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The Potential Involvement of Platelet Indices in Insulin Resistance in Morbid Obese Children

Orkide Donma, Mustafa M. Donma

***Abstract*—**Association between insulin resistance (IR) and hematological parameters has long been a matter of interest. Within this context, body mass index (BMI), red blood cells, white blood cells and platelets were involved in this discussion. Parameters related to platelets associated with IR may be useful indicators for the identification of IR. Platelet indices such as mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) are being questioned for their possible association with IR. The aim of this study was to investigate the association between platelet (PLT) count as well as PLT indices and the surrogate indices used to determine IR in morbid obese (MO) children. A total of 167 children participated in the study. Three groups were constituted. The number of cases was 34, 97 and 36 children in the normal BMI, MO and metabolic syndrome (MetS) groups, respectively. Sex- and age-dependent BMI-based percentile tables prepared by World Health Organization were used for the definition of morbid obesity. MetS criteria were determined. BMI values, homeostatic model assessment for IR (HOMA-IR), alanine transaminase-to-aspartate transaminase ratio (ALT/AST) and diagnostic obesity notation model assessment laboratory (DONMA-lab) index values were computed. PLT count and indices were analyzed using automated hematology analyzer. Data were collected for statistical analysis using SPSS for Windows. Arithmetic mean and standard deviation were calculated. Mean values of PLT-related parameters in both control and study groups were compared by one-way ANOVA followed by Tukey post hoc tests to determine whether a significant difference exists among the groups. The correlation analyses between PLT as well as IR indices were performed. Statistically significant difference was accepted as p-value < 0.05. Increased values were detected for PLT ($p < 0.01$) and PCT ($p > 0.05$) in MO group compared to those observed in children with N-BMI. Significant increases for PLT ($p < 0.01$) and PCT ($p < 0.05$) were observed in MetS group in comparison with the values obtained in children with N-BMI ($p < 0.01$). Significantly lower MPV and PDW values were obtained in MO group compared to the control group ($p < 0.01$). HOMA-IR ($p < 0.05$), DONMA-lab index ($p < 0.001$) and ALT/AST ($p < 0.001$) values in MO and MetS groups were significantly increased compared to the N-BMI group. On the other hand, DONMA-lab index values also differed between MO and MetS groups ($p < 0.001$). In the MO group, PLT was negatively correlated with MPV and PDW values. These correlations were not observed in the N-BMI group. None of the IR indices exhibited a correlation with PLT and PLT indices in the N-BMI group. HOMA-IR showed significant correlations both with PLT and PCT in the MO group. All of the three IR indices were well-correlated with each other in all groups. These findings point out the missing link between IR and PLT activation. In conclusion, PLT and PCT may be related to IR in addition to their identities as hemostasis markers during morbid obesity. Our findings have suggested that DONMA-lab index appears as the best surrogate marker for IR due to its discriminative feature between morbid obesity and MetS.

***Keywords*—**Children, insulin resistance, metabolic syndrome, plateletcrit, platelet indices.

Orkide Donma is with the Istanbul University Cerrahpasa, Cerrahpasa Medical Faculty, Department of Medical Biochemistry, Istanbul, Turkey (e-mail: odonma@gmail.com).

Mustafa M. Donma is with the Namik Kemal University, Faculty of Medicine, Department of Pediatrics, Tekirdag, Turkey (corresponding author, phone: 00-90-532-371-72-07; fax: 00-90-282-250-99-28; e-mail: mdonma@gmail.com).

I. Introduction

IR is a hallmark of metabolic disorders, including obesity, MetS and type 2 diabetes mellitus (T2DM). Various metabolic abnormalities caused by obesity can lead to the development of IR, which may be associated with PLT reactivity. Increased PLT count is associated with PLT reactivity. MPV is an important marker of PLT activation. Hyperglycemia and IR affect endothelial and PLT functions. Endothelial and PLT dysfunction may be involved in vascular complications in T2DM [1]-[7].

Insulin is reported to control PLT functions through insulin receptors present on PLT surface. The effect of hyperinsulinemia on PLT is complex and significant variations were noted in patients with IR compared to healthy individuals [8].

