FACTORS THAT LEAD TO MISINTERPRETATION OF ELEVATED MEAN PLATELET VOLUME LEVELS IN VARICOCELE PATIENTS: A NARRATIVE REVIEW

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Abstract

Varicocele is a condition characterized by abnormal dilation of the pampiniform plexus. It is estimated to have a prevalence of approximately 10– 15% among males, between 19–41% in men who are suffering from primary infertility, and around 80% in those with secondary infertility. A lot of work has been done to delve into the etiology of a varicocele, but to date the subject remains poorly understood. Necessitating further research regarding this topic is the fact that varicocele has been linked to many other vascular pathologies.

First of all, it is important to note that MPV is not directly associated with or a measure of platelet function in any way. Thus, these measurements of platelet indices such as mean platelet volume and PDW are not indicators of platelet function. Currently, a measure of platelet aggregation is the gold standard when platelet function is to be assessed. A study was done to check for links, but it did not find there to any correlation between platelet indices such as platelet count, mean platelet volume, platelet distribution width and that of platelet aggregation, which measures platelet function, such as platelet response with collagen, adenosine diphosphate and epinephrine which were recorded with the use of light transmission turbid metric platelet aggregometry in individuals deemed to be healthy.

Studies attempting to figure out the correlation between mean platelet volume and chronic inflammatory disease have found that greater mean platelet volume was observed among those suffering from rheumatoid arthritis particularly in the active phase and the inflammatory markers were elevated.

This article may be cited as: Arshad MA, Ahmad MR, Arshad W, Ullah I, A Zil-E-Ali. Factors that lead to misinterpretation of elevated mean platelet volume levels in varicocele patients: A narrative review. Ann Allied Health Sci.2019; 5(1):3-6.

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BACKGROUND

Varicocele is a condition characterized by abnormal dilation of the pampiniform plexus. It is estimated to have a prevalence of approximately 10– 15% among males, between 19–41% in men who are suffering from primary infertility, and around 80% in those with secondary infertility.[1-3]A lot of work has been done to delve into the etiology of a varicocele, but to date the subject remains poorly understood. Necessitating further research regarding this topic is the fact that varicocele has been linked to many other vascular pathologies.

In the medical field, a complete blood count is a routine examination that provides information regarding potential vascular pathology. In inflammatory conditions, mean platelet volume is a marker that is used to assess platelet function.[4] Mean platelet volume (MPV) is a useful indicator as a measure of platelet reactivity levels and it is recorded by an automatic haemogram device. The importance of mean platelet values is because a plethora of vascular disorders have been linked to abnormal mean platelet volumes. The size of platelets can have a significant bearing on their proper functioning. [5,6]Previous research has shown that mean platelet volume is very helpful when considering platelet activation and potential changes in function that could occur. [7-9]Mean platelet volume has shown to be markedly increased in vascular related pathologies such as cardiovascular diseases, cerebrovascular disease, and peripheral in light of this, there has been work done recently which has tried to define the relationship between mean platelet volume and its effect on varicocele in hopes of establishing a clinical link between the two MPV. [20-23]As past studies have shown, there is proof that the larger platelet size is linked strongly to platelets being more active, in both metabolic and enzymatic terms, when compared with smaller sized platelets. [24]Also, these platelet volume indices especially the mean platelet volume, have shown to increase in cases of a vascular disorders. [25-27]

artery disease. [9-13]Furthermore, a change in mean platelet volume can potentially contribute significantly to the pathogenesis of several diseases such as myocardial ischemia, stroke, coronary atherosclerosis, diabetes mellitus, hypertension, obesity and endometriosis.[13-19]

