Research Article

Liver enzymes, mean platelet volume, and red cell distribution width in gestational diabetes

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Aim: To investigate the value of measuring liver enzymes, red cell distribution width (RDW), and mean platelet volume (MPV) in predicting the development of gestational diabetes mellitus (GDM).

Materials and methods: The medical records of all pregnant women followed by the obstetrics clinic between January 2010 and November 2012 were systematically evaluated, and patients with a diagnosis of GDM were identified. A total of 68 patients with GDM and 61 healthy controls were included in the study. Results of relevant laboratory parameters were recorded.

Results: Out of all the parameters evaluated, mean values for platelet distribution width (PDW) and mean activities of alanine transaminase (ALT) and γ-glutamyl transferase (GGT) were significantly higher in the GDM group compared to healthy controls (P = 0.003, P = 0.015, and P = 0.021, respectively), whereas mean plateletcrit (PCT) levels were significantly lower in the GDM group (P = 0.002). No significant difference was observed between groups in terms of MPV, RDW, platelet count, and aspartate transaminase levels.

Conclusion: Our study results suggest that ALT, GGT, PCT, and PDW may be useful as predictors of impending GDM.

Key words: Gestational diabetes, alanine transaminase, γ-glutamyl transferase, platelet count, platelet distribution width

1. Introduction

Gestational diabetes mellitus (GDM) is a condition in which, during pregnancy, glucose intolerance and complex metabolic and hormonal changes occur. On the other hand, diabetic women who become pregnant are not classified with this condition. Prevalence of GDM ranges from <1% to 20% according to the data from developed countries. Due to the increased risk of developing future glucose intolerance and perinatal morbidity and mortality risk, diagnosis of GDM is very important (1,2).

Previous studies have investigated the activity of γ-glutamyl transferase (GGT), aspartate transaminase (AST), and alanine transaminase (ALT) as markers for impending impairment of glucose metabolism with conflicting results (3,4).

Red cell distribution width (RDW), which is calculated by most modern hemoanalyzers, quantifies variability in the size of circulating red blood cells with lower values indicating greater homogeneity in cell sizes. Although the most common clinical use of RDW, developed via red cell size distribution histograms, has been to distinguish

between etiologies of microcytic anemia and macrocytic anemia (5), several recent studies portrayed high RDW as an indicator of poor cardiovascular fitness as well as being associated with higher mortality rates in chronic heart failure (6). It has also been linked with an increased risk of death in patients with pulmonary hypertension (7).

Nearly 30 years ago Thompson et al. (8) postulated on the effect of platelet size on platelet aggregation. Mean platelet volume (MPV), which indicates platelet size, has subsequently been shown to increase in patients with coronary artery disease, diabetes mellitus (DM), thrombotic events, and other inflammatory disorders (9–11). The relationship between high MPV and GDM has been previously established in several studies (12,13). The prognostic values of RDW, AST, ALT, and GGT have been demonstrated in numerous studies on patients with DM (3,14,15). To the best of our knowledge, a similar evaluation of these 5 parameters in patients with GDM has not been published to date, and the aim of this study was to investigate the potential role of several hematological and biochemical parameters in predicting GDM.

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2. Materials and methods

This retrospective study was undertaken at the Ankara Numune Training and Research Hospital with the approval of the local ethics committee.

In our hospital, all pregnant women are screened for GDM by a 1-h 50-g oral glucose tolerance test (OGTT) performed between 24–28 weeks of gestation. In patients with a blood glucose level of more than 140 mg/dL, the diagnosis of GDM is confirmed by a subsequent 3-h 100-g OGTT according to international guidelines (1).

Patients with anemia, a previous diagnosis of DM, preeclampsia, active smoking habit, history of alcohol consumption, chronic viral hepatitis (hepatitis B surface antigen or anti-HCV positivity), HIV infection, or any other chronic disorders were excluded from the study. Patients were also required to have values for prothrombin time (PT), international normalized ratio (INR), white blood cell (WBC) count, and renal function tests within normal ranges to be eligible for inclusion in the study. The control group consisted of pregnant women who did not meet the criteria for GDM during the same study period. Following screening for eligibility, the records of 68 patients with GDM and 61 healthy controls were deemed suitable for inclusion in the final analysis.

