



A STUDY OF MEAN PLATELET VOLUME LEVELS IN PATIENTS WITH HYPOTHYROIDISM

General Medicine

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ABSTRACT

BACKGROUND: The effect of thyroid hormones on cardiovascular system, lipid profiles and other systems were documented in various studies. But the finding of elevated mean platelet volume in hypothyroid individual's gains enormous significance recently because of indirect effects on management and outcome of the hypothyroidism. **OBJECTIVES:** 1. To assess whether mean platelet volume levels are elevated in subclinical and overt hypothyroidism. 2. To assess whether the severity of hypothyroidism correlates with the mean platelet volume. **MATERIALS AND METHODS:** The study was done among 50 hypothyroid and equal euthyroid individuals as prospective observational study at Government Sivagangai Hospital, in medicine outpatient department during June 2018 to December 2018. After getting the IEC clearance and patient informed consent the study participants were subjected to Blood samples were collected to measure blood sugar, urea, creatinine and serum cholesterol. Total T3, total T4 and TSH were measured using the chemiluminescence method. **RESULTS:** The mean platelet volume was significantly higher in the overt and subclinical hypothyroidism group when compared with the euthyroid group. Also the mean platelet volume was greater in the overt hypothyroidism group when compared with the subclinical hypothyroidism. The p value was <0.001 which signifies that the difference in MPV among the three groups is statistically significant and not due to chance. The correlation coefficient for T3 and MPV is -0.73 whereas for T4 and MPV it is -0.69 indicating that both T3 and T4 are inversely proportional to MPV. Hence with decrease in levels of T3 and T4 there is a proportionate increase in MPV. The correlation coefficient for TSH and MPV is 0.751 indicating that there is a strong positive correlation. Thus MPV values increase with increase in TSH. **CONCLUSION:** Our study has shown that hypothyroidism increases platelet activation which can be seen from the increased MPV values.

KEYWORDS

Hypothyroidism, Mean Platelet Volume(MPV), Extradural, IDEM - Intradural Extramedullary, Intramedullary

INTRODUCTION

Hypothyroidism is a common endocrine disease caused by deficiency of thyroid hormone. It is more common in females. Incidence in females is 2% whereas in males it is 0.2%. The most common causes are iodine deficiency, autoimmune thyroiditis and iatrogenic causes (treatment of hyperthyroidism). According to a projection it has been estimated that about 42 million people in India suffer from thyroid disorders. Women are affected approximately six times more frequently than men.¹

Hypothyroidism commonly manifests as slowness of physical and mental activity. It can also be asymptomatic. Common symptoms are fatigue, lethargy, weight gain, cold intolerance, dry skin, myocardial depression and constipation. Lack of thyroid hormone results in multisystem derangement of physiological functions.

Effects on cardiovascular system – it is common knowledge that hypothyroidism causes reduction of contractility and bradycardia. It is also known that dyslipidemia is more common in hypothyroidism and hence atherosclerosis is accelerated in these patients.

Recent studies have associated hypothyroidism with decreased endothelium-dependent vasodilatation, and animal studies have proposed that the thyroid status alters the capacity for both formation and response to nitric oxide. Endothelial dysfunction in patients with hypothyroidism may result from reduction in nitric oxide availability, with resultant impairment of flow-mediated vasodilatation.

It is plausible that these effects can increase the risk of ischemic heart disease in hypothyroid patients. Additional evidence is accumulating in favour of this because recent studies have linked hypothyroidism (either subclinical or overt) with increased platelet activation as evidenced by an increased mean platelet volume in these patients. Mean platelet volume, a marker of platelet function is a newly emerging and independent risk factor for thrombotic events and coronary artery disease.

Since coronary artery disease is the leading cause of mortality worldwide and hypothyroidism is a common endocrine disorder, the finding of elevated mean platelet volume in hypothyroid individual's

gains enormous significance and has become the subject of interest for various ongoing studies conducted in hypothyroid patients.

AIMS AND OBJECTIVES

- To assess whether mean platelet volume levels are elevated in subclinical and overt hypothyroidism
- To assess whether the severity of hypothyroidism correlates with the mean platelet volume

MATERIALS AND METHODS

Study population: The study is to be conducted among 50 hypothyroid patients who attend the medicine OP at Government Sivagangai hospital, and 50 euthyroid subjects who will serve as controls. The study population will be divided into two groups - subclinical and overt hypothyroidism.

