Journal of Paediatrics and Child Health



doi:10.1111/jpc.12301

ORIGINAL ARTICLE

# Assessment of atherosclerosis in obese adolescents: Positive correlation of mean platelet volume and carotid intima media thickness

Nur Arslan,[1] Balahan Makay,[1] Şamil Hızlı,[1] Ali Koçyiğit,[2] Fatih Demircioğlu,[1] Alpaslan Sedat Tuncel[2] and Handan Çakmakçı[2]

Departments of [1]Pediatrics and [2]Radiology, Dokuz Eylul University Hospital, Izmir, Turkey

**Aims:** This study aims to assess the correlation of mean platelet volume (MPV) and common carotid artery (CCA) thickness in a population of obese adolescents.

**Methods:** Sixty-eight patients and 23 controls were enrolled. Anthropometric measurements, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, hemoglobin, white blood cell count, platelet count, MPV and insulin resistance by homeostasis model of assessment of insulin resistance were investigated. Furthermore, CCA thickness was measured by high-resolution ultrasound.

**Results:** MPV and the left CCA thickness were significantly higher in obese adolescents than the healthy controls. The association between MPV and left CCA was checked by linear regression analysis. MPV explained 19% of the variation in left CCA ($P < 0.001$). At multiple regression analysis, MPV maintained a positive association with the left CCA thickness ($P = 0.002$) independently of fatty liver grade, relative weight, total cholesterol and homeostasis model of assessment of insulin resistance.

**Conclusion:** MPV is significantly correlated with CCA thickness in obese adolescents.

**Key words:** carotid intima media thickness; childhood; mean platelet volume; non-alcoholic fatty liver disease; obesity.

**What is already known on this topic**

1 Carotid intima media thickness (IMT) is a widely used non-invasive marker to assess atherosclerosis.
2 Regarding large platelets are haemostatically more active, mean platelet volume (MPV) may be used as a marker of platelet activation, which is an important step in early atherosclerosis.
3 Obesity in childhood and adolescence has been shown to be related to increased IMT in many studies.

**What this paper adds**

1 MPV is significantly correlated with common carotid artery thickness independently of fatty liver grade, relative weight, total cholesterol and homeostasis model assessment-insulin resistance.
2 Thus, MPV may be used as a possible indicator of subclinical atherosclerosis.
3 MPV may, in part, help to determine atherosclerosis risk in patients with non-alcoholic fatty liver disease.

Obesity is a widespread medical problem affecting children and adolescents in many countries around the world.[1–3] Obesity means an excess fat deposition in the body. Non-alcoholic fatty liver disease (NAFLD) describes a condition caused by a build-up of fat within liver cells in the absence of alcohol consumption, which is linked to being obese or overweight in many cases.[4–8] NAFLD is also associated with increased risk of atherosclerosis and consequent cardiovascular disease[9–11] as well as increased risk of insulin resistance (IR) and type 2 diabetes mellitus.[12–14] Therefore, the increasing prevalence of obesity among children and adolescents represents an important health problem. Atherosclerosis, beginning in childhood, may be predictive of coronary artery disease in adulthood.[15,16] Therefore, early diagnosis of atherosclerosis is essential to prevent its future complications.

During atherogenesis, platelet activation and aggregation along with migration of smooth muscle cells from the media to endothelium and consequent proliferation are the early events. Previous studies showed that platelet size is correlated with platelet function and activation, and large platelets are hemostatically more active.[17,18] Therefore, mean platelet volume (MPV) may be used as a marker of platelet activation, which may also reflect atherosclerosis.[19,20] Similarly, carotid artery intima media thickness (IMT) is a widely used non-invasive marker to assess atherosclerosis in researches.[21] Obesity in childhood and adolescence has been shown to be related to increased IMT in many studies.[9–11,22–24] Besides, we recently showed that

**Correspondence:** Professor Nur Arslan, Department of Pediatrics, Dokuz Eylul University Hospital, 35340 Balçova-Izmir, Turkey. Fax: +90 232 4123649; email: nur.arslan@deu.edu.tr

Conflict of interest: The authors have no conflict of interest.

Accepted for publication 28 April 2013.

the mean MPV values were higher in obese adolescents, particularly in patients with NAFLD, than their healthy peers.[25] The aim of this study was to evaluate whether MPV is a reliable reflector of atherosclerosis such as carotid artery IMT in an obese adolescent population.

