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## Prospective study of relationship between deep vein thrombosis and homocysteine related group B vitamins

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### Abstract

**Introduction:** Hyper homocysteinemia has been considered as a potential risk factor for deep venous thrombosis (DVT) but it is still controversy. This study was aimed to assess the prevalence of hyper homocysteinemia in our population with DVT. Our second objective was to document the prevalence of folate, Vitamin B6, and Vitamin B12 level in this patient population.

**Results:** Mean serum homocysteine levels among DVT patients was  $15.12 \pm 5.47$   $\mu\text{mol/L}$ . Most of the patients of DVT were from 41-60 years of age group with mean age being  $50.11 \pm 13.66$  years. Of all the patients, 15 patients had homocysteine level above the  $15$   $\mu\text{mol/L}$ , 22 had folic acid level below  $3$   $\text{ng/ml}$ , 14 had vitamin B12 level below  $150$   $\text{pmol/L}$ , and 3 had vitamin B6 level below  $30$   $\text{nmol/L}$ . In the hyper homocysteinemic group, eleven patients had low folic acid level, ten had low vitamin B12 level and two had low vitamin B6 level.

**Conclusions:** Hyper homocysteinemia and related Vitamin B group deficiency are risk factors for Deep vein thrombosis. Hyper homocysteinemia and risk of DVT, this correlation is high among older age group and female patients.

**Keywords:** Deep venous thrombosis, hyper homocysteinemia, B group vitamins

### Introduction

Venous thromboembolism (VTE), a disease entity comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent and potentially life-threatening event. Venous thromboembolism (VTE) is the third most common vascular disease after myocardial infarction and ischemic stroke <sup>[1]</sup>. The annual incidence of symptomatic and objectively confirmed VTE, the collective term generally used for deep venous thrombosis, pulmonary embolism or both, is 2 to 3 per 1000 inhabitants <sup>[2]</sup>. VTE is not only disabling but also prolongs hospital stay and increases the cost of treatment.

The pathophysiology of venous thrombosis is considered to be multicausal <sup>[3]</sup>, with many inherited and acquired risk factors and their interaction playing a role in the etiopathogenesis. Risk factors for venous thrombosis can be divided into acquired and genetic risk factors. Knowledge of these factors is important for prevention purposes.

Among venous thrombosis risk factors, hyper homocysteinemia has been considered as a potential factor by most studies. Hyper homocysteinemia is a disorder of methionine metabolism <sup>[4]</sup>. Hyper homocysteinemia is proposed to be a modifiable risk factor of atherosclerosis <sup>[5, 6]</sup>, myocardial infarction <sup>[7, 8]</sup> peripheral arterial thrombosis <sup>[5]</sup> as well as venous thromboembolism <sup>[9, 10]</sup>.

Hyper homocysteinemia due to reduced B-group vitamins (folic acid, vitamin B12, and vitamin B6) levels is thought to be a part of the pathophysiologic link between B-group vitamins and venous thrombosis <sup>[11]</sup>.

This study is aimed to assess the prevalence of hyper homocysteinemia in our population with DVT.

### Aims and Objectives

1. To know the prevalence of hyper homocysteinemia in our urban and rural population with Deep vein thrombosis.
2. To document the homocysteine and Vitamin B12, Folic Acid and Vitamin B6 levels in this population affected by Deep Vein Thrombosis.

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**Materials & Methods**

It is a prospective and observational study. Study was conducted after approval from institute’s ethical and research committee.

60 patients of both genders with age 18 and above, who were admitted or referred to department of general surgery, DR. V.M. Govt medical college Solapur, Maharashtra between December 2017 to august 2019 with diagnosis of DVT were included after obtaining written informed consent from each patient.

Exclusion criteria were conditions like drug usage (metformin, cholestyramine, hypothyroidism, pernicious anemia, respiratory insufficiency, pregnant females, a history of antiphospholipid syndrome & sepsis may interfere with homocysteine levels, will be excluded from our study. Patient on Folic Acid, Vit B6, Vit B12 therapy were also excluded from the study.

Diagnosis of DVT was based on clinical history and thorough physical examination, Well’s scoring system and Venous doppler & duplex scan of limb. Laboratory investigations (lipid profile, coagulation profile) was done in All patients with established diagnosis of DVT. The total Serum homocysteine levels, Vitamin B6, Vitamin B12 levels and folic acid levels

were measured on heparinized blood samples collected after 12 hours of fasting.

