Original Research Article

Comparative study to establish significance of D-dimer, lipid profile and homocysteine level in cases of deep vein thrombosis

Vishal Sharma*, Mahendra Bendre, Shahaji Chavan, Sree Ganesh B.

Department of General Surgery, Dr. D.Y. Patil Vidyapeeth, Dr. D.Y. Patil University, Pimpri, Pune, Maharashtra, India

Received: 01 March 2019
Revised: 09 March 2019
Accepted: 20 March 2019

*Correspondence:
Dr. Vishal Sharma,
E-mail: vish.shrm91@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: The purpose of the study was to establish the relationship of D-dimer, lipid profile and homocysteine level in deep-vein thrombosis (DVT). The purpose of this study was to assess the value of D-dimer in the detection of early DVT.

Methods: A hospital based comparative study was conducted at Dr. D.Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune with 100 patients to compare the level of D-dimer and lipid profile in cases of Deep Vein Thrombosis (DVT) with healthy controls. The study was carried out with following two groups of 50 patients each: study group: 50 cases with DVT; control group: 50 healthy controls.

Results: The D-Dimer levels was significantly higher in study group as compared to control group (748.44±93.17 vs. 426.06±78.11 ng/ml) and statistically significant as per student t-test (p<0.05). It was observed that total cholesterol (r=0.714; p<0.05), triglyceride (r=0.534; p<0.05), LDL (r=0.662; p<0.05), HDL (r=0.655; p<0.05), homocysteine (r=0.285; p<0.05) and D-dimer (r=0.368; p<0.05) were strongly and directly correlated with DVT.

Conclusions: In our study most sensitive test for early diagnosis of DVT is D-dimer as it is considered to be useful as a screening test for DVT in hospitalized patients with acute medical diseases/episodes. D-dimer assay is an important preliminary test to detect deep vein thrombosis in post-operative cases. Its extreme sensitivity and high negative predictive value make it an ideal single test to screen patients suspected of having deep vein thrombosis. A negative test rules out deep vein thrombois and a positive test report needs further investigation for its confirmation. In case of increased lipid profile levels, patients are more prone to develop DVT hence there should be regular screening for DVT.

Keywords: DVT, D-dimer, Lipid profile, Homocysteine

INTRODUCTION

Deep vein thrombosis (DVT) affects approximately 0.1% of persons per year. The incidence is much lower in the young and higher in the elderly. Although many patients develop DVT in the presence of risk factors, such as malignancy and immobility, DVT can also occur without obvious provocation (idiopathic DVT). One of the dominant characteristics of this disease is that for every symptomatic pulmonary embolism diagnosed, there are 2.5 cases of venous thrombo-embolism (VTE) that we are not able to identify. Moreover, 40 to 60% of the deaths from VTE occurs in patients whom lacked a previous diagnosis of DVT, and 20% of the patients have a sudden death secondary to massive embolism as their first and only symptom. VTE events remain a relatively common cause of death in hospitalized patients and almost 75 per cent of all VTE-related deaths are from hospital-acquired
VTE. In India, General surgical operations are the most common cause of postoperative DVT and malignancy is the most common cause of secondary VTE. Postoperative DVT of the lower limbs is often asymptomatic; in many patients, fatal PE is the first clinical manifestation of postoperative VTE. Therefore, it is inappropriate to rely on early diagnosis and treatment of postoperative thromboembolism. Therefore, it is inappropriate to rely on early diagnosis and treatment of postoperative thromboembolism. In addition, routine screening for asymptomatic DVT of the lower limbs has a low sensitivity and is quite impractical.

D-dimer is one of the most commonly used clinical assays for the detection of active coagulation and in vivo fibrin formation and lysis. The D-dimer assay is widely used in clinical practice to rule out clinically suspected deep venous thrombosis and pulmonary embolism. In fact, a number of studies have demonstrated that normal D-dimer levels have a high negative predictive value for these medical conditions.

An elevated level of homocysteine in the body is known as homocysteinemia or hyperhomocysteinemia. The normal blood levels of homocysteine range from 5-15 μmol/L. Individuals with severe hyperhomocysteinemia have homocysteine concentrations in the range of 50 to 500 fmol/L. An elevated level of homocysteine is a risk factor for arterial and venous thromboembolism. There is a consistent relationship between plasma homocysteine levels and atherosclerotic vascular disease.

METHODS

A hospital based prospective comparative study was conducted at Dr. D. Y. Patil Medical College and hospital, Pune. Out of the patients visiting the Surgery OPD of Dr. D.Y. Patil Medical College between September 2016 and September 2018, 100 patients were selected with 50 acting as the test subjects and 50 as control group. The aim of the study is to compare the level of D-dimer, homocystine, lipid profile in 50 cases of DVT with 50 healthy control group subjects.