## Patients and Methods

Patients aged 11–18 years who were diagnosed as exogenous obesity in the Pediatric Gastroenterology Department of Dokuz Eylül University Hospital (Izmir, Turkey) were enrolled in this case control study. Ethics approval and informed consent of the parents and patients were obtained before entering the study. The body mass index (BMI) of all children was calculated as weight divided by height squared (kg/m$^2$). Obesity was defined as a BMI exceeding 95th percentile.[26,27] In addition, relative weight for height was calculated for each child.

A total of 68 exogenous obese patients (29 male and 39 female, mean age 13.8 ± 1.5 years) were enrolled in the study. The patients who had diabetes mellitus, Cushing syndrome, growth hormone deficiency, hypertension, familial hypercholesterolaemia, chronic liver disease and used corticosteroids were not included. The study population was divided into three groups: patients without hepatosteatosis (group 1), patients with grade 1 hepatosteatosis (group 2) and patients with grade 2 or 3 hepatosteatosis (group 3). Diagnosis of NAFLD was made by the paediatric gastroenterologist based on increased echogenicity via ultrasound compatible with fatty infiltration of the liver with or without elevated alanine aminotransferase (ALT) levels. NAFLD grading by ultrasound was done by the same radiologist (A.T.S.) as follows:[28,29] *Grade 1 (mild):* a slight diffuse increase in the hepatic parenchymal echogenity along with normal visualisation at intrahepatic vessel borders and diaphragm; *Grade 2 (moderate):* a moderately diffuse increase in the hepatic parenchymal echogenity along with a slightly impaired visualisation of the intrahepatic vessel borders and diaphragm; and *Grade 3 (severe):* a severe increase in the hepatic parenchymal echogenity along with poor or no visualisation of intrahepatic vessel borders, diaphragm and posterior portion of the right lobe.

After a 12-h fasting, the blood samples of the patients were drawn for the following parameters: glucose, insulin, triglyceride, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, ALT, aspartate aminotransferase (AST), γ-glutamyl transpeptidase, haemoglobin, white blood cell count (WBC), platelet count (PLT) and MPV. The estimate of IR was calculated by a homeostasis model assessment-IR (HOMA-IR) index (fasting insulin × fasting glucose/22.5), as described by Matthews *et al*.[30] A cut-off HOMA level of >4.0 in adolescents was used to identify an insulin-resistance status. Hepatitis A, B, C viruses, Epstein Barr virus and TORCH serologies, serum copper and ceruloplasmin levels, serum α-1-antitrypsin and autoantibodies against nuclear, smooth muscle, liver and kidney microsomal type-1 antigens were screened to eliminate infectious, metabolic and immunological liver pathologies in patients with elevated ALT levels.

Twenty-three age- and sex-matched healthy children constituted the control group (12 male and 11 female, mean age 14.5 ± 1.5 years, group 4). BMI and relative weight of children in the control group were in normal ranges. Complete blood count analyses were performed for healthy children.

Platelet measurements in blood samples with K3-ethylenediaminetetraacetic acid were analysed in an automated haematology analysis system (LH-780, Beckman Coulter, Brea, CA, USA) with the impedance method (intra-assay variation coefficient 1.6%, interassay variation coefficient 1.65%). Double-standard quality control was performed every day.

The same experienced radiologist (A.K.) performed the carotid artery ultrasound studies by the same ultrasonographer (ATL 5000, Philips Medical Systems, Bothell, WA, USA) with a linear wideband 5–12 mHz transducer, according to the recommendations of the American Society of Echocardiography Carotid Intima-Media Thickness Task Force.[31] During the ultrasound examination, patients were kept in the supine position, the head slightly extended and kept rotated to the opposite side. Left common carotid artery (CCA) was scanned by two longitudinal views: posterolateral, with the transducer positioned parallel to the posterior border of the sternocleidomastoid muscle, and anterolateral, with the transducer positioned parallel to the anterior border of the sternocleidomastoid muscle. Measurement points were obtained in the far wall of the vessel. Optimal B-mode settings of gain, depth, focal zone placement and compression were individually adjusted for left CCA to enhance arterial wall structures and image quality. Each image was recorded on a digital system and was analysed manually by the other radiologist blinded to the clinical data (H.Ç.). The mean of these measurements were used. Distal wall measurements were performed because of poor proximal imaging quality.

