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Mean platelet volume (MPV) levels in subclinical hypothyroidism and its relation to serum lipid levels

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ABSTRACT

Background: Subclinical hypothyroidism (SCH) is a term to define a mild and early thyroid deficiency. Some reports claim SCH has an association with increased cardiovascular disease (CVD), especially in individuals <70 years old. Mean platelet volume (MPV) is thought to be an independent marker for CVD. Dyslipidemia is also a common entity in thyroid related disorders and a tradational biomarker of increased risk of CVD. This study aims to reveal the MPV levels in SCH and to discuss its relation to lipid profile.

Material and Method: This retrospective single-center study was conducted between 2009 March and August. 94 newly diagnosed patients with SCH and 79 controller were enrolled in the study. Patients with normal serum levels of free T3 and T4 and >4 mIU/L TSH levels were labelled for SCH group. Both groups were evaluated for MPV, lipid profiles and epidemiological features.

Results: SCH group had higher levels of MPV, total cholesterol (TC) and LDL cholesterol (LDL-C) levels (P<0.05, for each parameter). MPV had a positive correlation to TC and LDL-C (r=0,175 ve p=0,025; r=0,154 and p=0,043). However, a multivariate analysis that rendered the impact of age and gender revealed that SCH had no impact on MPV after adjustment for those parameters gender revealed that SCH had no impact on MPV after adjustment for those parameters (B=0,304; 95% CI: -0,021 – 0,628; p=0,066).

Conclusion: SCH patients may have higher levels of MPV. However, age and gender had an impact on MPV levels and we think increased CVD risk in SCH patients is associated with factors other than MPV levels.

Keywords: MPV, lipids, subclinical hypothyroidism

INTRODUCTION

Subclinical hypothyroidism (SCH) refers to an elevated serum thyrotropin (or as commonly known, thyroid stimulating hormone [TSH]) accompanying with normal levels of free thyroxine (fT4). SCH effects 3% to 8% of the general population in the world while some regions are more incident (1,2). A common approach for the treatment of SCH involves to treat individuals with TSH >10 mU/L or elevated TSH accompanying with symptoms that thought to be related with hypothyroidism (2).

SCH may have some adverse impact on blood pressure, lipid levels, and atherosclerosis which all are the traditional strong risk factors for the future cardiovascular disease (CVD) or events. So it is logical to think on whether the SCH is a modifiable factors for CVD (3-6). Since it has been shown dyslipidemia reversed in overt hypothyroidism patients following levothyroxyine therapy (6,7), it is a key question whether to treat SCH may provide some benefits in those patients.

Mean platelet volume (MPV) is one of predictor parameters of platelet function which has been linked to cardiovascular disease (8-9). Some studies claim SCH is associated with higher MPV levels (9). In contrast, others have not indicated an association between those two parameters in their studies with diverse cohorts (10-12). However all studies are designed on completely various protocols and many factors may have effect on results.

We aimed to test whether SCH is associated with MPV and MPV levels is related to lipid levels in our cohort to contribute the data pool of the existing literature.

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MATERIAL AND METHOD

This single-center retrospective study was conducted between March and August 2009 in Yıldırım Beyazid University Dışkapı Education and Training Hospital. Ninety-four individuals with subclinical hypothyroidism and seventy-nine healthy individuals (laboratory findings were normal and with a disease-free history) were enrolled in the study. Laboratory and clinical features of the participants were noted.

- **SCH** was defined as; serum TSH levels >4 mIU/L plus normal serum fT3 and fT4.
- **Groups**: Group 1; SCH and Group 2; healthy individuals
- **Exclusion**: Existence of those clinical features; overt hypo-hyperthyroidism or being under a treatment for a known thyroid disease, diabetes mellitus, long-standing hypertension, coronary artery disease, dyslipidemia or being under lipid-lowering therapy, hematological disease, chronic kidney disease and all other conditions that indicates an acute systemic disease.
- **Comparision parameters**: serum TSH, fT4, fT3, MPV, total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density cholesterol (HDL-c), fibrinogen, high sensitive c-reactive protein (hsCRP), fasting glucose, platelet counts, hemoglobin and hemotocrit.
- **Blood sampling**: All blood samples were drawn between 08:00 and 10:00 at morning and all samples were studied in the central laboratory of the hospital at the admission day.
- **Data collection**: Data were collected via central hospital automation software, noted by a authorised doctor, and all individuals were queried again for exclusion criteria by phone calls.

This study was produced from the specialization thesis. The study was carried out with the permission of Health Ministry of Turkish Republic Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethical Commitee (Date: 13.12.2021, Decision No:126/03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Assessment

Dataset were analysed via using Statistical Package for the Social Sciences (S.P.S.S.) version 11.5 (IBM SPSS Corp. NY, USA). Normality of the parameters was assessed by performing the Kolmogorov-Smirnov test. Continuous parametric variables were presented as mean ± standard deviation and non-parametric variables as median with maximum and minimum levels. Categorical variables were expressed as percentiles (%), and qualitative measures were evaluated by using Chi-Square test. Continuous parametric and non-parametric variables were compared by independent Sample T test and Mann-Whitney U-test, respectively. Multivariate analysis were performed to describe the factors might have impact on MPV levels. A correlation between continuous parametric and non-parametric variables were analysed via Spearmen's and Pearson's correlation tests, respectively. P value <.05 was indicated as statistically significant. The power analysis of the data was calculated from the observed power of the parameters by considering Type b error (<0.2).