Inclusion criteria for patients in the study group: Patients suffering from DVT, age above 15 years, both genders.

Inclusion criteria for patients in the control group: patients that are not a known case of DVT, hypertension, diabetes mellitus, hyperlipidaemia; age above 15 years of age; both genders.

Exclusion criteria were patients not giving consent, patient less than 15 years of age, patients with bilateral leg swelling but with difference in circumference of less than 3 cm and patients with diabetes and hyperlipidaemia under pharmacological treatment such as statins, and patients suffering from terminal illness.

Ethics Committee clearance was obtained before start of study. Written and informed consent of all patients were taken prior to their enrolment in the study.

Fasting levels of D-dimer, Lipid profile and homocysteine levels were evaluated in these patients. These levels were compared with healthy controls. Venous color doppler and CT angiography of the lower limb were done to confirm the diagnosis. These along with the physical examination findings, lab data, ECG and chest radiograph were appropriately recorded. All patients were also asked to refrain from smoking and from doing vigorous exercise prior to giving their blood sample. The homocysteinemia levels above 15 μmol/l were considered as hyperhomocysteinemia. Values between 15 and 30 μmol/l were considered as mild, values between 30 and 100 μmol/l were regarded as intermediate, and values above 100 μmol/l were regarded as severe hyperhomocysteinemia.

Statistical analysis

Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student ‘t’ test and Chi-Square test. ‘p’ value less than 0.05 is taken as significant.

Pearson's chi-squared test

\[ X^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i} \]

Where \( X^2 \) = Pearson's cumulative test statistic.

\( O_i \) = an observed frequency;

\( E_i \) = an expected frequency, asserted by the null hypothesis;

\( n \) = the number of cells in the table.

Results were graphically represented where deemed necessary.

Appropriate statistical software, including but not restricted to MS Excel, SPSS ver. 20 will be used for statistical analysis. Graphical representation will be done in MS Excel 2010.

RESULTS

A hospital based comparative study was conducted with 100 patients to compare the level of D-dimer, homocystine, lipid profile in cases of DVT with healthy controls. The study was carried out with following two groups of 50 patients each.
As shown in Figure 1, majority of the patients in Study Group were in the age group of 51-60 years (38%) followed by 41-50 years (36%), 31-40 years (12%), 61-70 (6%), 21-30 years (6%) and 15-20 years (2%). The mean age of the patients was 48.62±10.91 years.

Majority of the patients in control group were in the age group of 51-60 years (34%) followed by 41-50 years (32%), 31-40 years (14%), 61-70 (10%), 21-30 years (4%) and 15-20 years (2%). The mean age of the patients was 49.22±11.12 years. There was no significant difference between the groups as per Student t-test (p>0.05).

As seen in Figure 2, there were 60% and 56% male patients in Study Group and Control Group respectively while female patients constituted 30% and 44% of the study groups respectively. There was no significant difference between the groups as per Chi-Square test (p>0.05).

As we see below in Figure 3, 1 (1.3%) and 20 (40%) patients in study group were underweight and in the normal range respectively while 19 (38%) and 10 (20%) patients were overweight and obese respectively. 22 (44%) patients in control group were in the normal range while 21 (44%) and 7 (14%) patients were overweight and obese respectively.

The mean BMI of patients in Study Group (26.30±3.63 kg/m²) was comparable to mean BMI of patients in control group (26.67±4.02 kg/m²) and statistically not significant as per Student t-test (p>0.05).
As shown in Figure 5, the fasting blood sugar (FBS) and post prandial blood sugar (PPBS) values of patients in Study Group and Control Group were comparable (95.56±5.39 mg/dl vs. 96.17±8.25 and 123.52±15.25 mg/dl vs. 126.23±15.04) and statistically not significant as per student t-test (p>0.05).

**Figure 6: Comparison of lipid profile parameters of patients.**

Figure 6 shows that the total cholesterol and triglyceride values of patients in study group were significantly higher as compared to control group (221.59±29.21 vs. 159.28±29.90 mg/dl; p<0.05 and 168.09±34.33 vs. 126.79±36.22 mg/dl; p<0.05). The LDL values was significantly higher in study group as compared to control group (75.62±10.85 vs. 103.51±10.32 mg/dl; p<0.05) while HDL values was significantly lesser in Study Group as compared to control group (34.58±8.97 vs. 45.12±7.11 mg/dl; p<0.05).

**Figure 7: Comparison of serum homocysteine levels of patients.**

As seen in Figure 7, the serum homocysteine values was significantly higher in study group as compared to control group (24.69±3.02 vs. 9.56±2.96 µmol/L) and statistically significant as per student t-test (p<0.05).