Normal reference values are as follows-

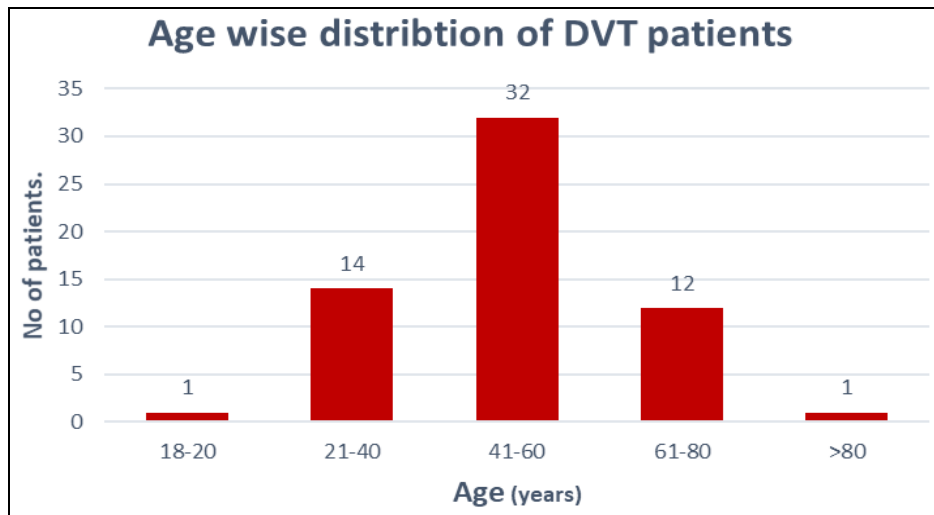
- Normal homocysteine level <15 µmol/L. Results were quantified as mild (15-30 µmol/L), moderate (30-100 µmol/L) and severe hyper homocystienemia. (>100 µmol/L)
- Normal Serum vitamin B12 levels (200-900 pg/ml)
- Normal Serum vitamin B6 levels (5.0-50 µg/L)
- Normal Serum folic acid levels (2-20 ng/ml)

Data collected, prevalence of hyper homocystienemia, prevalence of Vitamin B12, Vitamin B6 and folic acid deficiency were calculated among DVT cases.

**Observations and Results**

**Age and sex wise distribution**

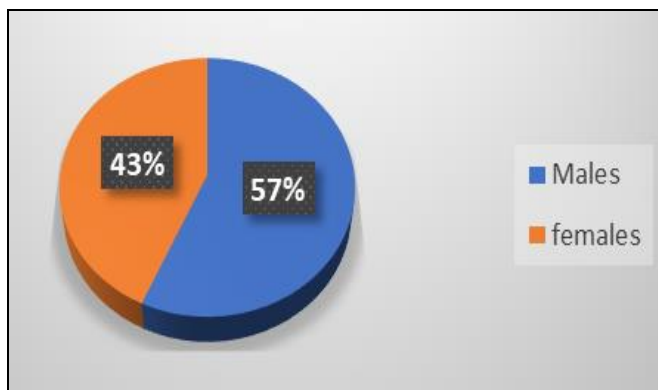
Most of patient were from 41-60 years age group. (Figure 1) Mean age of patients of DVT in our study was 50.11±13.64 years.



**Fig 1:** Age wise distribution of cases

Out of total 60 patients of DVT 34 (57%) were males and 26 (43%) were females (figure 2). Male to female ratio was 1.30:1.

Mean homocysteine levels in total 60 DVT patients is 15.12±5.47 µmol/L, mean homocysteine level among 34 male DVT patients is 13.78 µmol/L and homocysteine level among 26 female DVT patients is 16.87 µmol/L



**Fig 2:** Sex wise distribution of cases

**Table 1:** Serum homocysteine levels in patients of DVT

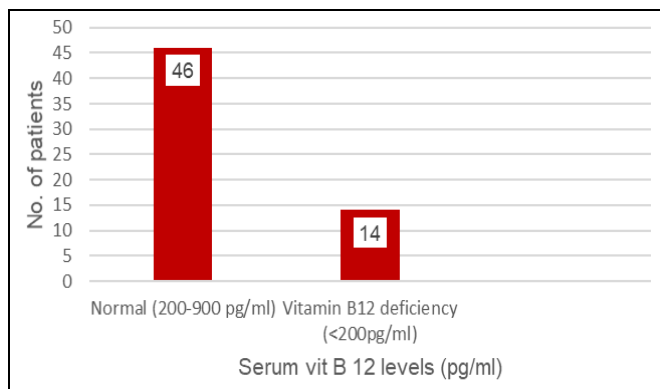
| Serum homocysteine levels (µmol/L)             | No. of patients | Percentage |
|--|-----------------|------------|
| Normal homocysteine level (<15 µmol/L)         | 45              | 75         |
| Mild hyper homocysteinemia (15-30 µmol/L)      | 13              | 21.67      |
| Moderate hyper homocysteinemia (30-100 µmol/L) | 2               | 3.33       |
| Severe hyper homocysteinemia (>100 µmol/L)     | 0               | 0          |
| Total  | 60              | 100        |