### Statistics

Data were evaluated using the Statistical Package for Social Sciences (SPSS) 11.0 program for Windows (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard deviation and median when appropriate. Kruskal–Wallis test was used for comparing the four groups. As a post hoc test, the Mann–Whitney *U*-test was used. $P < 0.05$ was considered statistically significant. Pearson correlation coefficients were computed between left CCA and all other parameters. A correlation coefficient indicated low correlation at 0.10–0.29, medium correlation at 0.30–0.49 and high correlation at ≥0.50. Multiple stepwise linear regression analysis with enter method was used to explore independent association between left CCA and MPV. Relative weight, total cholesterol, HOMA-IR and fatty liver severity were included in the final model as potential confounders.

## Results

Among 68 obese patients, 24 had no hepatosteatosis (group 1), 24 had grade 1 hepatosteatosis (group 2) and 20 had grade 2 or 3 hepatosteatosis (group 3). MPV was significantly higher in obese patients than healthy adolescents. Besides, there was a significant difference between group 1 and group 3 regarding the MPV (Table 1). The mean haemoglobin, WBC and PLT were comparable in three obese groups (Table 1). However, the mean WBC level was higher in patients with grade 2 or 3 hepatosteatosis (group 3) than healthy controls (Table 1).

**Table 1** Comparison of clinical and laboratory parameters between patients without hepatosteatosis (group 1), patients with grade 1 hepatosteatosis (group 2), patients with grade 2 or 3 hepatosteatosis (group 3) and the control group (group 4)

| | Group 1 ($n$ = 24) | Group 2 ($n$ = 24) | Group 3 ($n$ = 20) | Group 4 ($n$ = 23) | Group comparisons ($P$-value)* |
|---|---|---|---|---|---|
| Age (years) | 13.5 (12–16) | 14.2 (11–16) | 14 (11–16) | 14.5 (11.5–17) | 1–2 (0.201), 1–3 (0.729), 1–4 (0.629) 2–3 (0.440), 2–4 (0.346), 3–4 (0.123) |
| Weight (kg) | 70.0 (55–109) | 81.5 (64–107) | 83.9 (58–105) | 49.8 (39–80) | 1–2 (**0.003**), 1–3 (**0.010**), 1–4 (**0.000**) 2–3 (0.494), 2–4 (**0.000**), 3–4 (**0.000**) |
| Relative weight (%) | 139.5 (123–193) | 145 (129–202) | 167 (127–198) | 99 (90–113) | 1–2 (0.108), 1–3 (**0.004**), 1–4 (**0.000**) 2–3 (0.101), 2–4 (**0.000**), 3–4 (**0.000**) |
| Hb (gr/L) | 13 (11.6–14.3) | 13.5 (11.9–15.3) | 13 (10.2–15.8) | 13 (11–15.2) | 1–2 (0.173), 1–3 (0.841), 1–4 (0.594) 2–3 (0.357), 2–4 (0.079), 3–4 (0.542) |
| WBC ($\times 10^3/\mu L$) | 7.2 (4.1–10) | 7.4 (5.1–11.6) | 8.4 (4.3–11.5) | 6.7 (4.9–10.9) | 1–2 (757), 1–3 (0.075), 1–4 (0.573) 2–3 (0.137), 2–4 (0.338), 3–4 (**0.018)** |
| PLT ($\times 10^3/\mu L$) | 300 (206–392) | 317 (150–391) | 304 (169—386) | 289 (194–417) | 1–2 (0.789), 1–3 (0.795), 1–4 (0.401) 2–3 (0.706), 2–4 (0.406), 3–4 (0.551) |
| MPV (fL) | 8.3 (7.4–9.9) | 8.3 (7.3–10.3) | 8.9 (7.7–10.1) | 7.7 (5.7–8.7) | 1–2 (0.695), 1–3 (**0.025),** 1–4 (**0.000**) 2–3 (0.125), 2–4 (**0.000**), 3–4 (**0.000**) |
| Glucose (mg/dL) | 90 (71–109) | 88 (72–112) | 89 (74–105) | 85 (81–98) | 1–2 (0.828), 1–3 (0.777), 1–4 (0.238) 2–3 (0.813), 2–4 (0.233), 3–4 (0.177) |
| ALT (U/L) | 15 (6–34) | 19 (8–35) | 24 (12–84) | 18 (8–23) | 1–2 (**0.037),** 1–3 (**0.000**), 1–4 (0.200) 2–3 (**0.011**), 2–4 (0.138), 3–4 (0.**000**) |
| Triglyceride (mg/dL) | 99.5 (48–246) | 90 (63–271) | 129.6 (56–209) | 74 (45–124) | 1–2 (0.635), 1–3 (0.472), **1–4 (0.041)** 2–3 (0.207), 2–4 (**0.050),** 3–4 (0.**004**) |
| Total cholesterol (mg/dL) | 173 (122–257) | 162 (112–258) | 159 (133–274) | 136 (123–182) | 1–2 (0.177), 1–3 (0.305), 1–4 (**0.010**) 2–3 (0.207), 2–4 (0.075), 3–4 (**0.033)** |
| HDL cholesterol (mg/dL) | 51.5 (23–68) | 48.5 (24–63) | 43 (34–74) | 49.5 (42–68) | 1–2 (0.509), 1–3 (**0.019),** 1–4 (0.583) 2–3 (0.125), 2–4 (0.316), 3–4 (**0.006**) |
| LDL cholesterol (mg/dL) | 102 (52–158) | 91.5 (54–159) | 92.5 (62–188) | 75 (55–109) | 1–2 (0.312), 1–3 (0.563), 1–4 (0.100) 2–3 (0.750), 2–4 (0.226), 3–4 (0.113) |
| Insulin (uIU/mL) | 12.7 (6.4–48.9) | 15 (7.9–80) | 22.4 (9–51) | 7.8 (4.4–13) | 1–2 (0.216), 1–3 (**0.001**), 1–4 (**0.009**) 2–3 (**0.015),** 2–4 (**0.000**), 3–4 (**0.000**) |
| HOMA-IR | 2.9 (1.3–12.9) | 3.2 (1.9–22) | 4.9 (2–11.3) | 1.7 (0.97–2.9) | 1–2 (0.177), 1–3 (**0.002**), 1–4 (**0.006**) 2–3 **(0.033),** 2–4 (0.**000**), 3–4 (**0.000**) |
| Left CCA (mm) | 0.400 (0.259–0.561) | 0.430 (0.332–0.558) | 0.439 (0.287–0.631) | 0.324 (0.259–0.443) | 1–2 (0.137), 1–3 (0.083), 1–4 (**0.009**) 2–3 (0.612), 2–4 (**0.000**), 3–4 (**0.000**) |