REVIEW

First of all, it is important to note that MPV is not directly associated with or a measure of platelet function in any way. Thus, these measurements of platelet indices such as mean platelet volume and PDW are not indicators of platelet function. Currently, a measure of platelet aggregation is the gold standard when platelet function is to be assessed. A study was done to check for links, but it did not find there to any correlation between platelet indices such as platelet count, mean platelet volume, platelet distribution width and that of platelet aggregation, which measures platelet function, such as platelet response with collagen, adenosine diphosphate and epinephrine which were recorded with

the use of light transmission turbidimetric platelet aggregometry in individuals deemed to be healthy. [28] De Luca et al. (2013) conducted a cohort study which consisted of 1016 diabetic patients who were underwent coronary angiography, but the results showed that mean platelet volume did not show any association with platelet reactivity. However, the researchers found that the increased mean platelet volume in patients suffering from Bernard–Soulier syndrome was an indicator of possible relationship between mean platelet volume and thrombosis. Bernard–Soulier syndrome is a bleeding disorder (not causing thrombosis) which is because of a defect in platelet membrane glycoprotein Ib/IX/V. In this syndrome, the characteristic findings are giant platelets and platelet aggregation with ristocetin is either nonexistent or greatly lowered. Thus, this syndrome is used because it is entirely different and ideal to the investigate the background of the study.[29]

To date, the methodology used to assess mean platelet volume is not well understood. On the contrary, it is evident that the mean platelet volume rises with time in EDTA anticoagulated samples, and it was found to be proportionate to the gap between the time at sample collection and time when lab analysis was done. [30] This is important because it is suspected that the gap between time of blood collection and the analysis in the lab is a key factor to be considered as it can have a direct effect on the measurement of mean platelet volume. When impedance counting was done, the mean platelet volume was shown to rise over time as the platelets were becoming swollen in the presence of EDTA. The study found that there was a 7.9% rise in mean platelet volume within the first half hour, and an increase of 13.4% after 24 hours. It is recommended that the mean platelet volume be measured 2 hours after the vein has been punctured to withdraw the blood sample.[31]This is because it has been shown before that the majority of the change that is to occur in the mean platelet volume does so within the first 2 hours after the blood is drawn. [31]Therefore, any deviation in the time between the puncture of the vein and subsequent lab analysis of the sample can have a considerable effect and render the data unreliable. To reduce the chances of error and record the mean platelet volume with the optimal consistency, the present study considers only the laboratory analyses which were carried out inside the first 2 hours after blood sample was collected.

In their study, McManus et al concluded that there is a definite correlation between IL-6 and the activation of platelets, particularly in patients suffering from some cardiovascular disease or those in the obese category.[38]Past research has revealed that megakaryocytes treated with testosterone showed an increase in level of expression of androgen receptor. This is suggestive of a link between the effects on the genome of megakaryocytes stimulated by an endogenous or exogenous substance, and increase in transcription in platelets, which leads to much higher protein content in the platelets circulating in blood. Lee et al found that platelets become activated by testosterone and this leads to an increase in the chance of cardiovascular disease occurring.[39] Furthermore, studies conducted by Sakamoto et al and Lotti et al have also shown that there is a link between varicocele and disorders related to andrology. They predicted and also found that a clinically defined higher grade of varicoceleis correlated with enlargement of prostate gland, chronic prostatitis, and lower urinary tract related symptoms. In addition, studies have demonstrated that varicocele shares another link with disorders related to testicular volume, prostate volume and andrological disorders (such as erectile dysfunction), in that they all show raised levels of IL-6.[40, 41]Work done by Glueck et al and Garrido et al illustrated that there is a relation between testosterone levels in the blood and thrombosis. Moreover, Garrido et al also determined that sex steroid hormones play a definite part in regard to platelet activation and that platelets themselves are capable of producing these hormones. To further provide support of this, studies by Dogan et al and Kebapcilar et al have shown that there is a correlation between mean platelet volume, endothelial injury caused by platelet activation in patients suffering from polycystic ovary syndrome, and in obese patients linked to androgen levels. [42-45] Studies conducted by Lippi et al, and El-Sayed et al, are the only ones to date that show a definite relation between mean platelet volume and sport activity.[46-47]

