mu\text{g/ml}$ fibrinogen equivalent unit) has a negative predictive value of approximately 95% for the exclusion of thrombosis when there is low or moderate pre-test probability of pulmonary embolism. Increased D-dimer values do not indicate a specific disease state. D-dimer values may be increased as a result of clinical or subclinical disseminated intravascular coagulation and fibrinolysis. Other conditions associated with increased activation of the procoagulant and fibrinolytic mechanisms are recent surgery, active or recent bleeding, haematomas, trauma, pregnancy, liver disease, inflammation, malignancy or hypercoagulable (procoagulant) states.

There is sparse literature on the specific role of D-dimer in TAO. Only Undas *et al.*¹⁴ studied the characteristics of plasma fibrin clot in patients with atherosclerotic peripheral arterial disease and TAO, and concluded that elevated levels are associated with worse clinical outcomes. However, they studied only 10 patients with TAO and the levels of D-dimer were not provided. Therefore in our study, the elevated levels of D-dimer in patients with TAO provide evidence of an underlying thrombotic process.

TAO is currently treated with a combination of medical and surgical modalities. The use of antiplatelets, statins, prostaglandins, anticoagulants, steroids and immune-modulating drugs has been reported. However, these are small series in spite of the disease being so prevalent. There is a need to study the clinical role of medications targeted to modify the underlying thrombotic process. Cessation of smoking is the main step to prevent progression of the disease.

Our study has some limitations: the diagnosis was clinical and all patients did not undergo extensive investigations, e.g. prothrombotic work-up, echocardiogram, vasculitis work-up to rule out other factors causing vascular disease.

Conclusion

D-dimer levels are elevated in patients with TAO, which suggests

an underlying thrombotic process in this disease. Cessation of smoking is the only way known to prevent the progression of the disease. Hence, future studies can assess if these patients benefit from treatment with anticoagulants.

Conflicts of interest. None declared

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