Research Article / Araştırma Makalesi

Assessment of Mean Platelet Volume in Acromegaly And Its Relation With The Treatment

Akromegalide Ortalama Trombosit Volümünün Değerlendirilmesi ve Tedavi ile İlişkisi

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Abstract

Background: Mean platelet volume (MPV) is an independent risk factor of atherosclerosis and thrombotic events. We aimed this study evaluates the levels of MPV in acromegalic patients and its relationship with treatment.
Materials and Methods: In this study, we examined the levels of MPV in acromegalic patients before and after treatment and also at two years of remission. The results were also compared with a control group. A total of 80 patients treated at our clinic with the diagnosis of acromegaly age- and gender-matched nonacromegalic controls were reviewed retrospectively. Preoperative and postoperative MPV values as well as MPV values two years after controlling disease in patients with medical treatment were compared.
Results: MPV values were significantly higher in both the diabetic and non-diabetic acromegaly patients compared with the control subjects (p=0,02). Postoperative MPV values were significantly reduced compared to preoperative values in patients cured after surgery (p=0,001). Patients who achieved disease control with medical therapy after failure of surgical intervention demonstrated MPV values similar to those reported in patients cured with, even after two years from surgery (p=0,001).
Conclusions: Our findings suggested that MPV would be a beneficial marker for atherosclerosis and inflammation in patients with acromegaly.

Key Words: Acromegaly, Atherosclerosis, Inflammation, Mean Platelet Volume

Öz.

Amaç: Ortalama trombosit volümü (MPV) ateroskleroz ve trombotik olaylar için bağımsız bir risk faktörüdür. Çalışmamızda akromegalik hastalarda MPV düzeyini ve tedavi ile ilişkisini değerlendirmeyi amaçladık.
Materyal ve Metod: Çalışmamızda akromegali hastalarında tedavi öncesi, tedavi sonrası ve remisyondan 2 yıl sonraki MPV düzeylerini değerlendirdik. Ayrıca sonuçları kontrol grubu ile karşılaştırdık. Kliniğimizde takipli 80 akromegali hastası yaş ve cinsiyet açısından benzer kontrol grubu ile retrospektif olarak kıyaslandı. Preoperatif ve postoperatif MPV değerleri ile medikal tedavi alan hastalarda hastalık kontrolünden iki yıl sonraki MPV değerleri karşılaştırıldı.
Bulgular: Diyabetik ve non-diyabetik akromegali hastalarında MPV düzeyi kontrol grubuna göre anlamlı oranda yüksekti (p=0,02). Postoperatif kür sağlananlarda postoperatif MPV preoperatif MPV'ye göre anlamlı oranda düşüktü (p=0,001). Cerrahi tedavi başarısızlığından sonra medikal tedavi ile hastalık kontrolü sağlananlarda MPV düzeyi cerrahi ile kür sağlananlarla ameliyattan iki yıl sonra bile benzerdi (p=0,001).
Sonuç: Bulgularımız, MPV'nin akromegali hastalarında ateroskleroz ve inflamasyon için yararlı bir belirteç olabileceğini düşündürmektedir.

Anahtar kelimeler: Akromegali, Ateroskleroz, İnflamasyon, Ortalama trombosit volümü

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Introduction

Acromegaly is a rare condition caused by a pituitary adenoma that secretes growth hormone. Acromegaly has an estimated prevalence of around 60 per million and an annual incidence of 3-4 per million (1,2) Mortality among acromegaly patients is higher compared to the general population related to increased cardiovascular and cerebrovascular disorders. Cardiovascular causes are considered to be responsible for 60% of mortality in acromegaly (3). Glucose intolerance is observed in 29% - 45% of acromegalic patients, diabetes mellitus in 20%, hypertriglyceridemia in 19% - 40%-, and hypertension in 20%, all more common than the general population (4,5). Although the presence of these factors contributes to the increase in cardiovascular risk, it is thought that, increased cardiovascular risk might not only be due to these risk factors (6). Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are also believed to contribute to an increase in the risk of coronary artery disease and cardiovascular mortality due to their direct effects on endothelium (7) but the data in this regard are controversial.

Platelets play pivotal role in atherosclerosis and blood clotting (8,9). MPV is an indicator of platelet volume and activity. Larger platelets are younger, more reactive and hence they contain denser granules, secrete more serotonin and β-thromboglobulin and produce more thromboxane A2 than smaller platelets. All these biochemical agents may be responsible for MPV elevation during ischemia and atherosclerosis and rapid consumption of small platelets and production of new larger platelets may be associated with increased MPV (10,11). Therefore, higher MPV levels would predict atherosclerosis and ischemia. MPV is an independent risk factor for atherothrombosis (12). Several studies have shown that increased MPV is also an independent risk factor for myocardial infarction, cerebral ischemia and transient ischemic attacks (13).