Values are given as median (range), *$P < 0.05$ is significant and represented in bold characters; **$\chi^2$ test ($P$-value between the all groups). ALT, alanine aminotransferase; CCA, common carotid artery; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; LDL, low-density lipoprotein; MPV, mean platelet volume; PLT, platelet count; WBC, white blood cell count.

The mean ALT level was significantly higher in group 3 than in groups 1 and 2 ($P$ = 0.000 and $P$ = 0.011, respectively) (Table 1). Triglyceride, total cholesterol and LDL cholesterol levels were not significantly different among three obese groups (Table 1). HDL cholesterol was significantly lower in group 3 than group 1. Fasting blood glucose was similar in patient groups. Besides, HOMA-IR was significantly higher in group 3 than in group 1 and group 2 ($P$ = 0.002 and $P$ = 0.033, respectively) (Table 1).

The left CCA thickness was significantly higher in obese adolescents than the healthy controls; however, there was not a significant difference between three obese groups regarding the left CCA thickness (Table 1).

There was a positive correlation between left CCA thickness and MPV ($r$ = 0.439, $P$ = 0.000) (Table 2, Fig. 1). Besides, left CCA thickness was positively correlated with relative weight and ALT level ($r$ = 0.358 and $r$ = 0.249, respectively) (Table 2). Also, MPV was positively correlated with relative weight, insulin, HOMA-IR, ALT and triglyceride levels ($r$ = 0.483, $r$ = 0.422, $r$ = 0.410, $r$ = 0.278 and $r$ = 0.262, respectively) (Table 2). Furthermore, MPV was inversely correlated with HDL cholesterol and PLT ($r$ = –0.245, $r$ = –0.276, respectively) (Table 2).

The association between MPV and left CCA was checked using linear regression analysis. MPV explained 19% of the variation in left CCA (Beta = 0,041, SE: 0.009 $P < 0.001$).