Study Participants: patients who attend the medicine OP at government hospital and who satisfy the exclusion and inclusion criteria of our study.

Inclusion criteria:

- Patients with low T3, T4 and elevated TSH.
- Patients with normal T3, T4 and elevated TSH.
- Patients with normal thyroid profile will serve as controls.

Exclusion criteria:

- History of hypertension or detection of systolic blood pressure >140 mm hg and diastolic pressure >90 mm hg on three separate occasions.
- History of diabetes or fasting glucose >126 mg% or post prandial glucose >200 mg%
- History of smoking
- Consumption of alcohol
- Dyslipidemia (serum cholesterol >200 mg%)
- Patients with cardiac, renal, hepatic and other systemic diseases
- Patients on drugs which affect platelet function

Data collection:

A detailed medical history and physical examination was done. Laboratory investigations:

Blood samples will be taken to measure platelet count and mean platelet volume using an automated analyser. Samples will be collected in an EDTA coated tube and will be run in the automated analyser within 1 hr of collection to prevent swelling of platelets in EDTA.

Blood samples were collected to measure blood sugar, urea, creatinine and serum cholesterol. Total T3, total T4 and TSH will be measured using the chemiluminescence method.

Study protocol:

The subjects were classified into three categories – overt hypothyroidism, subclinical hypothyroidism and euthyroid subjects who serve as controls. The mean platelet volume levels of these three groups were compared and the relation between severity of hypothyroidism and mean platelet volume levels was analysed.

Design of study:

Prospective observational study

Period of study:

June 2018 to December 2018

Collaborating departments:

Departments of medicine, biochemistry, pathology and endocrinology

Ethical clearance: obtained

Consent: Individual written and informed consent.

STATISTICAL ANALYSIS

The data collected during the study was formulated into a master chart in Microsoft office excel and statistical analysis was done with help of computer using statistical software package SPSS V.17 for windows. Using this software, frequencies, range, mean, standard deviation and percentages were calculated. The statistical analysis was divided into three parts. The first part consists of the descriptive analysis, the second part includes multivariate analysis and the final part comprises of the calculation of correlation coefficient between the thyroid hormone levels and MPV.

RESULTS

Characteristics of the study population

The study population was divided into 3 groups. 20 patients with subclinical hypothyroidism, 30 patients with overt hypothyroidism and 50 healthy subjects with euthyroidism were included in the study.

Age distribution in overt, subclinical hypothyroidism and euthyroid status

The mean age of the patients included in overt hypothyroidism group was 34. The minimum age was 19 and the maximum age was 58 with a standard deviation of 10.56. The mean age of the patients included in subclinical hypothyroidism was 30. The minimum age was 17 and the maximum age was 43 with a standard deviation of 8.47. The mean age of the control group was 34 with a minimum age of 17, maximum age of 51 and a standard deviation of 7.47. The age distribution among the three groups is remarkably similar as one can see from the frequency distribution charts. Hence it can be said that the three groups are matched and similar with respect to age.

Sex distribution among overt, subclinical and euthyroid status

8 males and 22 females participated in overt hypothyroidism group. Males comprised 27% and females 73%. 6 males and 14 females participated in subclinical hypothyroidism. 30% were males and 70% were females. 15 males and 35 females were included in control group. 30% were males and 70% were females. The three groups were similar with respect to sex distribution.

Table – 1 Distribution of MPV values among three groups

The mean platelet volume in overt hypothyroidism ranged from 10.5 to 13 femtolitres with a mean of 11.5 femtolitres. The mean platelet volume in subclinical hypothyroidism group ranged from 8.5 to 12 femtolitres with a mean value of 9.9 femtolitres. The mean platelet volume in the euthyroid group ranged from 7 femtolitres to 9.5 femtolitres with a mean value of 8.1 femtolitres.

	mean	max	min	SD
MPV (fl) – Overt group	11.5	13	10.5	0.66
MPV (fl) – Subclinical	9.9	12	8.5	1
MPV (fl) – Euthyroid	8.1	9.5	7	0.6

