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Original Article

Mean platelet volume and varicocele: comparison between adolescents and adults

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Abstract: Purpose: To evaluate the association between varicocele and MPV values in pediatric and adult patients. And its association with different clinical parameters. Materials and methods: We retrospectively analyzed the medical charts of patients treated for varicocele at our Institution between December 2010 and December 2014. The study patients were divided into three groups: group 1- patients with varicocele without testicular hypotrophy treated for scrotal discomfort or infertility (percutaneous varicocelecomy-scheloembolization); group 2- (control group) patients without varicocele; group 3- patients with varicocele and testicular hypotrophy (laparoscopic varicocelectomy). The study compared the grade of varicocele and MPV before surgery; age-related MPV and MPV cumulative value between the groups. Results: After revision of the study 145 medical charts (group 1: 47 patients, group 2: 52 patients, group 3: 46 patients), and in compliance with the inclusion and exclusion criteria established, 127 patients were considered for the study; we evaluated 42 patients in group 1, 46 patients in group 2 and 39 patients in group 3. Patients with varicocele had higher MPV value than controls but only in adulthood. Testicular hypotrophy associated with varicocele is not a confusing factor. Conclusions: Even if MPV is higher in adults with varicocele as reported by other studies, but this result is not thrue in adolescents and its is not correlated with testicular hypotrophy; some confunding factors, i.e. andrological disease or smoking status, could be the reasons of different results present on medical literature.

Keywords: Mean platelet volume, pediatric, varicocele

Introduction

Idiopathic varicocele is the most commonly diagnosed peripubertal andrologic disease and the most treatable cause of male-related impaired fertility potential. In recent literature some authors tried to correlate varicocele with mean platelet volume (MPV), giving a new clinical value to this relationship [1-4].

These authors supported their findings suggesting that there is a correlation between grade of varicocele, defined as a vascular disease, and platelet activation which results in higher MPV value [1].

As reported by Beyan and Varol, in these studies there are some ambiguous data that could invalidate such relationship [5, 6].

The aim of this study was to evaluate the association between varicocele and MPV values in pediatric and adult patients trying to explain which factors may affect this parameter.

Materials and methods

We retrospectively analyzed the medical charts of patients treated for varicocele at our Institution between December 2010 and December 2014. The study was approved by interrnal scientific board.

Following the guidelines of the European Association of Urology, according to which varicocelectomy is indicated if associated with testicular hypotrophy and infertility, we retrospectively analyzed patients treated for varicocele in the pediatric age and adulthood. The study patients were divided into three groups: group 1-patients with varicocele without testicular hypotrophy treated for scrotal discomfort or infertility (percutaneous varicocelecomy-scheloembolization); group 2- (control group)

Table 1. MPV value per group

	Group 1	Group 2	Group 3	*P* value	*P* value
Age	28±8.7 years	10.2±2.3	16.7±2.2	P<0.05 (1 VS 2, 3)	P>0.05 (2 VS 3)
MPV value	8.4±0.9 fL	7.6±0.9 fL	7.6±0.8 fL	P<0.05 (1 VS 2, 3)	P>0.05 (2 VS 3)
	<18 YRS	>18 YRS	*P* value		
MPV value	8.1±0.9 fL	7.7±0.9 fL	P<0.05		
Group 1	7.9±1.0 fL	8.4±0.9 fL	P<0.05		
Group 2	7.7±0.9 fL	7.5±0.9 fL	P>0.05		
Group 3	7.6±0.8 fL	7.7±0.8 fL	P>0.05		

patients without varicocele and normal testicular volume; group 3-patients with varicocele and testicular hypotrophy (laparoscopic varicocelectomy).

Varicocele was classified into three groups: grade I-palpable at Valsalva only; grade II-palpable without Valsalva; grade III-visible. Testicular hypotrophy was defined as a testicular volume loss >20% with respect to the contralateral testis, assessed using Siemens Sonoline Elegra Ultrasound Imaging System (Siemens AG, Munich, Germany) with a 7.5 MHz probe. Measurements of the testicular length, width, and height were obtained by using electronic calipers. Testicular volume was calculated with the formula used for a prolate ellipsoid: [Vol (ml) = 523 × *L* × *W* × *H*].