**Serum homocysteine levels**

Out of 60 patients 45 had normal homocysteine levels and 15 patients had hyper homocysteinemia. Out of these 15 patients, 13 had mild hyper homocysteinemia, 2 had moderate hyper homocysteinemia & none of the patients had severe hyper homocysteinemia.

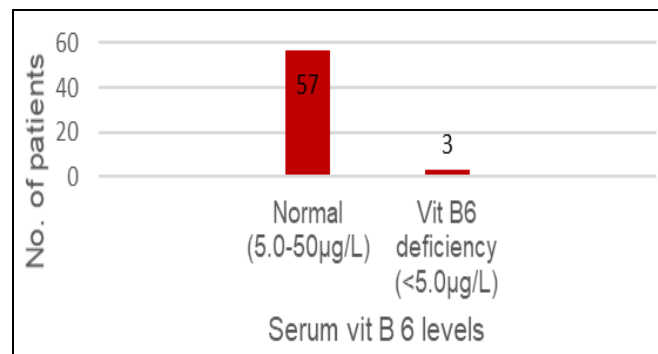
**Serum vitamin B12, vitamin B6 and folic Acid levels**

14 out of total 60 DVT patients (23.33%) were having Vitamin B12 deficiency. (fig. 3) Mean vitamin B12 level in our 60 DVT patients was 295.88±112.8 pg/ml.



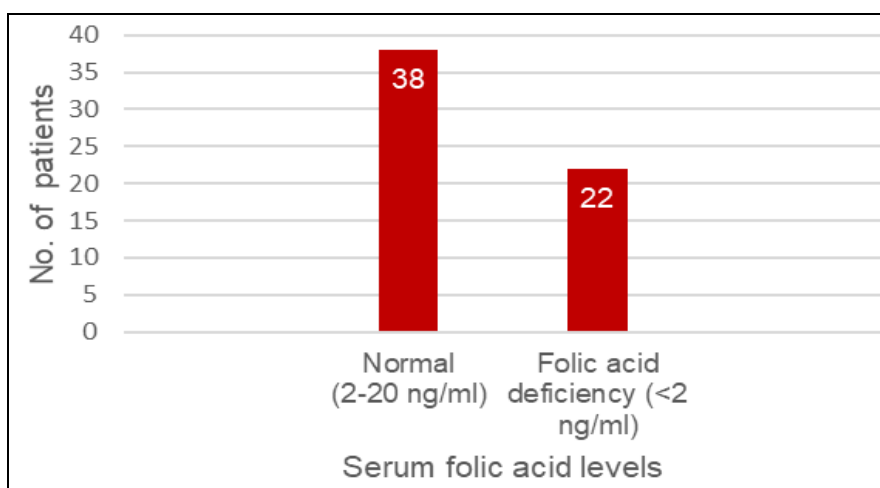
**Fig 3.** Distribution of DVT patients according to serum vitamin B12 level

3 out of total 60 DVT patients (5%) were having Vitamin B6 deficiency. (figure 4) Mean vitamin B6 level in our 60 DVT patients was  $15.57 \pm 7.64 \mu\text{g/L}$ .



**Fig 4.** Distribution of DVT patients according to serum vitamin B6 level

22 out of total 60 DVT patients (38.33%) were having folic acid deficiency. (figure 5) Out of these 22 patients 16 were female and 8 were males. Mean Serum folic acid level in our 60 DVT patients was  $5.64 \pm 4.2 \text{ ng/ml}$ .