When other potential confounders were included in the multiple regression analysis, MPV maintained a positive association with the left CCA thickness (Beta = 0.037, SE: 0.012, $P$ = 0.002) independently of fatty liver grade, relative weight, total cholesterol and HOMA-IR.

**Table 2** Correlation between laboratory parameters in obese adolescent

| | W/H | WBC | PLT | MPV | Glu | Ins | HOMA | ALT | Tri | HDL | LDL |
|---|---|---|---|---|---|---|---|---|---|---|---|
| WBC | 0.177 | | | | | | | | | | |
| PLT | 0.142 | 0.310** | | | | | | | | | |
| MPV | 0.483** | 0.070 | –0.276** | | | | | | | | |
| Glu | 0.185 | 0.070 | 0.083 | 0.110 | | | | | | | |
| Ins | 0.410** | 0.341** | 0.104 | 0.422** | 0.347** | | | | | | |
| HOMA | 0.392** | 0.328** | 0.119 | 0.410** | 0.463** | 0.981** | | | | | |
| ALT | 0.250* | 0.285** | 0.074 | 0.278** | –0.056 | 0.222* | 0.168 | | | | |
| Tri | 0.137 | 0.180 | 0.247* | 0.262* | 0.019 | 0.059 | 0.049 | 0.238* | | | |
| HDL | –0.201 | –0.031 | –0.064 | –0.245* | –0.184 | –0.194 | –0.209 | –0.119 | –0.395** | | |
| LDL | 0.287* | 0.209 | 0.159 | 0.186 | 0.053 | 0.112 | 0.082 | 0.211 | 0.401** | –0.085 | |
| Left CCA | 0.358** | 0.072 | –0.103 | 0.439** | 0.144 | 0.151 | 0.173 | 0.249* | 0.192 | –0.187 | 0.035 |

*Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level. ALT, alanine aminotransferase; CCA, common carotid artery; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; MPV, mean platelet volume; PLT, platelet count; WBC, white blood cell count.

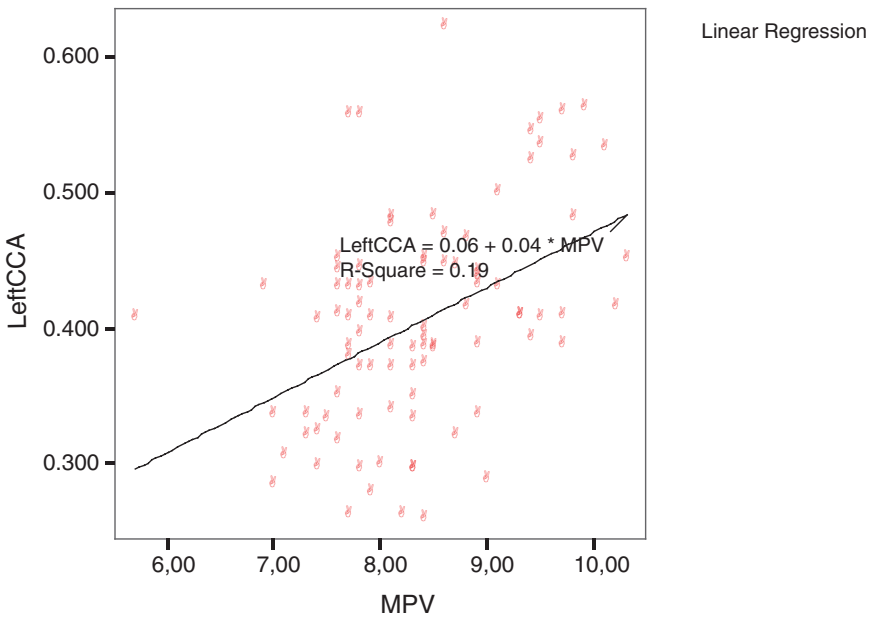


**Fig. 1** Scatter plot of left CCA and MPV. CCA, common carotid artery; MPV, mean platelet volume.

## Discussion

The findings of present study indicate that MPV may be associated with carotid atherosclerosis in adolescent patients with obesity. To the best of our knowledge, this is the first study investigating the correlation of CCA thickness and MPV in obese adolescents.