**Figure 8: Comparison of D-dimer levels of patients.**

As seen in Figure 8 the D-dimer levels was significantly higher in study group as compared to control group (748.44±93.17 vs. 426.06±78.11 ng/ml) and statistically significant as per student t-test (p<0.05).

**Figure 9: Correlation of DVT with various parameters in study group.**

As seen in Figure 9, it was observed that total cholesterol (r=0.714; p<0.05), triglyceride (r=0.534; p<0.05), LDL (r=0.662; p<0.05), HDL (r=0.655; p<0.05), Homocysteine (r=0.285; p<0.05) and D-dimer (r=0.368; p<0.05) were strongly and directly correlated with DVT.

**DISCUSSION**

Deep venous thromboembolic disease DVT is a polygenic disease with pathogenic contributions from both genetic and environmental risk factors. Various molecular dysfunctions in the protein C pathway, including factor V Leiden are among the currently most common identifiable genetic risk factors for DVT.

Although dyslipoproteinemia is associated with arterial thrombosis, especially in men, little is known about the
DVT and plasma lipids or lipoprotein subclasses. Several observations suggest a relationship between DVT and dyslipidemia. Spontaneous DVT is associated with clinically silent atherosclerotic vascular disease. The use of lipid-lowering statins reduces DVT.

Subnormal plasma levels of glucosylceramide, a glycosphingolipid that circulates in lipoproteins, are found in DVT patients. Because glucosylceramide and HDL enhance the anticoagulant activity of activated protein C. It has been speculated that glucosylceramide and HDL may help protect against DVT.

HDL cholesterol levels in particular are significantly lower in patients who experience DVT. Diabetes mellitus has been associated with a 42% increase in the risk of DVT or PE. Lipoprotein subclass analyses show that these differences reflect lower levels of large HDL particles and higher levels of small LDL particles. Confirming the NMR based demonstration of dyslipoproteinemia in DVT patients, antigenic assay data for the major apolipoprotein of HDL showed lower apoAI levels. The difference in the apoB/ apoAI ratio between DVT patients and controls was statistically stronger than differences in either apolipoprotein alone. DVT was associated with low levels of HDL particle concentration and appeared to be associated specifically with reduced plasma levels of large HDL particles and not with differences in medium and small HDL particles.

In the present study, majority of the patients in study group were in the age group of 51-60 years (38%) followed by 41-50 years (36%), 31-40 years (12%), 61-70 (6%), 21-30 years (6%) and 15-20 years (2%). The mean age of the patients was 48.62±10.91 years. Majority of the patients in control group were in the age group of 51-60 years (34%) followed by 41-50 years (32%), 31-40 years (14%), 61-70 (10%), 21-30 years (4%) and 15-20 years (2%). The mean age of the patients was 49.22±11.12 years. There was no significant difference between the groups as per student t-test (p>0.05).

There were 60% and 56% male patients in study group and control group respectively while female patients constituted 30% and 44% of the study groups respectively. There was no significant difference between the groups as per Chi-square test (p>0.05). This is similar to the studies of Bilal et al. Bilal et al descriptive cross-sectional study determining the frequency of dyslipidemia among patients with DVT reported dyslipidemia in 32 (20.38%) patients having DVT while 125 (79.62%) have not faced the dyslipidemia. Age wise distribution of dyslipidemia showed that majority of the dyslipidemia 12 (23.5%) were found in 51-65 years of age while 39 (76.5%) were non dyslipidemia, no patients have age groups of less than 20 years were dyslipidemia while 5 (100%) were non dyslipidemia, 6 (17.6%) have age range of (21-35) years were dyslipidemia while 28 (82.4%) were non dyslipidemia, 11 (22%) have age range of 36-50 years were dyslipidemia while 39 (78%) were non dyslipidemia and 3 (17.6%) cases have age range of more than 66 years of age were dyslipidemia while 14 (82.4%) were non dyslipidemia. The majority of females i.e. 16 (25.8%) presented with DVT were dyslipidemia while 79 (83.2%) were non dyslipidemia and 16 (16.8%) male patients were dyslipidemia while 46 (74.2%) were non dyslipidemia.

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels of patients in study group and control group were comparable (126.16±10.42 mmHg vs. 129.32±9.27 mmHg and 79.40±5.29 mmHg vs. 81.52±4.63 mmHg). The difference was statistically not significant as per student t-test (p>0.05).

It was observed in the present study that the FBS and PPBS values of patients in study group and control group were comparable (95.56±5.39 mg/dl vs. 96.17±8.25 and 123.52±15.25 mg/dl vs. 126.23±15.04) and statistically not significant as per student t-test (p>0.05).