**Fig 5:** Distribution of DVT cases according to serum folic acid level

**Table 2:** Clinical and Laboratory characteristics of Patients of DVT with hyperhomocysteinemia.

| Sr. No. | Age | Sex    | Homocysteine level ( $\mu\text{mol/L}$ ). | Vitamin B12 levels (ng/ml) | Vitamin B6 levels ( $\mu\text{g/L}$ ) | Folic acid levels (ng/L) |
|---------|-----|--------|---|----------------------------|---------------------------------------|--------------------------|
| 1       | 62  | Male   | 21.3                                      | 211                        | 19.9                                  | 1.9                      |
| 2       | 43  | Female | 35.6                                      | 178                        | 4.2                                   | 3.7                      |
| 3       | 55  | Male   | 19.70                                     | 189                        | 27.1                                  | 1.7                      |
| 4       | 45  | Male   | 15.24                                     | 256                        | 19.7                                  | 1.9                      |
| 5       | 54  | Female | 29.9                                      | 195                        | 4.3                                   | 4.7                      |
| 6       | 45  | Female | 32.8                                      | 148                        | 5.1                                   | 1.8                      |
| 7       | 44  | Female | 21.5                                      | 106                        | 5.5                                   | 3.4                      |
| 8       | 69  | Female | 16.9                                      | 244                        | 11.9                                  | 1.8                      |
| 9       | 60  | Male   | 22.4                                      | 159                        | 6.54                                  | 4.9                      |
| 10      | 50  | Female | 17.8                                      | 323                        | 8.8                                   | 1.8                      |
| 11      | 37  | Female | 26  | 159                        | 3.9                                   | 2.1                      |
| 12      | 62  | Female | 15.7                                      | 163                        | 6.4                                   | 1.9                      |
| 13      | 55  | Male   | 15.8                                      | 378                        | 17.1                                  | 1.9                      |
| 14      | 54  | Female | 22.8                                      | 166                        | 5.7                                   | 1.8                      |
| 15      | 65  | Male   | 21.6                                      | 192                        | 6.3                                   | 1.7                      |

Out of total 15 patients of DVT with hyperhomocysteinemia 9 patients were females and 6 were males. Among these 15 patients 13 had mild hyperhomocysteinemia and 2 had moderate hyperhomocysteinemia. Out of these 15 patients with hyperhomocysteinemia 10 patients had vitamin B12 deficiency, two patients had Vitamin B6 deficiency 11 patients had folic acid deficiency also. Mean serum homocysteine level among these 15 patients is  $22.336 \mu\text{mol/L}$ . Mean age of patients with hyperhomocysteinemia was 53.33 years.

**Discussion**

**Mean Age of DVT patients:** In our study most of the patients of DVT were from 41-60 years of age group with mean age being  $50.11 \pm 13.64$  years. Study by Sharma V *et al.* 2019 [12] found mean age of patients being  $48.62 \pm 10.91$  years, study by Ekim M *et al.* 2015 [13] found mean age of patients 50.5 years, study by Kokturk N *et al.* 2011 [14] found mean age of patients  $55 \pm 17$  years, study by Unlu Y *et al.* 2005 [15] found mean age of patients 52 years, study by Cattaneo M *et al.* 2001 [16] had mean

age of 42 years and study conducted by Den Heijer M *et al.* 1996<sup>[17]</sup> had mean age of patients 44 years. In contrast study by Oger E *et al.* 2006<sup>[18]</sup> having mean age of patients  $67.4 \pm 17.9$  years.

### Sex ratio of DVT patients

In our study out of total 60 DVT patients 34 were males and 26 were females and male to female ratio was 1.307:1, study by Sharma V *et al.* 2019<sup>[12]</sup> found male to female ratio 1.50:1, Ekim M *et al.* 2015<sup>[13]</sup> found male to female ratio 1.06:1 and Unlu Y *et al.* 2005<sup>[15]</sup> found with male to female ratio of 2.42:1. In contrast study by Kokturk N *et al.* 2011<sup>[14]</sup> had male to female ratio of 1:1.58 and study by Den Heijer M *et al.* 1996<sup>[17]</sup> having male to female ratio of 1:1.13.

### Prevalence of Hyper homocystienemia

In our study 15 out of 60 DVT patients (25%) were having hyper homocystienemia. study by Simioni P *et al.* 1996<sup>[19]</sup> found 25% DVT patients were having hyper homocystienemia, study by Ekim M *et al.* 2015<sup>[13]</sup> found 15% of DVT patients were having hyper homocystienemia.