RESULTS

A total of 173 individuals were evaluated. Group 1 was older (41.9±14.9 vs 30.1±9.3) and included more female (female= 144 and male= 29) individuals compared to Group 2; p <0.001 and p= 0.019, respectively. Laboratory features of both two groups were given in **Table 1**.

Table 1. Comparison of the laboratory findings of the two groups

Variables	Group 1, n= 94	Group 2, n= 79	P value
Hgb, gr/dl	13.5±1.39	13.8±1.43	0.146
HTC, %	39.4±3.72	39.8±4.06	0.432
PLT, µg/L	275 (140-552)	248 (118-443)	<0.001
MPV,fl	8.5 (6.2-11.0)	8.1 (6.1-11.4)	0.004
Glucose, mg/d	92 (72-120)	81 (58-138)	<0.001
TSH, mIU/L	5.8 (4.1-30.1)	1.6 (0.3-3.9)	<0.001
fT4, ng/dl	1.2 (0.3-4.97)	1.3 (0.99-1.8)	<0.001
fT3, pg/ml	3.3 (1.6-55.0)	1.27 (1.02-1.93)	0.065
TC, mg/dL	190.5 (110-298)	162 (99-260)	<0.001
TG, mg/dL	122 (46-376)	98 (39-430)	0.041
LDL-c, mg/dL	115.1±36.39	94.6±31.80	<0.001
HDL-c, mg/dL	45.5 (25-91)	49 (5-84)	0.052
Fibrinogen, mg/dl	341.5 (184-910)	240 (120-370)	<0.001

Hgb: hemoglobin, Htc: hematocrit, Plt: platelet, MPV: mean platelet volüme, TSH: thyroid stimulanting hormone, fT4: free T4, fT3: free T3

Pearsons' correlation test revealed a positive correlation between MPV and TSH (p<0.001, r2= 0.079) (**Figure 1**). Then after we divided Group 1 according to TSH levels into three subgroups to determine whether higher levels of TSH are associated with higher levels of MPV (TSH >4 and <6 mIU/L, TSH ≥6 and <10 mIU/L, and TSH ≥10 mIU/L) (**Table 2**). However, those three groups were found similar for MPV in Anova test; p=0.898. Age was similar among three subgroups; p=0.078.

Table 2. Comparison of MPV, fibrinojen, TG, TC, LDL-c, and HDL-c in subgroups of SCH

Variables	TSH >4 and <6 mIU/L	≥6 and <10 mIU/L	≥10 mIU/L	p
Age, years	39.2±12.1	42.1±16.7	40.1±13.1	0.872
MPV, fl	8.5±0.98	8.4±1.06	8.6±0.93	0.898
Fibrinogen, mg/dl	353 (189-804)	304.5 (184-910)	340.0 (253-866)	0.117
TG, mg/dl	122 (55-296)	135 (46-376)	120 (64-281)	0.613
TC, mg/dl	186 (110-298)	202.5 (136-284)	196 (113-298)	0.622
LDL-c, mg/dl	112.2±37.57	117.3±38.07	120.0±32.49	0.685
HDL-c, mg/dl	45 (29-91)	47 (30-68)	45 (25-60)	0.958

TSH: thyroid-stimulating hormone, TG: triglyceride, TC: total cholesterol, LDL-c: low-density lipoprotein cholesterol, HDL-c: high-density lipoprotein cholesterol

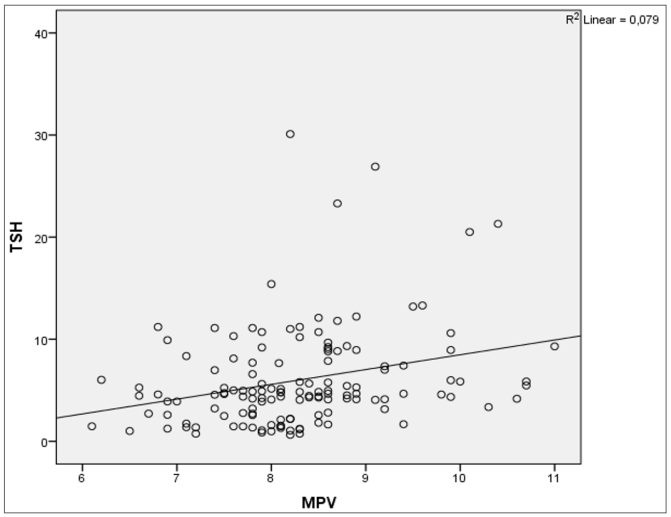

Figure 1. Corellation between TSH and MPV

Univariate analysis did not reveal a relation between MPV and age, TG, and HDL-c in Group 1 (p>0.05). MPV has also posed a positive correlation with TC and HDL-c (r= 0.175 and p= 0.025; r= 0.154 and p= 0.043, respectively).