We found a significant relation between MPV and increased carotid IMT, which strongly suggest an important role of systemic platelet activation in the course of the carotid wall disease and in progression of atherosclerosis. Indeed, earlier studies demonstrated that larger platelets are more reactive than the smaller platelets.[18] This remains true when platelet aggregability is referred to platelet volume. One potential explanation is that large platelets produce larger amounts of tromboxane A2.[17] Besides, previous studies demonstrated a role for platelets in carotid atherosclerosis and showed that P-Selectin stored in their secretory granules was crucial for the growth of atherosclerosis plaque and that the degree of plaque maturation, including the presence of smooth muscle cells and calcification, was dependent on the endothelial as well as the platelet P-Selectin as a product of the platelet activation.[32] Given this relationship, it is rational that high MPV is associated with increased CCA thickness, as platelet aggregability is known to be an important factor in the etiopathogenesis of atherosclerosis.

There are some studies about the MPV levels in obesity in the literature.[33–35] Coban *et al*.[33] demonstrated that MPV levels of obese patients were significantly higher than the healthy subjects. These authors suggested that higher MPV levels in obese individuals might be a possible cause for increased risk of atherosclerosis. Same authors also showed in another study that MPV levels significantly decreased after diet and consequent weight loss in obese patients.[34]

Several studies showed that patients with NAFLD had increased subclinical atherosclerosis compared with non-steatotic patients.[9–11] In these studies, carotid IMT was used to determine atherosclerosis. MPV, which is a parameter generated by full blood count analysers as part of the routine complete blood count test cycle, has recently become an interesting topic in cardiovascular researches.[20,36–38] The use of this parameter adds no extra cost and technical effort. Regarding that cardiovascular disease is one of the most common causes of morbidity and mortality in NAFLD patients,[39] MPV may, in part, help to determine atherosclerosis risk in this group of patients.

To date, controversial results have been reported about the relationship between carotid IMT and MPV in previous studies. Recently, Kilciler *et al*.[40] reported a study investigating the relationship between MPV and carotid atherosclerosis in adult patients with NAFLD. They compared 60 biopsy-proven NAFLD patients with 54 healthy subjects. In contrast to our study, they could not show any difference between two groups regarding MPV and CCA thickness. They concluded that MPV might not be involved in the mechanism of increased cardiovascular risk in NAFLD in the absence of other metabolic risk factors such as hypertension, diabetes and obesity. Our study population consisted of obese patients, and we found a positive correlation between relative weight and left CCA thickness as well as MPV. We suggest that obesity might have contributed to altered MPV and CCA thickness in our study.

Another study investigating the relationship between MPV and carotid atherosclerosis was reported by Yarlioglues *et al*.[41] They enrolled 80 newly diagnosed adult hypertensive patients and investigated the subclinical target organ damages such as proteinuria, left ventricular hypertrophy and carotid atherosclerosis. They assessed 24-h blood pressure monitoring, left ventricular mass index, carotid IMT and urine albumin/creatinine ratio in the patient population. They found a positive correlation between MPV and carotid IMT as well as left ventricular hypertrophy and renal damage.

Obesity creates a low-grade systemic inflammation.[42] In genetically susceptible individuals, excessive fat consumption leads to the derangement of adipose tissue architecture and homeostasis, the peripheral and hepatic resistance to insulin-stimulated glucose uptake, thus favouring a condition of chronic low-grade inflammation. Excessive fat cannot be stored in the adipose tissue and stored elsewhere, particularly to the muscle and liver.[4] The pathogeneses of both NAFLD and atherosclerosis include subclinical inflammation. The significantly higher WBC level of patients with grade 2 or 3 hepatosteatosis (group 3) according to the healthy controls supports the inflammatory state of this disease. Systemic inflammation may also drive MPV changes.[43,44] Obesity accompanied by chronic inlammatory state might also have contributed to the MPV levels in our study.

The results of the present study are in concordance with our previous study about MPV levels in obese adolescents with NAFLD.[25] This study also showed that MPV was significantly higher in obese adolescents than their healthy peers; besides, MPV was higher in patients with NAFLD than patients without NAFLD. We further showed the positive correlation of CCA thickness with MPV in this study, which we believe enhancing the reliability of MPV in pointing out atherosclerosis. Detection of CCA thickness is more expensive and needs physical and technical effort. MPV is an easy method to study and requires no extra skills. However, this is only a cross-sectional study, thus our results cannot indicate that MPV can replace ultrasonography in detecting atherosclerosis. In conclusion, we suggest that possible prognostic role of MPV in cardiovascular disease in children needs to be elicited by longitudinal studies including larger number of patients.