Relevant demographic information such as maternal and gestational age was retrieved from the medical records. Hematological parameters, which were measured by an automated hemoanalyzer (Sysmex XE-2100; Sysmex, Kobe, Japan), were also recorded, including hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC) count, RDW, platelet (PLT) count, MPV, platelet distribution width (PDW), plateletcrit (PCT), and WBC count. Serum activity of AST, ALT, GGT, creatinine, and urea, as well as results of all blood glucose measurements, which were taken using a commercial biochemistry analyzer (Roche P800 MODULAR; Roche Diagnostics, Indianapolis, IN, USA), were noted. Coagulation parameters were evaluated using a blood coagulation device (STA-Compact Analyzer; Diagnostica Stago-Roche, Mannheim, Germany), and values for activated partial thromboplastin time (aPTT), PT, and INR were recorded for each patient.

Statistical analyses were performed using PASW Statistics 18 software. Normality of distribution for continuous variables was evaluated using the Kolmogorov–Smirnov test, and comparisons between groups for variables with a normal distribution were made using the Student t-test with values provided as mean ± standard deviation (SD). The Mann–Whitney U test was used for comparisons of parameters with an abnormal distribution, the values of which are given as medians (minimum–maximum). A P-value of less than 0.05 was considered indicative of statistical significance.

3. Results

Ages of the patients with GDM and healthy controls included in the study were 31.84 ± 5.67 and 25.57 ± 5.30 years, respectively. Out of all the parameters evaluated, mean value for PDW and mean activity of ALT and GGT were significantly higher in the GDM group compared to healthy controls (P = 0.003, P = 0.015, and P = 0.021, respectively), whereas mean PCT levels were significantly lower in the GDM group (P = 0.002). There was no difference between the groups in terms of mean RDW, MPV, PLT, and AST. Results have been summarized in the Table.

Table. Characteristics of patients and controls.

Parameters	Control (n = 61)	GDM (n = 68)	P
ALT (IU/L) [median (min–max)]	10.50 (4–29)	12 (3–42)	0.015
GGT (IU/L) [median (min–max)]	8 (3–59)	9 (3–37)	0.021
AST (IU/L) [median (min–max)]	16 (11–53)	17.50 (11–30)	ns
RDW [median (min–max)]	14.3 (13.00–22.90)	14.4 (12.3–17.00)	ns
PLT (×10^9/L) (mean ± SD)	239.26 ± 90.37	214.62 ± 67.91	ns
MPV (mean ± SD)	11.15 ± 1.14	10.50 ± 2.94	ns
PDW (mean ± SD)	14.56 ± 2.80	16.19 ± 2.42	0.003
PCT [median (min–max)]	0.25 (0.10–0.55)	0.20 (0.11–0.59)	0.002

GDM: gestational diabetes mellitus, SD: standard deviation, ns: not significant, ALT: alanine aminotransferase, GGT: γ-glutamyl transferase, AST: aspartate aminotransferase, RDW: red blood cell distribution width, PLT: platelet count, MPV: mean platelet volume, PDW: platelet distribution width, PCT: plateletcrit.

4. Discussion

GDM is estimated to develop in up to 28% of pregnancies (2) with serious implications on fetal health, such as increased risks of macrosomia, bone fractures, nerve damage, and other biochemical disorders. Mothers with GDM are more than 50% more likely to develop overt DM within 10 years of initial diagnosis (16). The short- and long-term fetal/maternal risks associated with GDM highlight the importance of timely recognition and management of the condition.

Our study results suggest that among the parameters evaluated, GGT, ALT, PDW, and PCT could be useful as predictors of pregnancies with the potential of developing GDM. In recent years, several studies have investigated the predictive value of liver enzymes, and elevated GGT levels in particular have been found to be significantly correlated with impaired glucose tolerance (3,4). Other studies have demonstrated an increased risk of developing DM in the future in pregnant women with elevated ALT and GGT activities, and that liver steatosis and hepatic insulin resistance play a role in this process (4,17). Additionally, GGT has been shown to facilitate the stress response of the endoplasmic reticulum (15). In our study, the GDM group had significantly higher mean GGT and ALT activities than the healthy controls. While our findings conflict with those of previous studies on patients with GDM (8), similar results have been reported in patients with DM (4).

RDW is a measure of variability in the size of circulating erythrocytes (5) that is routinely calculated by automated hemoanalyzers. In a previous study, it was suggested that increased RDW may be associated with an increased risk of all-cause mortality in patients with DM (14). In a subsequent metaanalysis including 7 studies published in 2010, Patel et al. (14) managed to confirm the presence of an added risk posed by elevated RDW. It was reported that a 1% increment in RDW increased mortality risk by 14% regardless of hemoglobin concentration in all 7 studies of the metaanalysis. In the third National Health and Nutrition Examination Survey study, higher RDW values were found to be associated with an increased risk of developing nephropathy in patients with DM (18). In another prospective study, patients with diabetic foot osteomyelitis had higher RDW values by the end of 1 year compared to a control group (19). In a different study by Johnston et al. (20), no significant association between RDW values and risk of celiac disease was observed in patients with insulin-dependent DM. We also could not demonstrate the presence of a significant link between RDW and risk of developing GDM.