ANOVA – Table – 2

PARAMETERS		Sum of Squares	df	Mean Square	F	P value
AGE	Between Groups	251.560	2	125.780	1.664	.195
	Within Groups	7331.430	97	75.582		
	Total	7582.990	99			
T3	Between Groups	18.654	2	9.327	123.582	.001
	Within Groups	7.321	97	.075		
	Total	25.974	99			
T4	Between Groups	80763.710	2	40381.855	108.153	.001
	Within Groups	36217.720	97	373.379		
	Total	116981.430	99			
TSH	Between Groups	25611.518	2	12805.759	55.909	.001
	Within Groups	22217.620	97	229.048		
	Total	47829.138	99			
MPV	Between Groups	213.162	2	106.581	209.214	.001
	Within Groups	49.415	97	.509		
	Total	262.578	99			

MULTIVARIATE ANALYSIS USING ANALYSIS OF VARIANCE

The p value for various parameters between the three groups was calculated using analysis of variance test (ANOVA).

The mean platelet volume was significantly higher in the overt and subclinical hypothyroidism group when compared with the euthyroid group. Also the mean platelet volume was greater in the overt hypothyroidism group when compared with the subclinical hypothyroidism. The p value was <0.001 which signifies that the difference in MPV among the three groups is statistically significant and not due to chance.

The p value was also calculated for age of the individuals in the three groups. It was 0.195 which is higher than the statistically significant value of 0.05. Hence we can conclude that there is no statistically significant difference among the three groups with regard to the age composition.

Obviously the p value for T3, T4 and TSH is <0.001 since the three groups were formed based on the difference in the level of their thyroid function.

TABLE 3 – CORRELATION ASSESSMENT Correlations between thyroid hormone levels and MPV

		T3	T4	TSH	MPV
T3	Pearson Correlation	1	.768**	-.681**	-.731**
	Sig. (2-tailed)		.000	.000	.000
	N	100	100	100	100
T4	Pearson Correlation	.768**	1	-.700**	-.691**
	Sig. (2-tailed)	.000		.000	.000
	N	100	100	100	100
TSH	Pearson Correlation	-.681**	-.700**	1	.751**
	Sig. (2-tailed)	.000	.000		.000
	N	100	100	100	100
MPV	Pearson Correlation	-.731**	-.691**	.751**	1
	Sig. (2-tailed)	.000	.000	.000	
	N	100	100	100	100

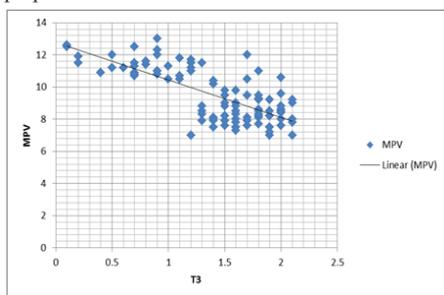
** . Correlation is significant at the 0.01 level (2-tailed).

The Pearson coefficient of correlation for any two variables can be calculated in order to find out whether the variables are positively related, negatively related or not related at all.

The value of the correlation coefficient ranges between -1 and +1. If the correlation coefficient is zero then it means there is no association between two variables. If the value is +1 then it indicates there is a positive correlation between variables and if the value is -1 then there is a negative correlation. The correlation coefficient for T3 and T4 is 0.77 showing that they are positively correlated ie if one of the variables increases or decreases the other variable also increases or

decreases correspondingly. The correlation coefficient for T3 and TSH is -0.68 which is easy to understand because whenever T3 levels fall the level of TSH rises.

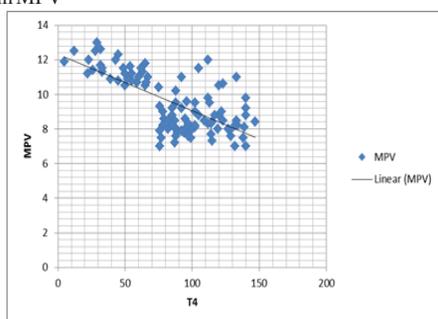
The correlation coefficient for T4 and TSH is -0.7 showing that T4 is inversely proportional to TSH.



Scatter diagram showing negative correlation between T3 and MPV

The correlation coefficient for T3 and MPV is -0.73 whereas for T4 and MPV it is -0.69 indicating that both T3 and T4 are inversely proportional to MPV.