The inclusion criteria for this study were the following: left varicocele with or without testicular hypotrophy; no previous infections of the urinary system; no previous testicular traumas nor previous inguinal and scrotal surgeries. Control group: patients treated for phimosis without varicocele with normal testicular volume. For group 2 and 3 we considered only non-smokers with normal Body Mass Index per age who practised regular sport activity (at least 2 times a week for at least 2 hours). We also evaluated the pubertal status of each patient. Patients lost to follow-up were excluded from the study. The clinical status of patients in group 1 (i.e. hypertension, hystory of coronary artery disease, BMI, smoking status) was not considered in term of exclusion criteria in order to have a cohort of adult patients similar to those reported in other studies (no data are available about exclusion criteria or patients' clinical status).

Evaluation criteria

The study compared the grade of varicocele and MPV before surgery; age-related MPV and MPV cumulative value between the groups. The values collected from all the varicocele groups were compared with the values recorded for the control group.

Blood samples were collected in primary blood tubes containing K_2EDTA (Terumo Europe N.V., Leuven, Belgium) before surgery. All samples were sent to the same laboratory (University Hospital) and analyzed under controlled conditions of temperature and humidity within 2 hours. A range of 7-10 fL was considered as normal.

The primary outcome of the study was to define a clinical relationship between MPV value and presence of varicocele; the secondary outcome was to evaluate the correlation between pubertal status, age and testicular hypotrophy. We also tried to identify the MPV cutoff value for a prognostic indication of vascular risk.

Statistical analysis was performed using the student t-test, chi-square and Fischer exact tests. Significance value was set at P<0.05. The analysis was conducted with the Statistical Package for Social Sciences (SPSS) software version 15 for Windows SPSS Inc., Chicago, USA.

Results

After revision of 145 medical charts (group 1: 47 patients, group 2: 52 patients, group 3: 46 patients), and in compliance with the inclusion and exclusion criteria established, 127 patients were considered for the study; 18 were excluded from the study, 5 form group 1, 6 from group 2 and 7 from group 3, since lost to follow-up. We evaluated 42 patients in group 1, 46 patients in group 2 and 39 patients in group 3.

None of the patients had grade I varicocele; 36 had grade II and 45 had grade III varicocele. There were not significant statistical differenc-

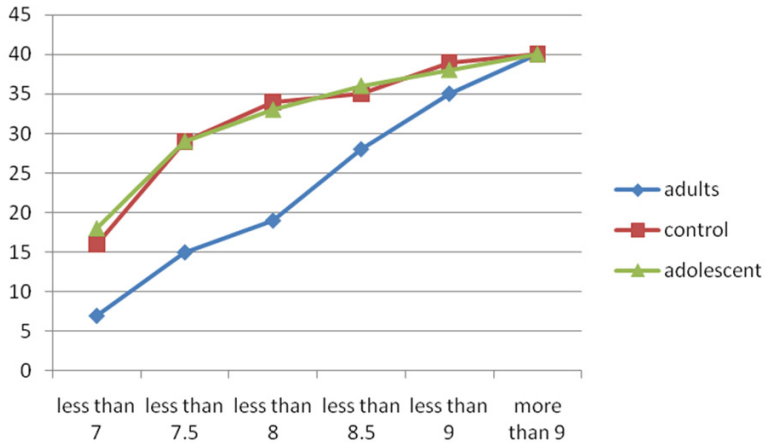

Figure 1. Cumulative percentage of patient per group per MPV value.

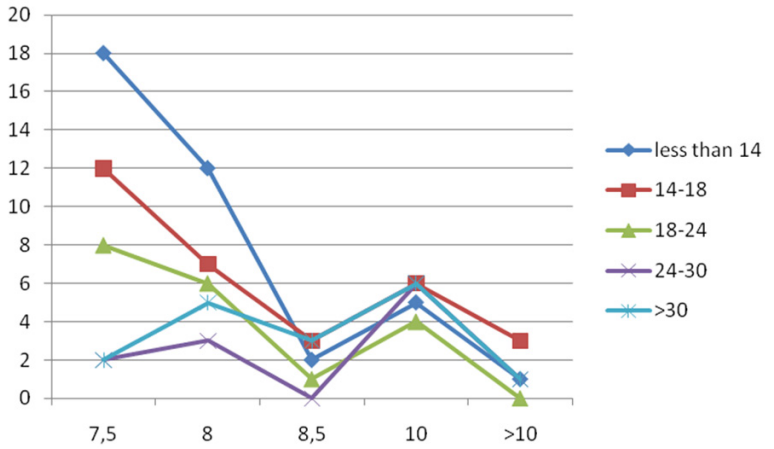

Figure 2. Patients distribution per age range and MPV value.

es as for grade of varicocele at surgery in the groups (group 1 vs. 3) (P>0.05). It was not possible to correlate testicular hypotrophy (group 3) with varicocele grade (II vs III) (P>0.05). There was not a significant statistical difference between groups 2 and 3 in terms of pubertal status. All patients in group 2 and 3 had BMI less than 20. Results are reported in **Table 1**.