Studies in the past have shown that increased mean platelet volume correlates with diseases such as Familial Mediterranean Fever, Behcet's syndrome and Alzheimer's. [48-50]An interesting finding by Çoban and colleagues showed that there was a significantly greater mean platelet volume in obese patients (BMI greater than 30) compared to non-obese patients.[51]Furthermore, they found that obese patients after substantial weight loss showed a decrease in mean platelet volume that was of significance. This is very important because lower mean platelet volume lessens the risk of cardiovascular disease and this is done by a mechanism which is to reduce plaque formation and fatty deposits and thus suppressing the activation of thrombocytes. [52]In support of this, Kario and colleagues found that mean platelet volume and thrombocyte count was significantly greater among smokers and patients who had atherosclerosis compared to non-smokers and patients without any atherosclerosis. This indicates that the higher mean platelet volume contributes to advancement and progression of atherosclerosis. Also, among their key findings is that a 10% drop in mean platelet volume was observed in smokers who had atherosclerosis, 1 to 3 months after of cessation of smoking.[53]

Studies attempting to figure out the correlation between mean platelet volume and chronic inflammatory disease have found that greater mean platelet volume was observed among those suffering from rheumatoid arthritis particularly in the active phase and the inflammatory markers were elevated. [54]Also, mean platelet volume was shown to decrease upon treatment in patients suffering from ankylosing spondylitis. [55]Additionally, a study consisting of 95 subjects found that mean platelet volume was significantly greater in patients suffering from severe obstructive sleep apnea that lead to cardiovascular complications in comparison with a control group, further establishing a potential link between mean platelet volume and cardiovascular disease.[56] Similarly, a study tracked patients with sleep apnea and found that after 6 months of using CPAP device, there was a

significant reduction in mean platelet volume.[57]