So far, association of IR with some liver enzymes as well as some hematological parameters including erythrocytes, leukocytes, PLTs and their indices or subgroups has been discussed in many studies [9]-[12].

Within this context, PLT count and some related indices gained significant importance in recent years [13]- [16]. In this study, aside from MPV, PCT, PDW, also a liver enzyme-related ratio; ALT/AST were examined. A commonly used IR index, the HOMA-IR, was also included into the discussion. Finally, a very recently introduced IR index; $DONMA_{LAB}$ index was considered for the evaluation and interpretation with the other parameters to give some light to the provision of the missing link between IR and PLT activation.

The purpose of this study was to find out possible associations between the surrogate IR indices and PLT count as well as PLT indices in MO children.

II. Patients and Methods

A. Patients

One hundred and sixty seven participants were included in the study. Group 1 was composed of 34 children with normal body mass index (N-BMI). Group 2 was composed of 97 MO children. Thirty-six children with MetS were included in Group 3. Written informed consent forms were signed by the parents of the participants.

B. Obesity Classification

MO children were defined as those; whose BMI-based percentile values were above 99. Tables prepared by World Health Organization according to sexes and ages of the individuals were used [17].

TABLE I
BMI, PLT-RELATED PARAMETERS, IR INDICES OF STUDY GROUPS

Parameter	Group 1 N-BMI	Group 2 MO	Group 3 MetS
BMI (kg/m^2)	17.6 ± 2.8	27.4 ± 5.9	30.6 ± 8.1
PLT ($*10^3$)	291 ± 78	342 ± 85	357 ± 95
MPV (fL)	9.0 ± 0.9	8.5 ± 0.8	8.5 ± 0.7
PDW (%)	15.2 ± 2.5	13 ± 41	3.9 ± 1.7
PCT (%)	0.260 ± 0.074	0.286 ± 0.061	0.303 ± 0.084
ALT/AST	0.54 ± 0.1	20.96 ± 0.46	1.01 ± 0.34
HOMA-IR	2.4 ± 2.4	4.2 ± 3.1	5.6 ± 2.9
$DONMA_{LAB}$	2.2 ± 1.1	3.4 ± 1.1	4.3 ± 1.0

[$BMI^{1-2 < 0.01, 1-3 < 0.01, 2-3 < 0.05}$, $PLT^{1-2 < 0.01, 1-3 < 0.01}$, $MPV^{1-2 < 0.01, 1-3 < 0.05}$, $PDW^{1-2 < 0.01}$, $PCT^{1-3 < 0.05}$, $ALT/AST^{1-2 < 0.01, 1-3 < 0.01}$, $HOMA\text{-}IR^{1-2 < 0.05, 1-3 < 0.01}$, $DONMA_{LAB}^{1-2 < 0.01, 1-3 < 0.01, 2-3 < 0.01}$]

C. MetS Criteria

MetS criteria were determined [18]. The presence of central obesity, elevated blood pressure values (systolic blood pressure > 130 mm Hg and diastolic blood pressure > 85 mm Hg), elevated fasting blood glucose (FBG) (> 100 mg/dl), increased triglycerides (TRG) (> 150 mg/dl) or decreased high density lipoprotein cholesterol (HDL-C) (< 40 mg/dl) were considered as MetS components. Children with two or three of the above components were included in MetS group.

D. Laboratory Analyses

Platelet count and indices were analyzed using automated hematology analyzer. Blood samples were obtained after an overnight fasting. Serum insulin, FBG, TRG and HDL-C concentrations as well as ALT and AST activities were determined by autoanalyzer.

E. Obesity and IR Indices

BMI (kg/m^2) values were obtained using weight and height of the children. HOMA-IR, ALT/AST ratio and $DONMA_{LAB}$ index [19] values were calculated.

F. Statistical Evaluation

Data were evaluated using the statistical package program (SPSS for Windows). Descriptives were calculated. Mean values of platelet-related parameters and IR indices in three groups were compared by one-way ANOVA followed by Tukey post hoc tests to observe significant differences between the groups, if there exists any. Correlation coefficients and p values were determined between platelet and IR indices. A p-value < 0.05 was considered as statistically significant.