Age range: group 1 28±8.7 years (age range 15-51 years), group 2 10.2±2.3 years (age range 8-22 years), and group 3 16.7±2.2 years (age range 9-21 years). There was a statistical difference in terms of age range (P<0.05) between group 1 and groups 2 and 3 but not between group 2 and 3 (P>0.05).

MPV value: if we consider the value per group, 2 patients in group 1, 8 patients in group 2 and 6 patients in group 3 respectively had MPV abnormal values (P>0.05). MPV was 8.4±0.9 fL in group 1 (range 7-11.1), 2 7.6±0.9 fL in group (range 6.1-10.5) and 7.6±0.8 fL in group 3 (range 6.4-10.2). There was a statistical difference between group 1 and groups 2 and 3 (P<0.05) but not between group 2 and group 3 (P>0.05) (P=0.91). Age adjustment (groups 1, 2 and 3) gave interesting results when we considered patients aged <18 years vs. >18 years: the first group had 8.1±0.9 fL while the second group had 7.7±0.9 fL (P<0.05 with P=0.002). Age-adjusted MPV values in group 3 (varicocele with testicular hypotrophy) and group 2 (control group) showed no significant statistical differences between patients aged <18 years vs. >18 years (P>0.05), while there was a statistical difference between these two subgroups in group 1 (P<0.05).

MPV values were then grouped considering the cumulative % in patients according to the following ranges: <7.0 fL, <7.5 fL, <8 fL, <8.5 fL, <9 fL, >9.5 fL (**Figure 1**). The distribution of patients per MPV range was significantly higher with MPV less than 8.5 fL for groups 2 and 3 while group 1 had higher rates of distribution with MPV >8.5 fL. As showed in **Figure 2**, there was a progressive reduction of subjects with an age-adjusted MPV value less than 8.5 fL. The chi-square test was used to evaluate the association between the MPV value and the distribution of patients considering 8.5 fL as the cut-off value (with and without varicocele). In general the data collected did not show a statistically significant difference, *p* value >0.05, but observation of data collected for group 1 vs. 3 showed a statistical differences between these two groups with a *p* value less than 0.05 (P=0.02). This means that adults with varicocele had a MPV value higher than pediatric patients. Although 8.5 fL is still within

the normal range, a comparison with the results obtained in other studies confirmed that adults with varicocele showed higher MPV values. It is clear that some ambiguous factors in adulthood, i.e. infertility and andrologcial conditions or BMI, may be the cause for such higher value. The presence of testicular hypotrophy seems to be an indipendent factor without consequences on MPV values. This finding is supported by comparing the data collected from group 2 (patients without varicocele with normal testicular volume) and group 3.

Discussion

Some Authors reported the correlation between varicocele and higher MPV values, but at present this relationship is still under scientific consideration in order to better understand the real scope of such a finding [1-4].

Other Authors maintain that the results obtained in these studies should be further investigated and that MPV can be used for diagnostic purposes only if it is carefully standardized [5, 6].

Bozkurt et al first reported the relationship between MPV and varicocele. They found that MPV was higher in patients with varicocele with a positive correlation between grade of varicocele, MPV value and diameter of left spermatic vein. Their study had some limits, i.e. no data were collected about control group or study group, especially for infertility status, prostatisis or other factors such as Body Mass Index or presence of infection. The results of semen analysis showed that progressive motility and sperm count in the varicocele group are higher than in the control groups, but the study did not offer any observation regarding this finding. Another point of criticism was that the study did not consider either testicular volume or hormonal values, especially for patients with varicocele and infertility [1].

Also Mahdavi-Zafarghandi et al and Coban et al had such limits because they did not consider patients' smoking status, BMI or if they were affected by testicular hypotrophy. An interesting result obtained by Coban et al is the normalization of MPV values after surgery but, again, this new finding was not thoroughly explained [2-4].

All these Authors maintained that platelet activation may play a role in the pathophysiologic basis of varicocele. But it is necessary to give reasons for such activation and this is why in this study we tried to explain the mechanism of platelet activation from a pathophysiological point of view.

Platelets drive coagulation and they also play an important role in inflammation. As reported by Davila et al, platelets from patients with sickle cell disease circulate in an activated state, as judged by phosphatidyl serine exposure and P-salectin expression on their surface, as well as by platelet microparticle formation. This activated state was shown to persit at baseline and during crisis [7]. When platelets are activated they produce cytokines, like Il-6 [7]. McManus et al demonstrated that there is a clear relationship between il-6 and platelets activation, especially in obesity and cardiovascular disease. Their results reported a strong connection between the circulating inflammatory biomarkers C-reactive protein and IL-6 and platelet gene expression [8].