There are several platelet activation markers that contribute to atherosclerosis. Most of the markers in use today are expensive and time-consuming to measure, requiring special education and larger samples (14,15) MPV is easily determined as a part of routine complete blood count at a relatively low cost (10).

To the best of our knowledge, this is the first study evaluating MPV levels in acromegaly patients with long term follow up after treatment

Materials and Methods

Eighty acromegalic patients and 65 healthy subjects (matched for age, gender and presence of diabetes mellitus) as a control group were evaluated retrospectively. Demographic, laboratory and treatment details of all patients were reviewed from a prospectively designed database. Exclution criterias are as follows: known congenital or acquired platelet disease, abnormal platelet count, active infection, haematologic or chronic inflammatory diseases, pregnancy and those receiving anticoagulant and/or antiaggregant treatments. Diagnosis of acromegaly in suspected population was made by laboratory values including, GH> 1 µg/L, higher IGF-1 levels adjusted for age and gender and GH> 1 µg/L after 75 gr oral glucose tolerance test (OGTT). Remission at 6th month was accepted as GH< 0.4ng/ml at baseline or after OGTT and IGF-1 between normal range adjusted for age and gender (16). Initially, MPV data of patients and controls were assessed and compared. In both groups hemoglobin A1c (HbA1c) levels and their relationship with MPV were determined Secondly, Preoperative and 6th month postoperative MPV values, MPV values during medical treatment if cure was not achieved with surgery and also MPV values at two years follow up were evaluated and compared. Serum GH was assessed by electrochemiluminescence immunoassay (ECLIA) (hGH kit, Architect c8000 Chemistry Analyzer, Abbott Diagnostics, IL,USA). Serum total IGF-1 was assessed by immunometric chemiluminescence assay (IMMULITE 2000, SIEMENS, USA). MPV was measured from EDTA-K2 (3.6 mg) anticoagulated whole blood within 2 hours of collection. . These blood samples were analyzed with an automatic blood counter (sysmex XE-2100 , japan coefficient of variation%3). The expected values for MPV in our laboratory range from 6 to 11 fl

This study was approved by the local ethics committee of our hospital (KOÜ KAEK 2015/176)

Statistical analyses were performed using SPSS 17.0 software. (indicate the source and year released) The data were first analyzed for normality using Kolmogorov–Smirnov tests. Nonparametric tests were employed when the distribution of the data was not normal. Variables were also evaluated with Pearson's and exact χ^2 tests. A P value <0.05 was considered statistically significant.

Results

Mean age of patients and control group was 46 and 48 years, respectively, without statistical significance (p=0.240). 47% of acromegaly group (n=38) and 48% of the control group (n=31) were female (p =0,320). Diabetes mellitus was diagnosed in 24 (30 %) acromegalic patients and in 23 (35%) control subjects (p=0.143). Also the mean HbA1c levels were similar in two groups (p=0.640). Forty-one patients (51%) were surgically cured; 30 patients (38%) were cured after surgery with somatostatin analog treatment. The remaining 9 patients (11%) had uncontrolled disease.

Preoperative mean MPV values were significantly higher in both diabetic (8,50± 1,40) and non-diabetic (8,60± 0,78) acromegaly patients compared with the control subjects (7,6± 1,5 in diabetics, 7,8± 0,9 in nondiabetics) (p=0,02) (Table 1).

Table 1. Comparison of demographic data and MPV values between groups

	Acromegaly (n=80)		Control (n=65)		P Value
Gender (women/men)	38/42		31/34		0,320
Age (years)	46 ± 11		48 ± 11		0,240
Preoperative MPV (fl)	8,62 ± 1,48		7,77 ± 0,85		0,001
HbA1c % (for diabetics)	7,1± 2,8		6,9± 1,1		0,640
	DM	nonDM	DM	nonDM	
Preoperative MPV	8,50 ± 1,40	8,68± 0,78	7,65± 1,50	7,83± 0,90	0,02 *

DM: Diabetes mellitus, nonDM: non diabetes mellitus
**There is no significant differences between DM and non-DMgroups*

The MPV values were significantly lower compared with preoperative values in patients who were completely cured after surgery (7,50± 1,02 versus 8,52± 1,46 and p=0,001). Patients who achieved disease control with medical therapy after the failure of surgical intervention demonstrated decreased mean MPV values similar to that reported in patients cured with surgery (8,66± 1,56 versus 8,02± 1,36 and p=0,001) (Table 2) There was no correlation between HbA1c and MPV values (p=0,06,r:0.251). Also no correlation was observed between MPV values and IGF-1 (P=0,838 r=0,024).

Table 2. Evaluation of MPV values of acromegaly patients according to treatment modalities.