REFERENCES

1. Sabanegh E, Agarwal A (2012) Male Infertility. Campbell Walsh Urology, 10th edn. Editors: Kavoussi LR, Partin AW, Novick AC, Peters CA. Volume 1. Chapter 21. pp 617–642.
2. Karag€uzel E (2013) LeydigH€ucresiveislevleri. Erkek €uremesistemihastaliklarivetedavisi. Edit€orler: Asci R, C ayan S, Erdemir F, Orhan I, Yaman €O, Usta MF, Kendirci M, Ekmekcioglu O, Kadioglu A. Istanbul Tip Kitabevipp 79– 86.
3. Jungwirth A, Diemer T, Dohle GR, Giwercman A, Kopa Z, Tournaye H, Krausz C. EAU guidelines on male infertility. Eur Urol. 2013;7.
4. Balta S, Demirkol S, Kucuk U, Unlu M. Hemostatic markers can be pivotal roles of risk factors for new-onset atrial fibrillation. Platelets. 2014 Nov 1;25(7):554-5. DOI:10.3109/09537104.2013.778398
5. Mangalpally KK, Siqueiros-Garcia A, Vaduganathan M, Dong JF, Kleiman NS, Guthikonda SJ: Platelet activation patterns in platelet size sub-populations: differential responses to aspirin in vitro. J Thromb Thrombolysis 2010;30:251-262.2
6. Honisch S, Gu S, Vom Hagen JM, Alkahtani S, Al Kahtane AA, Tsapara A, Hermann A, Storch A, Schöls L, Lang F, Stournaras C. Chorein Sensitive Arrangement of Cytoskeletal Architecture. Cell PhysiolBiochem 2015;37:399-408
7. Kai H, Kitadai Y, Kodama M, Cho S, Kuroda T, Ito M, Tanaka S, Ohmoto Y, Chayama K: Involvement of proinflammatory cytokines IL-1beta and IL-6 in progression of human gastric carcinoma. Anticancer Res 2005;25:709-713.
8. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD: Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des 2011;17:47-58.
9. Mutlu H, Artis TA, Erden A, Akca Z: Alteration in mean platelet volume and platicrit values in patients with cancer that developed thrombosis. ClinAppl Thromb Hemost 2013;19:331-333
10. Muscari A, Puddu GM, Cenni A, Silvestri MG, Giuzio R, Rosati M, Santoro N, Bianchi G, Magalotti D, Zoli M: Mean platelet volume (MPV) increase during acute non-lacunar ischemic strokes. Thromb Res 2009;123:587-591.
11. Berger JS, Eraso LH, Xie D, Sha D, Mohler ER 3rd: Mean platelet volume and prevalence of peripheral artery disease, the National Health and Nutrition Examination Survey, 1999-2004. Atherosclerosis 2010;213:586591.
12. Chu SG, Becker RC, Berger PB, Bhatt DL, Eikelboom JW, Konkle B, Mohler ER, Reilly MP, Berger JS. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. J Thromb Haemost. 2010 Jan;8(1):148-56.
13. Bath P, Algert C, Chapman N, Neal B; PROGRESS Collaborative Group (2004) Association of mean platelet volume with risk of stroke among 3134 individuals with history of cerebrovascular disease. Stroke 35:622–626.
14. Nadar S, Blann AD, Lip GY (2004) Platelet morphology and plasma indices of platelet activation in essential hypertension: effects of amlodipine-based antihypertensive therapy. Ann Med 36:552–557.
15. Papanas N, Symeonidis G, Maltezos E, Mavridis G, Karavageli E, Vosnakidis T, Lakasas G (2004) Mean platelet vol€ume in patients with type 2 diabetes mellitus. Platelets 15:475–478.
16. Coban E, Ozdogan M, Yazicioglu G, Akcit F (2005) The mean platelet volume in patients with obesity. Int J ClinPract 59:981–982.
17. Pikija S, Cvetko D, Hajduk M, Trkulja V (2009) Higher mean platelet vol€ume determined shortly after the symptom onset in acute ischemic stroke patients is associated with a larger infarct volume on CT brain scans and with worse clinical outcome. Clin Neurol Neurosurg 111:568–573.
18. Yasar AS, Bilen E, Yuksel IO, Arslantas U, Karakas F, Kirbas O, Bilge M (2010) Association between admission mean platelet volume and coronary patency after thrombolytic therapy for acute myocardial infarction. Turk Kardiyol DernArs 38:85–89.
19. Avcioglu SN, Altinkaya S€O, K€ uc € uk M, Demircan-Sezer S, Y€uksel H (2014) Can platelet indices be new biomarkers for severe endometriosis? ISRN ObstetGynecol, DOI: 10.1155/2014/713542.
20. Bozkurt Y, Soylemez H, Sancaktutar AA, Isla- moglu Y, Kar A, Penbegul N, Atar M, Bodakci MN, Hatipoglu NK. Relationship between mean platelet volume and varicocele: a preliminary study. Urology 2012; 79: 1048-51.
21. Mahdavi-Zafarghandi R, Shakiba B, Keramati MR, Tavakkoli M. Platelet volume indices in patients with varicocele. ClinExpReprod Med 2014; 41: 92-5.
22. Çoban S, Keleş I, Biyik I, Güzelsoy M, Türkoğlu AR, Özgünay T, Ocak N. Is there any relationship between mean platelet volume and varicocele? Andrologia 2015; 47: 37-41
23. Coban S, Keles I, Biyik İ, Guzelsoy M, Turkoglu AR, Ocak N. Does varicocele correction lead to normalization of preoperatively elevated mean platelet volume levels? Can UrolAssoc J 2015; 9: E5
24. Nena E, Papanas N, Steiropoulos P, Zikidou P, Zarogoulidis P, Pita E, et al. Mean Platelet Volume and Platelet Distribution Width in non-diabetic subjects with obstructive sleep apnoea syndrome: new indices of severity? Platelets 2012;23:447-54.
25. Corash L, Tan H, Gralnick HR. Heterogeneity of human whole blood platelet subpopulations. I. Relationship between buoyant density, cell volume, and ultrastructure. Blood 1977;49:71-87.
26. Thompson CB, Eaton KA, Princiotta SM, Rushin CA, Valeri CR. Size dependent platelet subpopulations: relationship of platelet volume to ultrastructure, enzymatic activity, and function. Br J Haematol 1982;50:509-19.
27. Khandekar MM, Khurana AS, Deshmukh SD, Kakrani AL, Katdare AD, Inamdar AK. Platelet volume indices in patients with coronary artery disease and acute myocardial infarction: an Indian scenario. J Clin Pathol 2006;59:146-9.
28. Beyan C, Kaptan K, Ifran A (2006) Platelet count, mean platelet volume, platelet distribution width, and plateletcrit do not correlate with optical platelet aggregation responses in healthy volunteers. J Thromb Thrombolysis 22:161–164.