But there are other interesting findings reported in the literature: administration of il-6 to humans was associated with an increase in circulating platelet counts and dose-dependently il-6 increased thrombopoietin levels [9]. Thrombopoietin appears to have a major role in controlling platelet development from megakaryocytes and this action is probably modulated by a series of cytochines such as il-6; therefore, higher il-6 is associated with higher MPV value [10-12].

Clinically, it was reported that megakaryocytes treated with testosterone resulted in an increased expression of the androgen receptor thus suggesting that the genomic effects induced by endogenous or esogenous molecules in megakaryocytes may contribute to increase platelet transcript levels which, in its turn, may result in increased levels of the proteins in circulating platelets. In their study Lee et al concluded that testosterone may activate platelets and thus can be associated with higher cardiovascular risk [13].

Also Glueck et al and Garrido et al reported the association between testosterone levels and thrombosis; Garrido et al concluded that sex steroid hormones have a role in the regulation

of platelet activation and that platelets have a capacity to produce sex steroid hormones. This association is also demonstrated by Dogan et al and Kebapcilar et al who found a relationship between MPV value, endothelial injury by platelet activation in patients with polycystic ovary syndrome and obesity with androgen levels [14-17].

The association between varicocele and hypogonadism, as well as between varicocele and other andrological diseases is well known. [18-23].

This mechanism of interaction between varicocele and andrological disorders is well documented by Sakamoto et al and by Lotti et al. They speculated and demonstrated that a higher varicocele grade is associated with enlarged prostate and chronic prostatitis and other low urirary tract symptoms (LUTS). Varicocele, testicular volume, prostate volume and andrological disorders (i.e. premature ejaculation, erectile dysfunction) seem to be strictly associated, since they all result in increased il-6 levels [24, 25].

The explanation of the pathophysiological correlation between varicocele, infertility, andrological disease and pro-inflammatory levels of il-6 and other platelets activators is an essential part of scientific studies as well as the accurate enrolment of patients.

For these reasons all reported results about the relationship between MPV and varicocele showed many ambiguous elements; for instance, data about infertile patients without any indication of the patient's andrological status, i.e. hormonal levels or the presence of prostatisis or possible causes of infertility, could represent a significant bias for a study. As reported in literature, the Body Mass Index is essential to assess andrological disorders and should therefore be included in the study data. Other confusing factors included the absence of data regarding the patient's smoking status (associated with infertility and higher il-6 levels) and sport activity, being Lippi et al and El-Sayed et al the only authors who report the essential relationship between sport activity and MPV value [25-27].

The results obtained in this study demonstrate that an accurate selection of the cohort of subjects, leads to minimum differences in MPV values between varicocele and non-varicocele groups in pediatric-adolescent patients; MPV values are higher in adults probably because there are more ambiguous factors that are not considered when recording the data (i.e. hypertension, metabolic syndrome, obesity or high BMI, smoking status), among which the most clinically significant is the patient's infertility with andrological disorders. In this study only 16 out of 127 patients had an abnormal MPV value (normal range: 7-10 fL); our results showed that MPV in adults tends to be higher than in adolescents or in the control group, but always within normal range values. Focusing on uroandrological disorders, no data are available about prostatitis, LUTS or hormonal values in any of the studies regarding the association between MPV value and varicocele. As reported in this study, testicular hypotrophy associated with varicocele does not seem to be an important factor affecting MPV values. If we consider the association between testicular demage, varicocele and possible development of hypogonadism, the presence of testicular hypotrophy does not represent real hypogonadism; for this reason the testis should never suffer any damage if adequately treated. This is an interesting point to study in patients with varicocele and the MPV value could be probably used as a predicting factor for testicular hypotrophy.

This study also has some limits: it was not possible to evaluate the clinical status of adults; adults patients were treated for infertility and in this study no data about patients' fertility status are reported (i.e. semen analysis, azoospermia, hypogonadism, hormonal levels); postoperative MPV value was not evaluated, as suggested by Coban et al [4] and no data were recorded about the hormonal levels in adolescent patients.

Conclusions

This is the first study in medical literature comparing MPV values in young and adults patients with and without varicocele. The data collected from the study groups showed that there is a progressive age-related increase in MPV values and this is due to many factors which include, but are not limited to, varicocele. Other possible causes of infertility, presence of andrological disorders (i.e. prostatitis), smoking status

and metabolic syndrome are only some of the ambiguous factors that may affect MPV values. For this reason such factors should always be taken into account since varicocele alone may not be the sole cause of higher MPV values in this group of patients.