The mechanism(s) responsible for the increase in RDW values in patients with DM remain elusive. RDW has previously been shown to be an indirect indicator of nutritional status, anemia, inflammation, and several age-associated diseases (14), and higher values have been linked with increased morbidity and mortality. Although erythrocytes are equipped with extensive antioxidant systems, reactive oxygen species, which are produced on membrane surfaces and eventually released into circulation, contribute towards their elimination by the reticuloendothelial system, thus resulting in higher RDW values (21). Inflammatory cytokines as well as an increase in circulating erythropoietin production have been implicated as contributors to the increase in RDW (22). However, RDW has also been shown to be affected by nutritional deficiencies and other conditions leading to inadequate production of erythropoietin (6). All the participants in our study were taking multivitamin/iron supplements, which may explain the statistical insignificance of the RDW values observed.

Numerous studies have firmly established a link between MPV, which indicates platelet size, and DM (9,10,23,24). According to the National Health and Nutrition Examination Survey study, participants with DM and poor glycemic control had significantly higher MPV values than healthy controls (24). In another study, Kodiatte et al. (9) demonstrated significantly higher MPV values in patients with DM compared to a nondiabetic control group. They also observed that patients with DM had higher PLT counts, although the difference was statistically insignificant. PDW, investigated in a similar setting, was also found to be significantly higher in diabetic individuals compared to healthy controls (23). In the same study, mean PDW, but not MPV, was found to be significantly different in diabetic patients with complications compared to those with noncomplicated DM (23). Kodiatte et al. observed higher mean MPV in diabetic subjects with microvascular complications than in those without complications, although the difference was statistically insignificant (9).

MPV was reported to be an independent predictor of morbidity in women with GDM in 2 different studies by Bozkurt et al. (13) and Erikçi et al. (12). Our study differs from those studies in that we investigated the value of measuring MPV during early pregnancy as a predictor of impending GDM. We did not observe a significant difference between groups in terms of PLT count, a finding shared by Bozkurt et al. (13). Furthermore, as reported in the study by Erikçi et al. (12), we demonstrated significantly higher PDW values in patients with GDM compared to healthy controls. Our study also differs from that by Erikçi et al. (12) in that we observed significantly lower PCT values in patients with GDM.

It has been suggested that platelets and the coagulation system are important determinants of atherogenesis and atherothrombosis (25). Although diabetes is considered a "prothrombotic state", the underlying mechanism

behind increased platelet reactivity and higher MPV in diabetic subjects is not completely understood (9). DM-associated thrombocytopathy could be due to reduced membrane fluidity; altered Ca^{2+} and Mg^{2+} homeostasis; increased arachidonic acid metabolism and thromboxane A_2 (TXA_2) synthesis; decreased prostacyclin production, nitric oxide production, and antioxidant levels; and increased expression of activation-dependent adhesion molecules (26). Increased MPV, on the other hand, may be explained by the osmotic swelling effect of hyperglycemia as well as the effects of insulin, which increases platelet turnover, resulting in an increase in the number of younger and consequently larger platelets (9). Tschope et al. (25) also suggested that glycoprotein IB expression, which plays an important role in thrombus formation, increases in patients with diabetes.

It has been well documented that larger platelets are younger with more potent metabolic and enzymatic activity, making them more "agreeable" (9). However, accurate measurement of platelet indices requires diligence since results may be affected by several factors, such as anticoagulants used after blood sampling, storage temperature, and processing delays (11). For example, platelets have been shown to swell with time when they are stored in tubes containing ethylenediaminetetraacetic acid

(EDTA) as an anticoagulant, resulting in a time-dependent increase in MPV (11).

The main limitation of this study is its retrospective nature, which translates to many factors being beyond our control. It has been established that blood samples need to be processed within 1 h if stored in tubes containing EDTA to prevent platelet swelling (11), and unfortunately the medical records of our study population did not contain any information regarding the processing time. Even though our hospital has a "rapid transfer and processing" policy for blood samples during the preanalytic stage, the time factor would have been better controlled in a prospective study. Another limitation of this study is the small number of patients, as well as the age difference between patients with and without GDM, which may have affected the study results.

Our results show that ALT, GGT, and some platelet indices may be useful in predicting the development of GDM, a condition with potentially serious complications. Very few studies have investigated the possible link between MPV and GDM, and to the best of our knowledge, this is the first study to evaluate RDW as a predictor of GDM. There is a need for more comprehensive prospective studies on larger study populations to help better identify predictors of GDM.

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