	Preoperative MPV	Postoperative MPV	MPV after-surgery + medical treatment	P value
Entire group (n:80)	8,62± 1,48	8,10± 1,50	7,50± 1,90	0,001*
Surgical cure (n=41)	8,52± 1,46	7,50± 1,02	-	0,001*
Controlled disease (surgery + medical) (n:30)	8,66± 1,56	8,02± 1,36	7,38± 1,03	0,001
uncontrolled disease (surgery + medical) (n:9)	8,26± 0,86	8,05± 0,8	7,38± 0,63	0,64-0,32 Respectively

**There is significant differences between all MPV values*

In patients with postoperative complete cure mean MPV value following at least 2 years postoperatively was decreased compared to the levels at 6th month but the difference was not significant (p=0,059). The mean MPV level 2 years after remission in patients with medical treatment (7,30±1,01) was also decreased significantly compared to the levels at 6th month after remission (p=0,005). (Table 3).

Discussion

In this study we found that MPV values were significantly higher in acromegalic group than in the control group. Also, there was significant decrease in MPV values in acromegalic patients whose disease was adequately controlled by surgical and medical treatments.

Table 3. Evaluation of acromegaly patients after 6 Months and 2 Years of treatment

	Post-op MPV	MPV after-surgery + medical treatment	MPV at two years follow-up	P value
All acromegaly group (n:80)	8,10± 1,50	7,50± 1,90	7,30 ± 1,01	0,001*
Controlled Disease (surgery + medical) (n:71)	7,50± 1,02	-	7,30 ± 1,01	0,059
Uncontrolled disease (surgery + medical) (n:9)	-	7,38± 1,03	7,30 ± 1,10	0,018

**There are significant differences between all MPV values*

Acromegalic patients have higher prevalence of cardiovascular disorders, such as hypertension, cardiomyopathy, arrhythmia, valvular heart disease, insulin resistance, dyslipidemia, and hyperfibrinogenemia. GH and IGF-1 may also contribute to the early development of atherosclerosis through their direct effects on vascular endothelium (17-20). However, studies investigating premature atherosclerosis in acromegaly had conflicting results (7,21-23).
Atherosclerosis has been associated with chronic inflammation (24). MPV is also related to inflammation and there was elevation in increased atherosclerotic lesions (25,26). Some previous studies showed that there is relationship between acromegaly and both atherosclerosis and inflammation markers (27-29).
Unubol et al. (30) show that MPV higher in active acromegalic patients than healthy subjects similar our study. We have also observed in our study that MPV was significantly higher in both diabetic and non-diabetic acromegaly patients compared with the control subjects.
Another study showed that MPV levels were higher in acromegalic patients compared to controls similar our study. They also found that MPV did not change after treatment, as opposed to our study (31).
In contrast to our study Ersoy et al. (32) reported that when MPV levels were compared, no significant differences were detected between acromegalic patients and control group, however, they observed a significant decrease in MPV with treatments aslike results of our study. Although positive correlation between MPV and increased elevated plasma glucose levels has been shown in previous studies, (33-35) we did not find any correlation between HbA1c and MPV levels.
Ucler and et al. (36) was to evaluate the effect of disease control on MPV and RDW in acromegalic patients. They

have found significant increases in MPV and RDW in patients receiving SSA therapy but not significant changes found in MPV and RDW in groups of surgical treatment alone. In our study, MPV showed a significant decrease in patients who achieved remission on surgical treatment. Furthermore, MPV values also decreased in patients who did not achieve remission, although not statistically significant. Patients who achieved control with medical therapy after the failure of surgical intervention demonstrated MPV values similar to those reported in patients cured with surgery. The MPV values at least two years after remission of acromegaly were further decreased compared to postoperative sixth month levels. This result might show that, the risk of cardiovascular disease in acromegalic patients would disappear as healthy subjects on long term follow-up. We also demonstrated that, the MPV levels of patients on medical treatment continued to decrease reaching normal levels after long term treatment.

There are some limitations of the current study. We did not evaluate the markers of atherosclerosis and inflammation such as homocysteine and endothelin-1. Also the relation between MPV and atherosclerosis indicators such as CIMT, epicardial fatt tissue and aortic stiffness were not evaluated. We did not assessed body mass indexes and drug history of the patients and control group. Because our study had a retro¬spective design and we don't have information of all patients. It is possible that BMI and drug history changes may affect MPV measurements.

Conclusion

In conclusion, our study showed MPV, which is a marker of atherosclerosis and inflammation, was decreased after GH and IGF-1 normalization in patients with acromegaly. Also maintaining remission in these patients caused further decrease in MPV levels. This result might indicate the improvement of atherosclerosis and inflammation in patients with acromegaly after treatment. Also, well-designed trials that include other atherosclerotic markers are warranted to confirm this association

Ethical Approval: Ethics committee approval was obtained from the Clinic Ethical Committee of the Kocaeli University (decision number 2015/176).

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