Mean Platelet Volume and Lipid Profile in Non-obese Prolactinoma Patients Without Insulin Resistance

İnsülin Direnci Olmayan Non-obez Prolaktinoma Hastalarında Lipid Profili ve Ortalama Trombosit Hacmi

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ABSTRACT Objective: Hyperprolactinemia has been associated with dyslipidaemia, hypercoagulability, impaired endothelial function, and decreased insulin sensitivity. Several reports have demonstrated the close relationship between mean platelet volume (MPV) and cardiovascular risk factors. The aim of our study was to investigate the relationship between MPV and prolactin, androgen hormones, and lipid profiles in premenopausal prolactinoma patients without insulin resistance. **Material and Methods:** Thirty-nine newly diagnosed premenopausal prolactinoma patients and twenty normoprolactinemic healthy control females were enrolled in the study. We assessed MPV, serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, total testosterone, free testosterone, androstenedione, dehydroepiandrosterone-sulfate, insulin, fasting glucose levels, homeostasis model assessment insulin resistance (HOMA-IR) and lipid profile, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, in the venous blood samples of all the subjects. **Results:** There were no differences between patients with prolactinoma and healthy controls with regard to age, BMI, and waist circumference. Prolactin, free testosterone, and MPV levels were significantly higher in prolactinoma patients compared to control group ($p<0.01$, $p<0.01$, $p=0.013$; respectively). HDL-C, LDL-C, triglyceride, FSH, LH, total testosterone, androstenedione, dehydroepiandrosterone-sulfate levels, and HOMA-IR were similar between the two groups ($p>0.05$). MPV correlated positively with prolactin ($r=0.727$, $p<0.001$) and triglyceride ($r=0.357$, $p=0.026$) but negatively with HDL-C levels ($r=-0.437$, $p=0.005$). **Conclusion:** Hyperprolactinemia and hypertriglyceridemia might cause atherosclerosis through elevating MPV levels in prolactinoma patients.

Key Words: Atherosclerosis; prolactinoma

ÖZET Amaç: Hiperprolaktinemi ile endotel disfonksiyonu, hiperkoagulopati, azalmış insulin duyarlılığı ve lipid bozuklukları arasındaki ilişki literatürde gösterilmiştir. Ortalama trombosit hacminin (OTH), kardiyovasküler hastalık ve tromboz riskini arttırdığını gösteren çalışmalar mevcuttur. Çalışmamızın amacı, insulin direnci olmayan premenopozal prolaktinoma hastalarında, prolaktin hormonu ile lipid parametreleri, OTH ve androjen hormon düzeyleri arasındaki ilişkiyi incelemek idi. **Gereç ve Yöntemler:** Çalışmamıza 39 yeni tanı almış, premenopozal, prolaktinomalı kadın hasta ve kontrol grubu olarak 20 sağlıklı kadın alındı. Her iki gruptaki katılımcılardan tam kan sayımı (OTH içeren), açlık kan şekeri, insulin, folikul uyarıcı hormon (FSH), luteinizan hormon (LH), östradiol, total testosteron, serbest testosteron, androstenedion, dehidroepiandrosteron-sulfat (DHEAS), high-density lipoprotein kolesterol (HDL-C), low-density lipoprotein kolesterol (LDL-C), trigliserid düzeylerinin tayini için venöz kan örneği alındı. İnsülin direnci HOMA-IR ile değerlendirildi. **Bulgular:** Hasta grubu ile kontrol grubu arasında; yaş, beden kutle indeksi ve bel çevresi özellikleri açısından anlamlı fark saptanmadı ($p>0,05$). Prolaktinoma hastalarında prolaktin, serbest testosteron ve OTH değeri kontrol grubuna kıyasla yuksek saptandı (sırasıyla; $p<0,01$, $p<0,01$, $p=0,013$). Gruplar arasında HDL-C, LDL-C, trigliserid, HOMA-IR, FSH, LH, total testosteron, serbest testosteron, androstenedion ve DHEAS düzeyleri acisindan anlamlı fark saptanmadı ($p>0,05$). Prolaktinomalı hastaların prolaktin değeri ile trigliserid ve OTH seviyesi arasında pozitif korelasyon gözlendi ($r=0,727$, $p<0,001$, $r=0,357$, $p=0,026$). HDL-C ve OTH arasında ise negatif korelasyon saptandı ($r=-0,437$, $p=0,005$). **Sonuç:** Prolaktinomalı hastalarda, hiperprolaktinemi ve hipertrigliseridemi OTH değerini artırarak ateroskleroza neden olabilir.