A regression model was used to investigate the impact of SCH, age, TC, HDL-c and gender on MPV, and we found that SCH had no impact on MPV levels after adjustment (p= 0.06, B= 0.304, CI %95; -0.021 – 0.628) (**Table 3**) (however if CI would have been set up as 90%, p value could demonstrate a significant level, or if the study had a larger sample size result would be significant since p=0.06 was close to p=0.05). On the other hand, when the same model was applied to fibrinogen in Group 1, it was observed that SCH and age remained to have an impact on fibrinogen (p<0.001, B=0,334; 95% CI; 0,236 – 0,431) (**Table 4**).

Table 3. Multivariate analysis of the factors impact on MPV

Variables	Regresyon Coefficient (B)	p	%95 CI (B)	
			Lower	Upper
SCH	0.304	0.066	-0.021	0.628
Age	0.0002	0.980	-0.014	0.014
Male	-0.307	0.127	-0.701	0.088
TC	0.001	0.809	-0.007	0.009
TG	0.001	0.593	-0.002	0.003
HDL-c	-0.0002	0.966	-0.009	0.008

SCH: subclinical hypothyroidism, TC: total cholesterol, TG: triglyceride, HDL-c: high-density lipoprotein

Table 4. Multivariate analysis of the factors impact on fibrinogen

Variables	Regresyon Coefficient (B)	p	%95 CI (B)	
			Lower	Upper
SCH	0.334	<0.001	0.236	0.431
Age	0.004	0.038	0.0003	0.009
Male	-0.037	0.542	-0.155	0.082
TC	-0.001	0.616	-0.003	0.002
TG	-0.001	0.252	-0.001	0.0004
HDL-c	-0.002	0.516	-0.006	0.003

DISCUSSION

Subclinical hypothyroidism has dysmetabolic effects such as dyslipidemia, increased blood pressure and glucose which are all traditional cardiovascular risk factors (13). MPV is the average size of platelets found in blood and is thought to be an marker of platelet activity which is relavent to atherothrombotic events (14,15). Overt hypo/hyperthyroidism have been found to associated with increased MPV, however, impact of SCH on MPV is doubtful. Our clinical trial indicates SCH has no impact on MPV and is also not related to lipid profiles.

SCH is a common type of thyroid hormone disorder worldwide and has well-known dyscardiometabolic effects. Myocardial and vascular endothelial tissues are sensitive to changes in the concentrations of circulating thyroid hormones and adverse events may occur even in the case of SCH (16). However, the mechanism involved in the pathogenesis of SCH-related cardiovascular adverse events is still speculative (16,17). Moreover, guidelines recommend to treat the SCH individuals with cardiovascular disease due to probable benefits of to treat and evidence of adverse events related to not treated patients (17).

Thyroid hormone receptor is expressed by hematopoietic stem cells and a low/high concentration of thyroid hormone is associated with clonogenecity and apoptosis of hematopoietic system (18,19). Plateles are enucleated cells and produced by megakaryocytes in bone marrow, have a lifespan of 7-10 days. MPV is determined during megakaryocytogenesis and influenced by many factors which play key role in thrombopoiesis, as well as thyroid hormone (20). Additionally, thyroid hormones are associated with increased platelet levels, however, the mechanism is unknown (21). MPV is thought to be an activity marker of platelets so it is plausible to establish the strategies to determine the factors might result in increase of MPV. Impact of SCH on MPV is controversial and our study also has not determined a relation between MPV and SCH. Nevertheless, in our cohort we found a positive correlation between TSH and MPV levels considered all individuals of the cohort. Then after we tried to find a hazard range for TSH which would determine a risk for increased MPV. However, we could not find such a link between two parameters. This might be due to some other factors that have effects on MPV. Platelet levels were found higher in SCH group in our study.

SCH has been found associated with a higher level of blood glucose and dyslipidemia as expected, as demonstrated in previous studies. MPV levels have not had an association with lipid levels.

Our study has some limitations. Some factors which might have impact on MPV levels, such as smoking, blood pressure, body mass index, were not investigated due to the lack of data. Our cohort has a small sample size and only one hemogram and biochemical study results could have been evaluated. Despite all, we think our findings may contribute to the literature on the topic.

CONCLUSION

Our study reveals SCH have no impact on MPV. SCH might be contributing to cardiovascular adverse events via various pathways other than MPV levels.

ETHICAL DECLARATION

Ethics Committee Aproval: The study was carried out with the permission of Health Ministry of Turkish Republic Dışkapı Yıldırım Beyazıt Training and Research Hospital Ethical Commitee (Date: 13.12.2021, Decision No:126/03).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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