III. RESULTS

The values of BMI, PLT count, MPV, PDW, PCT as well as IR indices (ALT/AST, HOMA-IR, $DONMA_{LAB}$) calculated for Group 1, Group 2, and Group 3 were given in Table I.

Platelet count ($p < 0.01$) and PCT ($p > 0.05$) were higher in Group 2 and Group 3 [PLT ($p < 0.01$) and PCT ($p < 0.05$)] than those in Group 1. Significantly decreased MPV and PDW values were detected in Group 2 in comparison with those of Group 1 ($p < 0.01$). All of IR indices [HOMA-IR ($p < 0.05$), $DONMA_{LAB}$ ($p < 0.001$) and ALT/AST ($p < 0.001$)] were significantly elevated in Group 2 and Group 3 when compared to those calculated in Group 1.

Differences between Group1 vs. Group2, Group 1 vs. Group3 and Group 2 vs. Group3 were statistically significant when $DONMA_{LAB}$ index values were considered ($p < 0.001$).

Negative correlations were obtained between PLT and MPV ($r = -0.524$; $p < 0.001$) as well as PDW ($r = -0.330$; $p < 0.001$) in Group 2 (Figs. 1 (a) and (b)). In Group 1, there was no such a correlation.

None of IR indices exhibited a correlation with PLT and platelet indices in N-BMI group. HOMA-IR showed significant correlations both with PLT ($r = 0.262$; $p < 0.05$) and PCT ($r = 0.256$; $p < 0.05$) in Group 2 (Figs. 2 (a) and (b)).

All of three IR indices were well-correlated with each other in all groups.

The correlations between HOMA-IR and $DONMA_{LAB}$ were ($r = 0.598$; $p < 0.001$), ($r = 0.602$; $p < 0.001$) and ($r = 0.658$; $p < 0.001$) in groups 1, 2, and 3, respectively. Corresponding values for correlations between HOMA-IR and ALT/AST were ($r = 0.524$; $p < 0.001$), ($r = 0.276$; $p < 0.01$) and ($r = 0.481$; $p < 0.01$). Correlations between $DONMA_{LAB}$ and ALT/AST were calculated as ($r = 0.595$; $p < 0.001$), ($r = 0.492$; $p < 0.001$) and ($r = 0.414$; $p < 0.05$).

IV. DISCUSSION

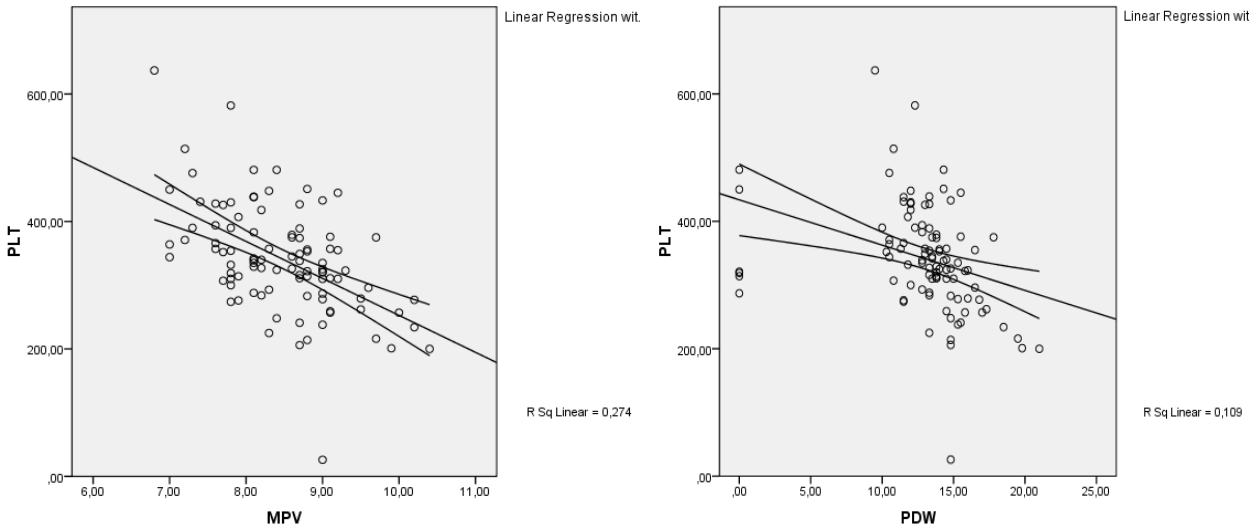
The mechanisms related to the association between PLT activation and IR are not clear yet [1].