29. De Luca G, Verdoia M, Cassetti E, Schaffer A, Di GG, Bertoni A, Di VC, Sampietro S, Aimaretti G, Bellomo G, Marino P, Sinigaglia F; Novara Atherosclerosis Study (NAS) group (2013) Mean platelet volume is not associated with platelet reactivity and the extent of coronary artery disease in diabetic patients. Blood Coagul Fibrinolysis 24:619–624.
30. Bath PM, Butterworth RJ (1996) Platelet size: measurement, physiology and vascular disease. Blood Coagul Fibrinolysis 7:157–161.
31. Lance MD, van Oerle R, Henskens YM, Marcus MA (2010) Do we need time adjusted mean platelet volume measurements? Lab Hematol 16:28–31.
32. Corash L (1983) Platelet sizing: techniques, biological significance, and clinical applications. Curr Top Hematol 4:99–122
33. Jackson SR, Carter JM (1993) Platelet volume: laboratory measurement and clinical application. Blood Rev 7:104–113
34. Threatte GA (1993) Usefulness of the mean platelet volume. Clin Lab Med 13:937–950
35. Howarth S, Marshall LR, Barr AL, Evans S, Pontre M, Ryan N (1999) Platelet indices during normal pregnancy and preeclampsia. Br J Biomed Sci 56:20–22
36. Papanas N, Symeonidis G, Maltezos E et al. (2004) Mean platelet volume in patients with type 2 diabetes mellitus. Platelets 15:475–478
37. Yilmaz MB, Saricam E, Biyikoglu SF et al. (2004) Mean platelet volume and exercise stress test. J Thromb Thrombolysis 17:115–120
38. McManus DD, Beaulieu LM, Mick E, Tanriverdi K, Larson MG, Keaney JF Jr, Benjamin EJ, Freedman JE. Relationship among circulating inflammatory proteins, platelet gene expression, and cardiovascular risk. Arterioscler Thromb VascBiol 2013; 33: 2666-73.
39. Lee SJ, Kwon JA, Cho SA, Jarrar YB, Shin JG. Effects of testosterone and 17β-oestradiol on expression of the G protein-coupled receptor P2Y12 in megakaryocytic DAMI cells. Platelets 2012; 23: 579-85.
40. Moretti E, Collodel G, Mazzi L, Campagna M, Iacoponi F, Figura N. Resistin, interleukin-6, tumor necrosis factor-alpha, and human semen parameters in the presence of leukocytospermia, smoking habit, and varicocele. FertilSteril 2014; 102: 354-60.
41. Koçak I, Yenisey C, Dündar M, Okyay P, Serter M. Relationship between seminal plasma interleukin-6 and tumor necrosis factor alpha levels with semen parameters in fertile and infertile men. Urol Res 2002; 30: 263-7
42. Glueck CJ, Friedman J, Hafeez A, Hassan A, Wang P. Testosterone, thrombophilia, thrombosis. Blood Coagul Fibrinolysis 2014; 25: 683-7.
43. Garrido A, Munoz Y, Sierralta W, Valladares L. Metabolism of dehydroepiandrosterone sulfate and estrone-sulfate by human platelets. Physiol Res 2012; 61: 381-8.
44. Dogan BA, Arduc A, Tuna MM, Karakılıc E, Dagdelen I, Tutuncu Y, Berker D, Guler S. Association of mean platelet volume with androgens and insulin resistance in nonobese patients with polycystic ovary syndrome. Int J Endocrinol Metab. 2014 Oct;12(4).