Anahtar Kelimeler: Ateroskleroz; prolaktinoma

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According to the World Health Organization, cardiovascular diseases (CVDs), representing 30% of all global deaths, are the number one cause of death globally. The most important cause of CVD is atherothrombosis, and several endocrine disorders have been linked to this pathological process. In a few studies, hormonal dysbalances have been shown to be associated with CVDs. Recent clinical and experimental studies have suggested that prolactin, a pleiotropic pituitary hormone, may potentially contribute to CVD, either through direct modulation of local cellular processes within atherosclerotic thrombi, and/or effecting conventional cardiovascular metabolic risk factors such as dyslipidemia, hypercoagulability, impaired endothelial function, and decreased insulin sensitivity.[1-5] Although the precise role of prolactin in the pathophysiology of CVD remains largely unknown and prospective studies have not yet confirmed that correlation between prolactin and CVDs risk factors, increased prolactin levels in atherosclerotic disease such as stroke and myocardial infarction had been documented.[6,7]

Platelet activity and aggregation potential, which are essential components of thrombogenesis and atherosclerosis, can be conveniently estimated by measuring mean platelet volume (MPV). Several reports have demonstrated the close relationship between MPV and cardiovascular risk factors.[8,9] Although some studies indicated that high prolactin levels affect platelet function or the coagulation cascade, thereby influencing thrombosis by thrombotic and pro-inflammatory plasma changes, the relationship between prolactin levels and MPV has not yet been investigated. To our knowledge, no other study has investigated the relationship between MPV levels and prolactin, androgen hormones, and lipid profiles, which would be risk factors of atherosclerosis in patients with prolactinoma. Therefore the aim of our study was to investigate the relationship between MPV and prolactin, androgen hormones, and lipid profiles in premenopausal prolactinoma patients without insulin resistance.

MATERIAL AND METHODS

A retrospective cross-sectional study was conducted on non-obese premenopausal patients with prolactinoma between the dates of January 2011 and January 2012. This research followed the tenets of the Declaration of Helsinki.

STUDY GROUPS

Thirty-nine newly diagnosed premenopausal prolactinoma patients [mean age 28.6±6.6 years, mean body mass index (BMI) 23.6±1.9 kg/m^2, mean Homeostasis Model of Assessment-IR (HOMA-IR) 1.33±0.4] and twenty normoprolactinemic age- and BMI-matched healthy control females (mean age 27±7.8 years, mean BMI 23.7±3 kg/m^2) were enrolled in the study (Table 1). None of the patients had ever received any treatments for prolactinoma. Patients who were pregnant or nursing, those chronic pulmonary, heart, liver or renal disease, those with chest trauma or any other chest disease (mastitis, zona, burn, etc.), and on any medication that could affect prolactin levels were excluded. Patients who had a specific anterior pituitary hormone deficiency, primary hypothyroidism, or polycystic ovary syndrome were also excluded. Besides, the patients who had the diseases such as diabetes mellitus, insulin resistance, atherosclerotic heart disease, obesity, chronic obstructive lung disease, malignancy, overt vascular disease, congenital or acquired thrombophilia or any other hematological abnormalities were excluded because of potential effects on the value of MPV.

Physical examination was performed; weight, height, waist circumference and calculated BMI values were recorded for each patient. The presence of a pituitary adenoma was confirmed with

TABLE 1: Demographic and clinical features of study groups.

Variables	Control Group	Prolactinoma Group	p
Number of cases	20	39	
Age, years	27.0±7.8	28.6±6.6	0.110
BMI, kg/m^2	23.7±3.0	23.6±1.9	0.230
Waist circumference, cm	73.3±4.6	73.4±4.9	0.350

BMI: Body mass index.

magnetic resonance imaging of pituitary region.