Aside from its role as a marker of hemostasis, PLT count has recently been linked to IR and MetS. MPV has been known to represent PLT activity. MetS was reported to be inversely associated with MPV [4], [20].

Some studies reported that children with MetS had higher levels of PLT and lower levels of MPV. Platelet count was positively whereas MPV was negatively associated with the risk of developing MetS. MPV was found to be negatively correlated with PLT count. It was reported that as MPV level is becoming lower, the PLT aggregation function becomes weaker. Therefore, more PLTs are produced to support metabolism. Platelet lifespan appears to be shorter in individuals with IR. This increases PLT count [4], [21], [22].

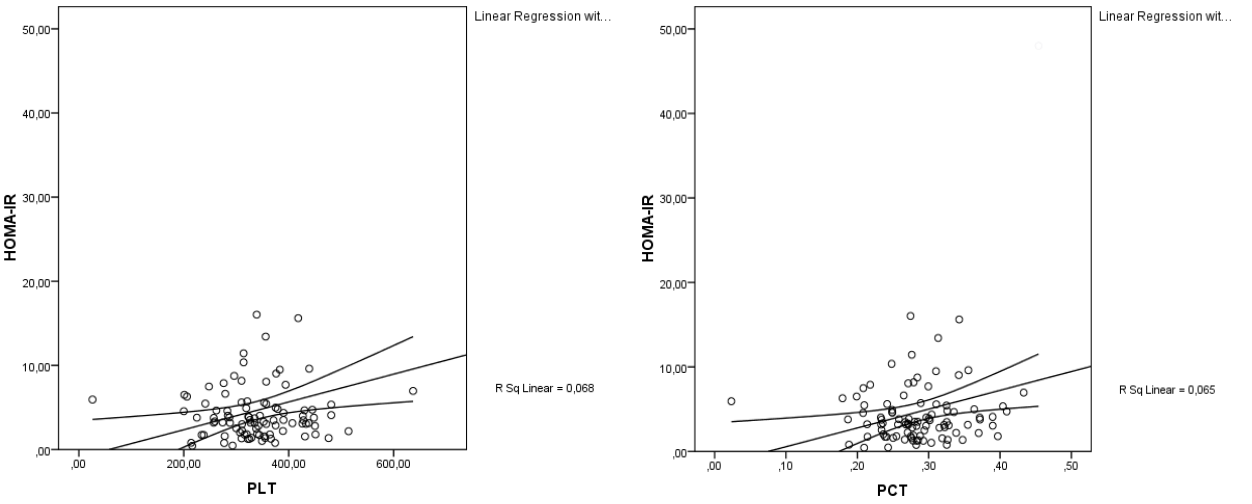
Our results were in agreement with the results of these studies. Negative correlations were obtained between PLT and MPV as well as PLT and PDW in Group 2.

These results may be evaluated as milestones in the way towards the missing link between IR and platelet activation. In conclusion, well-known hemostasis markers; PLT and PCT, appear to be related to IR during morbid obesity. Also, in this study, DONMA-lab index was suggested as the best surrogate marker for IR because it was the only index, which was capable of differentiating morbid obesity from MetS.



(a) (b)

Fig. 1 Negative correlations between platelet count and MPV as well as PDW in MO children (Linear Regression wit… = Linear Regression with 95.0% Mean Prediction Interval)



(a) (b)

Fig. 2 Bivariate correlations between HOMA-IR and platelet count as well as PCT in MO children (Linear Regression wit… = Linear Regression with 95.0% Mean Prediction Interval)

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