45. Kebapcilar L, Taner CE, Kebapcilar AG, Sari I. High mean platelet volume, low-grade systemic coagulation and fibrinolytic activation are associated with androgen and insulin levels in polycystic ovary syndrome. Arch Gynecol Obstet. 2009 Aug 1;280(2):187-93.
46. Lippi G, Salvagno GL, Danese E, Skafidas S, Tarperi C, Guidi GC, Schena F. Mean platelet volume (MPV) predicts middle distance running performance. PloS one. 2014 Nov 11;9(11): e112892.
47. El-Sayed MS. Exercise and training effects on platelets in health and disease. Platelets 2002; 13: 261-6.
48. Acikgoz N, Karincaoglu Y, Ermis N, Yagmur J, Atas H, Kurtoglu E, Cansel M, Barutcu I, Pekdemir H, Ozdemir R, (2010) Increased mean platelet volume in Behcet's disease with thrombotic tendency. Tohoku J Exp Med 221:119–123.
49. Arica S, Ozer C, Arica V, Karakus¸ A, Celik T, G€unes ac ar R (2012) Evaluation of the mean platelet volume in children with familial Mediterranean fever. RheumatolInt 32:3559– 3563.
50. Yesil Y, Kuyumcu ME, Cankurtaran M, Uz B, Kara A, Kilic MK, Halil M, Ulger Z, Yavuz BB, Haznedaroğlu IC, Ariogul S. Increased mean platelet volume (MPV) indicating the vascular risk in Alzheimer's disease (AD). Arch Gerontol Geriatr Suppl. 2012 Sep 1;55(2):257-60.
51. Çoban E, Özdoğan M, Yazıcıoğlu G, et al. The mean platelet volume in patients with obesity.Int J ClinPrac 2005;59:981-2. DOI:10.1111/j.1742-1241.2005.00500.x
52. Coban E, Yilmaz A, Sari R. The effect of weight loss on the mean platelet volume in obese patients. Platelets. 2007 Jan 1;18(3):212-6. DOI:10.1080/09537100600975362
53. KARIO K, MATSUO T, NAKAO K. Cigarette smoking increases the mean platelet volume in elderly patients with risk factors for atherosclerosis. Clin Lab Haematol. 1992 Dec;14(4):281-7. DOI:10.1111/j.1365-2257.1992. tb00103.x
54. Milovanovic M, Nilsson E, Järemo P. Relationships between platelets and inflammatory markers in rheumatoid arthritis. ClinChimacta. 2004 May 1;343(1-2):237-40. DOI:10.1016/j.cccn.2003.12.030
55. Yazici S, Yazici M, Erer B, Erer B, Çalik Y, Bulur S, Ozhan H, Ataoglu S. The platelet functions in patients with ankylosing spondylitis: anti-TNF-α therapy decreases the mean platelet volume and platelet mass. Platelets. 2010 Jan 1;21(2):126-31. DOI:10.3109/09537100903470306
56. Varol E, Ozturk O, Gonca T, Has M, Ozaydin M, Erdogan D, Akkaya A. Mean platelet volume is increased in patients with severe obstructive sleep apnea. Scand J Clin Lab Invest. 2010 Nov 1;70(7):497-502. DOI:10.3109/00365513.2 010.520733
57. Varol E, Ozturk O, Yucel H, Gonca T, Has M, Dogan A, Akkaya A. The effects of continuous positive airway pressure therapy on mean platelet volume in patients with obstructive sleep apnea. Platelets. 2011 Nov 1;22(7):552-6. DOI:10.3109/09537104.2011.578182