Disclosure of conflict of interest

None.

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References

[1] Bozkurt Y, Soylemez H, Sancaktutar AA, Islamoglu 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.

[2] Mahdavi-Zafarghandi R, Shakiba B, Keramati MR, Tavakkoli M. Platelet volume indices in patients with varicocele. Clin Exp Reprod Med 2014; 41: 92-5.

[3] 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.

[4] 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 Urol Assoc J 2015; 9: E5-9.

[5] Beyan C. Re: Bozkurt et al.: relationship between mean platelet volume and varicocele: a preliminary study (urology 2012; 79: 1048-1051). Urology 2012; 80: 962.

[6] Varol E, Ozaydin M. The relationship between mean platelet volume and varicocele. Andrologia 2015; 47: 245.

[7] Davila J, Manwani D, Vasovic L, Avanzi M, Uehlinger J, Ireland K, Mitchell WB. A novel inflammatory role for platelets in sickle cell disease. Platelets 2014; 30: 1-4.

[8] 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 Vasc Biol 2013; 33: 2666-73.

[9] Kaser A, Brandacher G, Steurer W, Kaser S, Offner FA, Zoller H, Theurl I, Widder W, Molnar C, Ludwiczek O, Atkins MB, Mier JW, Tilg H. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. Blood 2001; 98: 2720-5.

[10] Liu R, Gao F, Huo J, Yi Q. Study on the relationship between mean platelet volume and platelet distribution width with coronary artery lesion in children with Kawasaki disease. Platelets 2012; 23: 11-6.

[11] Engelhardt PF, Seklehner S, Brustmann H, Lusuardi L, Riedl CR. Immunohistochemical expression of interleukin-2 receptor and interleukin-6 in patients with prostate cancer and benign prostatic hyperplasia: Association with asymptomatic inflammatory prostatitis NIH category IV. Scand J Urol 2014; 3: 1-7.

[12] Oncel MY, Ozdemir R, Yurttutan S, Canpolat FE, Erdeve O, Oguz SS, Uras N, Dilmen U. Mean platelet volume in neonatal sepsis. J Clin Lab Anal 2012; 26: 493-6.

[13] 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.

[14] Glueck CJ, Friedman J, Hafeez A, Hassan A, Wang P. Testosterone, thrombophilia, thrombosis. Blood Coagul Fibrinolysis 2014; 25: 683-7.

[15] Garrido A, Munoz Y, Sierralta W, Valladares L. Metabolism of dehydroepiandrosterone sulfate and estrone-sulfate by human platelets. Physiol Res 2012; 61: 381-8.

[16] 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; 12: e18642.

[17] 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; 280: 187-93.

[18] Dabaja A, Wosnitzer M, Goldstein M. Varicocele and hypogonadism. Curr Urol Rep 2013; 14: 309-14.

[19] Sakamoto H, Ogawa Y. Is varicocele associated with underlying venous abnormalities? Varicocele and the prostatic vemous plexus. J Urol 2008; 180: 1427-31.

[20] Lotti F, Corona G, Mancini M, Biagini C, Colpi GM, Innocenti SD, Filimberti E, Gacci M, Krausz C, Sforza A, Forti G, Mannucci E, Maggi M. The association between varicocele, premature ejaculation and prostatitis symptoms: possible mechanisms. J Sex Med 2009; 6: 2878-87.

[21] Lotti F, Corona G, Vignozzi L, Rossi M, Maseroli E, Cipriani S, Gacci M, Forti G, Maggi M. Metabolic syndrome and prostate abnormalities in male subjects of infertile couples. Asian J Androl 2014; 16: 295-304.

[22] Ciftci H, Gumuş K, Yagmur I, Sahabettin S, Çelik H, Yeni E, Savas M, Gulum M. Assessment of Mean Platelet Volume in men with vasculogenic and nonvasculogenic erectile dysfunction. Int J Impot Res 2015; 27: 38-40.

[23] Gat Y, Gornish M, Heiblum M, Joshua S. Reversal of benign prostate hyperplasia by selective occlusion of impaired venous drainage in the male reproductive system: novel mechanism, new treatment. Andrologia 2008; 40: 273-81.

[24] 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. Fertil Steril 2014; 102: 354-60.

[25] 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.

[26] 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; 9: e112892.

[27] El-Sayed MS. Exercise and training effects on platelets in health and disease. Platelets 2002; 13: 261-6.