## References


1 Mirmiran P, Sherafat-Kazemzadeh R, Jalali-Farahani S, Azizi F. Childhood obesity in the Middle-East: a review. *East. Mediterr. Health J.* 2010; **16**: 1009–17.
2 Lobstein T, Frelut ML. Prevalence of overweight among children in Europe. *Obes. Rev.* 2003; **4**: 195–200.
3 Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA* 2006; **295**: 1549–55.
4 Manco M, Bottazzo G, DeVito R, Marcellini M, Mingrone G, Nobili V. Nonalcoholic fatty liver disease in children. *J. Am. Coll. Nutr.* 2008; **27**: 667–76.
5 Arslan N, Büyükgebiz B, Oztürk Y, Cakmakçi H. Fatty liver in obese children: prevalence and correlation with anthropometric measurements and hyperlipidemia. *Turk. J. Pediatr.* 2005; **47**: 23–7.
6 Patton HM, Sirlin C, Behling C, Middleton M, Schwimmer JB, Lavine JE. Pediatric nonalcoholic fatty liver disease: a critical appraisal of current data and implications for future research. *J. Pediatr. Gastroenterol. Nutr.* 2006; **43**: 413–27.
7 Fu JF, Shi HB, Liu LR *et al*. Nonalcoholic fatty liver disease. An early mediator predicting metabolic syndrome in obese children? *World J. Gastroenterol.* 2011; **17**: 735–42.
8 Mencin AA, Lavine JE. Nonalcoholic fatty liver disease in children. *Curr. Opin. Clin. Nutr. Metab. Care* 2011; **14**: 151–7.
9 Aygun C, Kocaman O, Sahin T *et al*. Evaluation of metabolic syndrome frequency and carotid artery intima-media thickness as risk factors for atherosclerosis in patients with nonalcoholic fatty liver disease. *Dig. Dis. Sci.* 2008; **53**: 1352–7.
10 Kim HC, Kim DJ, Huh KB. Association between nonalcoholic fatty liver disease and carotid intima-media thickness according to the presence of metabolic syndrome. *Atherosclerosis* 2009; **204**: 521–5.
11 Pacifico L, Cantisani V, Ricci P *et al*. Nonalcoholic fatty liver disease and carotid atherosclerosis in children. *Pediatr. Res.* 2008; **63**: 423–7.
12 Fan JG, Li F, Cai XB, Peng YD, Ao QH, Gao Y. Effects of nonalcoholic fatty liver disease on the development of metabolic disorders. *J. Gastroenterol. Hepatol.* 2007; **22**: 1086–91.
13 Koebnick C, Getahun D, Reynolds K *et al*. Trends in nonalcoholic fatty liver disease-related hospitalizations in US children, adolescents, and young adults. *J. Pediatr. Gastroenterol. Nutr.* 2009; **48**: 597–603.
14 Shoelson SE, Herrero L, Naaz A. Obesity, inflammation, and insulin resistance. *Gastroenterology* 2007; **132**: 2169–80.
15 Li S, Chen W, Srinivasan SR *et al*. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *JAMA* 2003; **290**: 2271–6.