In contrast Our study doesn't confirm with study by N.kokturk *et al.* 2011<sup>[14]</sup> with 63% of DVT patients were having hyper homocystienemia, study by Oger M *et al.* 2006<sup>[18]</sup> with 66% of DVT patients were having hyper homocystienemia and study conducted by Cattaneo M *et al.* 2001<sup>[16]</sup> with 10% of DVT patients were having hyper homocystienemia. Possible explanation for this is study conducted by Oger M *et al.* 2006<sup>[18]</sup> was having relatively older population mean age ( $67.4 \pm 17.9$  years) and study conducted by Cattaneo M *et al.* 2001<sup>[16]</sup> was relatively younger population (mean age 42 years) In comparison to our study. (mean age  $50.11 \pm 13.64$  years)

### Mean homocysteine levels

In our study mean serum homocysteine levels among DVT patients was  $15.12 \pm 5.47$   $\mu\text{mol/L}$ . study by conducted by Sharma V *et al.* 2019<sup>[12]</sup> found mean homocysteine levels  $24.62 \pm 3.02$   $\mu\text{mol/L}$ , study by Kokturk N *et al.* 2011<sup>[14]</sup> found mean homocysteine levels  $21.1 \pm 12.5$   $\mu\text{mol/L}$ , study by Oger E *et al.* 2006<sup>[18]</sup> found mean homocysteine levels  $17.5$   $\mu\text{mol/L}$  and study by Unlu Y *et al.* 2005<sup>[15]</sup> found mean homocysteine levels  $17.1 \pm 5.3$   $\mu\text{mol/L}$ .

In contrast Our study doesn't confirm with study conducted by Cattaneo M *et al.* 2001<sup>[16]</sup> having mean homocysteine levels of  $9.5$   $\mu\text{mol/L}$ . There are two possible reason for this, study conducted by Cattaneo M *et al.* 2001<sup>[16]</sup> was having relatively lesser number of DVT patients with hyper homocystienemia (38 out of 397, prevalence 10%) in comparison to our study (15 out of 60, prevalence 25%) and study conducted by Cattaneo M *et al.* 2001<sup>[16]</sup> was having younger DVT population (mean age 42 years) in comparison to our study (mean age 50.11 years) and other above mentioned studies.

### Clinical characteristic of DVT patients with hyper homocystienemia with various studies

In our study 9 out of 15 (60%) patients with hyper homocystienemia were females. study by Ekim M *et al.* 2015<sup>[13]</sup> found 6 out of 9 (66.66%) patients with hyper homocystienemia were females and study by Kokturk N *et al.* 2011<sup>[14]</sup> found 35 out of 59 (59%) patients with hyper homocystienemia were females.

Mean age of 15 patients of DVT with hyper homocystienemia in our study was 53.33 years, which is comparable to study by Ekim M *et al.* 2015<sup>[13]</sup> having mean age of patients of DVT with

hyper homocystienemia 53.3 years and study by Kokturk N *et al.* 2011<sup>[14]</sup> having mean age of patients of DVT with hyper homocystienemia 53.3 years.

### Serum Vit B12, Vit B6 and folic acid

In our study 14 out of 60 DVT patients (23.33%) were vitamin b12 deficiency. study by Oger E *et al.* 2006<sup>[18]</sup> found 30.17% of DVT patients were having vitamin B12 deficiency; study by Cattaneo M *et al.* 2001<sup>[16]</sup> found 26.47% DVT patients were having vitamin b12 deficiency. In contrast Our study doesn't confirm with study by Ekim M *et al.* 2015<sup>[13]</sup> with only 1.67% (1 out of 60) patients having vitamin B12 deficiency.

In our study 3 out of 60 DVT patients (5%) were vitamin B6 deficiency. study conducted by Ekim M *et al.* 2015<sup>[13]</sup> found 2 out of 60 patients (3.33%).

In our study 22 out of 60 DVT patients (36.66%) were having folic acid deficiency. study by Ekim M *et al.* 2015<sup>[13]</sup> found 43.33% patients having folic acid deficiency, study by Cattaneo M *et al.* 2001<sup>[16]</sup> found 33.24% DVT patients were having folic acid deficiency. in contrast Our study doesn't confirm with study conducted by Oger E *et al.* 2006<sup>[18]</sup> with 6.8% of DVT patients were having folic acid deficiency. Possible reason of for this high prevalence of folic acid deficiency that in our population majority are having vegetarian diet and prolonged cooking of vegetable dishes may result in diminished folate content.

### Conclusions

Hyper homocystienemia and related Vitamin B group deficiency are risk factors for Deep vein thrombosis. Hyper homocystienemia and risk of DVT, this correlation is high among older age group and female patients. All at risk patients should receive vitamin B12, vitamin B6 and folic acid supplementation.

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