Hence with decrease in levels of T3 and T4 there is a proportionate increase in MPV



Scatter diagram showing T4 is inversely proportional to MPV

The correlation coefficient for TSH and MPV is 0.751 indicating that there is a strong positive correlation. Thus MPV values increase with increase in TSH

DISCUSSION

Hypothyroidism is known to be associated with endothelial dysfunction and atherosclerosis and various studies have proven the increased risk of adverse cardiovascular events in hypothyroid individuals. A study was conducted by Chan hee jung et al in Korea among 66,260 individuals to find out the association between thyroid dysfunction and cardiovascular risk factors such as dyslipidemia, elevated hsCRP and waist hip ratio.(2) The mean plasma total cholesterol and LDL cholesterol levels were significantly higher in the overt hypothyroid group (202 mg% and 122 mg% respectively versus 197 mg% and 120 mg%). In our study we excluded the subjects with dyslipidemia to show that hypothyroidism elevates mean platelet volume even in the absence of dyslipidemia. Also the hsCRP and waist to hip ratio were higher in the hypothyroid group. Our study concentrated only on mean platelet volume and we did not take into account these cardiovascular risk factors. Kim et al conducted a study among 7000 asymptomatic Korean adults to assess the relationship between hypothyroidism and mean platelet volume.(3) The subjects were divided into four groups such as tertiles based on TSH values. The mean MPV values in the whole population was 8.12 ± 0.75 femtolitres and the mean MPV values differed significantly among the 4 groups. The MPV values were found to be positively correlated to TSH values. In comparison we divided our study population into three groups including symptomatic adults also. We also found a strong positive correlation between TSH and MPV values ($r = 0.75$). Yilmaz et al studied MPV values in 60 patients with subclinical hypothyroidism in Turkey. The study was done to evaluate mean platelet volume in subclinical hypothyroidism before and after 12 weeks of levothyroxine replacement.(4) They found that MPV, serum triglycerides was significantly elevated before levothyroxine replacement and serum HDL cholesterol levels were significantly lower before thyroxine replacement and the P value was <0.001 . In our study also we found significant increase in MPV values in both

subclinical and overt hypothyroidism with a similar P value of <0.001 . However we did not evaluate MPV following thyroxine replacement as ours is not prospective study. Chu et al performed a systematic review and meta-analysis to evaluate the association between elevated MPV and acute myocardial infarction, mortality in CAD and restenosis following angioplasty. They pooled results from 16 cross sectional studies. MPV was significantly higher in those with AMI than those without AMI [mean difference 0.92 fL, 95% confidence interval (CI) 0.67–1.16, $P < 0.001$]. Also there was a significant elevation in MPV in acute MI and unstable angina when compared to stable angina. Our study shows that MPV values are elevated in hypothyroidism and this can be extrapolated to say that hypothyroidism increases the risk of CAD and MI. Soysal et al conducted a study in Turkey to study the effects of thyroxine replacement on MPV in cases of autoimmune thyroiditis.(5) The study included 20 euthyroid controls and 30 patients with Hashimoto thyroiditis. The fasting glucose, lipid profile and platelet count were all similar between the two groups and MPV was significantly higher in the hypothyroid group ($P < 0.01$) and decreased to normal following thyroxine replacement. The MPV values were directly proportional to level of anti TPO antibodies. In our study we did not measure anti TPO antibodies since iodine deficiency is still the commonest cause of hypothyroidism in our country. Nicolas et al studied around 55,000 subjects and found the prevalence of subclinical hypothyroidism to be 6%.(6) On follow up of these people 2,200 died of coronary heart disease and 4,500 had non-fatal CHD events. The risk of mortality due to CHD and the incidence of CHD events increased with increase in TSH levels. Ours is not a prospective study and hence we have excluded the people with coronary artery disease so that the effect of CAD on MPV does not interfere with our results. Newer studies have concentrated on C-reactive protein, homocysteine, arterial stiffness, endothelial dysfunction and coagulation parameters such as MPV, platelet distribution width, platelet aggregability etc to study their role as a marker for atherosclerotic coronary artery disease. A study done in Poland shows that serum homocysteine levels are significantly elevated in patients with hypothyroidism. In hypothyroidism the remethylation of homocysteine to methionine is affected since the activity of the enzyme MTHFR (methyl tetra hydrofolate reductase) is reduced. Okuyan et al studied 604 patients admitted to coronary ICU between 2004 and 2009 retrospectively.(7) He found that the incidence of subclinical hypothyroidism was much higher among patients with MI. In hospital deaths and heart failure occurred with increased frequency among patients with TSH values of 10 and above. Also the incidence of comorbid conditions such as diabetes and hypertension and fatal MI was higher in the patients having TSH >4.5 when compared with those having euthyroidism. Anita Chaudary et al studied the influence of hypothyroidism on platelet aggregation. 32 females with hypothyroidism and 32 healthy females (who served as control) were selected. Blood samples were collected and platelet aggregability was measured using O'Brien method where ADP is used to activate platelets and platelet aggregation is measured using colorimetry. The result was platelet aggregability was significantly higher in study group than in the control group. In our study we were not able to measure platelet aggregability because of the cumbersome procedure and the cost involved and the limitation of available facilities. Eriksi et al studied the effect of subclinical hypothyroidism on platelet parameters. 47 patients with subclinical hypothyroidism and 30 euthyroid and healthy control group were studied.(8) They concluded that patients with subclinical hypothyroidism had higher mean platelet volume and platelet distribution width values than control group. We did not use platelet distribution width in our study because the association between increase in PDW and CAD was not found to be as significant as MPV in various studies.