16 Raitakari OT, Juonala M, Kähönen M *et al*. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA* 2003; **290**: 2277–83.
17 Martin JF, Trowbridge EA, Salmon G, Plumb J. The biological significance of platelet volume: its relationship to bleeding time, thromboxane B2 production and megakaryocyte nuclear DNA concentration. *Thromb. Res.* 1983; **32**: 443–60.
18 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.
19 Berger JS, Eraso LH, Xie D, Sha D, Mohler ER. Mean platelet volume and prevalence of peripheral artery disease, the National Health and Nutrition Examination Survey, 1999–2004. *Atherosclerosis* 2010; **213**: 586–91.
20 Chu SG, Becker RC, Berger PB *et al*. Mean platelet volume as a predictor of cardiovascular risk: a systematic review and meta-analysis. *J. Thromb. Haemost.* 2009; **8**: 148–55.
21 Bonithon-Kopp C, Touboul PJ, Berr C *et al*. Relation of intima-media thickness to atherosclerotic plaques in carotid arteries. The Vascular Aging (EVA) Study. *Arterioscler. Thromb. Vasc. Biol.* 1996; **16**: 310–6.
22 Lamotte C, Iliescu C, Libersa C, Gottrand F. Increased intima-media thickness of the carotid artery in childhood: a systematic review of observational studies. *Eur. J. Pediatr.* 2011; **170**: 719–29.
23 Fang J, Zhang JP, Luo CX, Yu XM, Lv LQ. Carotid intima-media thickness in childhood and adolescent obesity relations to abdominal obesity, high triglyceride level and insulin resistance. *Int. J. Med. Sci.* 2010; **7**: 278–83.
24 Yilmazer MM, Tavli V, Carti OU *et al*. Cardiovascular risk factors and noninvasive assessment of arterial structures and function in obese Turkish children. *Eur. J. Pediatr.* 2010; **169**: 1241–8.
25 Arslan N, Makay B. Mean platelet volume in obese adolescents with nonalcoholic fatty liver disease. *J. Pediatr. Endocrinol. Metab.* 2010; **23**: 807–13.
26 Kuczmarski RJ, Ogden CL, Guo SS *et al*. CDC growth charts for the United States: methods and development . *Vital Health Stat*. 2002; **11**: 1–190
27 Shriver LH, Harrist AW, Tait LH, Topham G, Page M, Barrett A. Weight status, physical activity, and fitness among third-grade rural children. *J. Sch. Health* 2011; **81**: 536–44.
28 Quinn SF, Gosink BB. Characteristic sonographic signs of hepatic fatty infiltration. *AJR Am. J. Roentgenol.* 1985; **145**: 753–5.
29 Scatarige JC, Scott WW, Donovan PJ, Siegelman SS, Sanders RC. Fatty infiltration of the liver: ultrasonographic and computed tomographic correlation. *J. Ultrasound Med.* 1984; **3**: 9–14.
30 Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–19.
31 Stein JH, Korcarz CE, Hurst RT *et al*.; American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J. Am. Soc. Echocardiogr.* 2008; **21**: 93–111.
32 Burger PC, Wagner DD. Platelet P-selectin facilitates atherosclerotic lesion development. *Blood* 2003; **101**: 2661–6.
33 Coban E, Özdoğan M, Yazıcıoglu G, Akcit F. The mean platelet volume in patients with obesity. *Int. J. Clin. Pract.* 2005; **59**: 981–2.
34 Coban E, Yılmaz A, Sarı R. The effect of weight loss on the mean platelet volume in obese patients. *Platelets* 2007; **18**: 212–6.
35 Toplak H, Wascher TC. Influence of weight reduction on platelet volume: different effects of a hypocaloric diet and a very low calorie diet. *Eur. J. Clin. Invest.* 1994; **24**: 778–80.
36 Lippi G, Filippozzi L, Salvagno GL *et al*. Increased mean platelet volume in patients with acute coronary syndromes. *Arch. Pathol. Lab. Med.* 2009; **133**: 1441–3.
37 Sen N, Basar N, Maden O *et al*. Increased mean platelet volume in patients with slow coronary flow. *Platelets* 2009; **20**: 23–8.
38 Tavil Y, Sen N, Yazici HU, Hizal F, Abaci A, Cengel A. Mean platelet volume in patients with metabolic syndrome and its relationship with coronary artery disease. *Thromb. Res.* 2007; **120**: 245–50.
39 Lizardi-Cervera J, Aguilar-Zapata D. Nonalcoholic fatty liver disease and its association with cardiovascular disease. *Ann. Hepatol.* 2009; **8** (Suppl. 1): S40–3.
40 Kilciler G, Genc H, Tapan S *et al*. Mean platelet volume and its relationship with carotid atherosclerosis in subjects with non-alcoholic fatty liver disease. *Ups. J. Med. Sci.* 2010; **115**: 253–9.
41 Yarlioglues M, Kaya MG, Ardic I *et al*. Relationship between mean platelet volume levels and subclinical target organ damage in newly diagnosed hypertensive patients. *Blood Press.* 2011; **20**: 92–7.
42 Cave MC, Hurt RT, Frazier TH *et al*. Obesity, inflammation, and the potential application of pharmaconutrition. *Nutr. Clin. Pract.* 2008; **23**: 16–34.
43 Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? *Curr. Pharm. Des.* 2011; **17**: 47–58.
44 Gasparyan AY. Platelets in inflammation and thrombosis. *Inflamm. Allergy Drug Targets* 2010; **9**: 319–21.