The total cholesterol and triglyceride values of patients in study group were significantly higher as compared to control group (221.59±29.21 vs. 159.28±29.90 mg/dl; p<0.05 and 168.09±34.33 vs. 126.79±36.22 mg/dl; p<0.05). The LDL values was significantly higher in study group as compared to control group (75.62±10.85 vs. 103.51±10.32 mg/dl; p<0.05) while HDL values was significantly lesser in study group as compared to control group (34.58±8.97 vs. 45.12±7.11 mg/dl; p<0.05). This is comparable to the studies of Bilal et al and Gonzalez-Ordonez et al.
Gonzalez-Ordonez et al reported an association of dyslipidemia with DVT that was stronger in men than women.\textsuperscript{19} Bilal et al descriptive cross-sectional study determining the frequency of dyslipidemia among patients with DVT found a modest association of VTE with dyslipidemia in men, i.e. with low HDL-C or with elevated LDL-C.\textsuperscript{19} A stronger correlation was observed between DVT and dyslipidoproteinemia than between VTE and dyslipidemia, emphasizing the importance of apolipoproteins and lipoprotein particles compared with bulk plasma lipid levels, consistent with the concept that certain HDL particles may be protective for VTE and/or that certain LDL particles directly contribute to increase DVT risk.

It was observed in our study that the serum homocysteine values was significantly higher in study group as compared to control group (24.69±3.02 vs. 9.56±2.96 µmol/l) and statistically significant as per student t-test (p<0.05).

In our study, the D-dimer levels was significantly higher in study group as compared to control group (748.44±93.17 vs. 426.06±78.11 ng/mL) and statistically significant as per student t-test (p<0.05). This is concordant to the studies of Ekim et al and Kaul et al.\textsuperscript{20,21} Ekim et al evaluating the prevalence of hyperhomocysteinemia in patients with DVT observed D-dimer levels in 48 (80\%) of the patients.\textsuperscript{20} All patients had normal liver and renal functions.

Kaul et al study evaluating the diagnostic reliability of D-dimer assay in detecting DVT reported D-dimer was positive in eight out of the 40 patients out of which 5 were confirmed to have DVT.\textsuperscript{23} In rest of the 35 patients doppler sonography was negative. The sensitivity, specificity, positive predictive value and negative predictive value were 100\%, 91.42\%, 2.5% and 100\% respectively.

It was observed that total cholesterol (r=0.714; p<0.05), triglyceride (r=0.534; p<0.05), LDL (r=0.662; p<0.05), HDL (r=0.655; p<0.05), homocysteine (r=0.285; p<0.05) and D-dimer (r=0.368; p<0.05) were strongly and directly correlated with DVT. Similar observations were noted in the studies of Ekim et al, Jang et al.\textsuperscript{20,22} Ekim et al evaluating the prevalence of hyperhomocysteinemia in patients with DVT reported hyperhomocysteinemia, especially in women older than 40 years, may be a risk factor for DVT.\textsuperscript{20}

Jang et al case-control study of 208 DVT patients and 300 control subjects demonstrated that both low levels of HDL cholesterol and elevated fasting glucose correlated with a doubling in the risk of VTE.\textsuperscript{22}

CONCLUSION

From above study, we conclude that DVT is common in 50-60 year age with incidence being more common in males than in females.

In our study most sensitive test for early diagnosis of DVT is D-dimer as it is considered to be useful as a screening test for DVT in hospitalized patients with acute medical diseases/episodes. D dimer assay is an important preliminary test to detect DVT in post-operative cases. Its extreme sensitivity and high negative predictive value make it an ideal single test to screen patients suspected of having DVT. A negative test rules out deep vein thrombosis and a positive test report needs further investigation for its confirmation.

In case of patients with higher levels of homocysteine there is a increase chance of developing DVT.

In case of increased lipid profile levels, patients are more prone to develop DVT hence there should be regular screening for DVT.

ACKNOWLEDGEMENTS

This study has been a period of intense learning for me, not only in the clinical arena but also on a personal level. I would like to reflect on all the people who have supported and helped me through this.

First of all I would like to thank Dr. D.Y. Patil University for giving me an opportunity to do this research.

I would like to express my profound and heartfelt gratitude to Dr. M. Bendre, Professor, Department of Surgery, Dr. D.Y Patil Medical College and Hospital, Pimpri, Pune for being a constant support, inspiration and guiding light throughout this period.

I would like to mention his univalued devotion to the art that is surgery and the values that I inculcated under his guidance. I would like to extend my sincerest gratitude to our HOD Dr. Shahaji Chavan, for treating us like family and showing us the way in difficult times. His conduct, unparalleled knowledge and passion for the subject surgery will always be the guiding principle for me. To Dr. Vinayak, Dr. Niles, Dr. Amit, I extend my humblest thanks. Their disciplined foresight and counsel was invaluable in shaping this dissertation and I shall always be grateful for the opportunity to work under them and learn from them.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee.
REFERENCES