Conclusion:

Our study has shown that hypothyroidism increases platelet activation which can be seen from the increased MPV values. Hence it may increase the risk of atherothrombotic complications such as coronary artery disease which is a major cause of mortality worldwide. This increased risk can be reduced by the effective treatment of hypothyroidism. Since subclinical hypothyroidism is also associated with CAD and increase in MPV, we strongly recommend the treatment of subclinical hypothyroidism rather than postponing it till overt hypothyroidism sets in. It is also recommended that all patients aged >40 and having cardiovascular risk factors should undergo thyroid function test to rule out hypothyroidism.

REFERENCES:

1. Study of Effect of Hypothyroidism on Platelet Aggregability. A. Chaudhary et al /

- Research Journal of Biology (2012), Vol. 02, Issue 06, pp. 182-185
2. Jung CH1, Sung KC, Shin HS, Rhee EJ, Lee WY, Kim BS, Kang JH, Kim H, Kim SW, Lee MH, Park JR, Kim SW. Thyroid dysfunction and their relation to cardiovascular risk factors such as lipid profile, hsCRP, and waist hip ratio in Korea. *Korean J Intern Med.* 2003 Sep;18(3):146-53.
 3. Kim JH1, Park JH, Kim SY, Bae HY, The mean platelet volume is positively correlated with serum thyrotropin concentrations in a population of healthy subjects and subjects with unsuspected subclinical hypothyroidism.
 4. Yılmaz, Hamiyet & Ertuğrul, Ozden & Ertugrul, Bulent & Ertuğrul, Derun. (2011). Mean platelet volume in patients with subclinical hypothyroidism. *Platelets.* 22. 143-7. 10.3109/09537104.2010.508130.
 5. Soysal Atila, Neslihan & Bilir, Bilgen & Bilir, B & Guldiken, S. (2012). Mean platelet volume levels in patients with overt hypothyroidism before and after levothyroxine treatment. *Choroid Plexus - Pineal Gland Correlations Medical Anthropology - Computed Tomography Studies Intracranial Physiological Calcification.* 8. 607-613. 10.4183/aeb.2012.607.
 6. Christine Baumgartnera , Manuel R. Bluma , Nicolas Rodondia. Subclinical hypothyroidism: summary of evidence in 2014. *Swiss Med Wkly.* 2014;144:w14058
 7. Okuyan, Ertugrul & Ahmet, Uslu & Enhoş, Asim & E Gulcin, Heppul & Ayca, Burak & Murat, Avsar & S Sezai, Yildiz & Ibrahim Biter, Halil & M Hakan, Dinckal. (2011). Prevalence of Subclinical Hypothyroidism among Patients with Acute Myocardial Infarction. *ISRN endocrinology.* 2011. 810251. 10.5402/2011/810251.
 8. Erikci AA1, Karagoz B, Ozturk A, Caglayan S, Ozisik G, Kaygusuz I, Ozata M. The effect of subclinical hypothyroidism on platelet parameters. *Hematology.* 2009 Apr;14(2):115-7. doi: 10.1179/102453309X385124.