BIOCHEMICAL ANALYSES

Venous blood samples were obtained for all patients from the antecubital region at 8.00 am after an 8-12 hour overnight fast. A non-stressed state without prior intercourse or breast stimulation was ensured. Baseline serum prolactin levels were measured using the Unicel DxI 800 (Access Immunoassay Systems, Beckman Coulter) immunoassay kit. Normal values were 3.34-26.72 ng/mL in premenopausal women. Serum glucose levels were measured by the hexokinase method, whereas serum levels of triglyceride, very low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) were determined by the colorimetric method using a UniCel DxC 800 Systems autoanalyzer (Beckman Coulter, Fullerton, CA) with original reagents. LDL-C levels were calculated using the Friedewald method. Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, dehydroepiandrosterone-sulfate (DHEAS) levels were measured by the chemiluminescent microparticle immune method (paramagnetic particle, chemiluminescent immunoassay) using a Unicel DxI 800 System immune-analyzer (Beckman Coulter) with original reagents. Serum free testosterone and androstenedione levels were determined by RIA using commercial kits (for FT: BioSource, Nivelles, Belgium; for A: Radim, Roma, Italy). Plasma insulin was assayed chemilumunescende paramagnetic particle immunoasseys (Unicel DxI 800 System, Becman coulter USA).

Venous blood (1.8 mL) was taken and mixed with 0.2 mL of 3.8% sodium citrate solution (9:1) in order to perform a total blood count and MPV measurement. Measurements were completed within 1 hour using Coulter Beckman LH 750 equipment.

MEASURING INSULIN RESISTANCE

Insulin resistance was calculated by HOMA-IR (fasting glucose (mg/dl) x serum insulin (μIU/ml)/ 405) and was considered significant at a value of ≥2.7.

STATISTICAL ANALYSES

All results were expressed as mean±standard deviation (SD). Statistical package for social sciences

TABLE 2: The hormones and metabolic measurements of study groups.

Variables	Control Group	Prolactinoma Group	p
Number of cases	20	39	
Prolactin, ng/ml	11.6 (6.8-19.2)	84 (12.8-1370)	<0.001
DHEAS, μg /dl	154.5 (44.8-357.8)	192.4 (30-582)	0.147
Total Testosterone, ng/ml	0.5 (0.2-0.9)	0.4 (0.1-17.1)	0.153
Free Testosterone, ng/ml	1.3 (0.4-3.0)	0.8 (0.1-11.0)	<0.001
FSH, mIU/ml	7.1 (3.9-8.9)	6.4 (0.5-19.6)	0.486
LH, mIU/ml	4.9 (2.2-10.2)	4.3 (0.3-12.0)	0.200
Eustradiole, pg/ml	72 (21-181)	55 (15-390)	0.283
LDL-Cholesterol, mg/dl	104.1±30.2	111.6±27.8	0.349
HDL-Cholesterol, mg/dl	40.5 (33-63)	43 (32-76)	0.742
Triglyceride, mg/dl	74.5 (47-178)	95 (36-253)	0.192
Insulin, μIU /ml	6.4±2.1	6.3±2.4	0.870
HOMA-IR	1.29±0.5	1.33±0.4	0.749
Fasting glucose, mg/dl	81 (68-101)	81 (64-117)	0.841
MPV, fl	7.8 (7.1-8.4)	8.2 (6.7-10.9)	0.013

DHEAS: Dehiydroepiandrotenedione-sulphate; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; LDL: Low density lipoprotein; HDL: High density lipoprotein; MPV: Mean platelet volume.

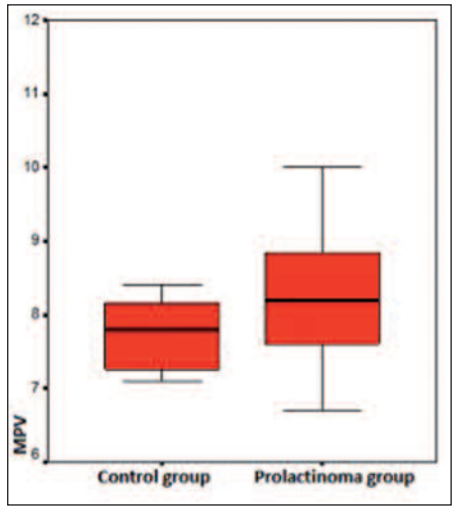

FIGURE 1: Distribution of levels of MPV in study groups.

cumference (Table 1). In hormone tests including prolactin and free testosterone levels were significantly higher in prolactinoma patients than in healthy controls (for both p<0.001) (Table 2). Prolactinoma group had significantly higher MPV levels compared to control group (8.2 and 7.8, respectively; p= 0.013) (Table 2, Figure 1). No significant differences were noted between groups with regard to serum HDL-C, LDL-C, triglyceride, fasting glucose, insulin, FSH, LH, total testosterone, androstenedione levels, and HOMA-IR (Table 2).

Mean platelet volume correlated negatively with prolactin (Figure 2) and triglyceride (Figure 3) levels but positively with HDL-C levels (Figure 4) (Table 3).

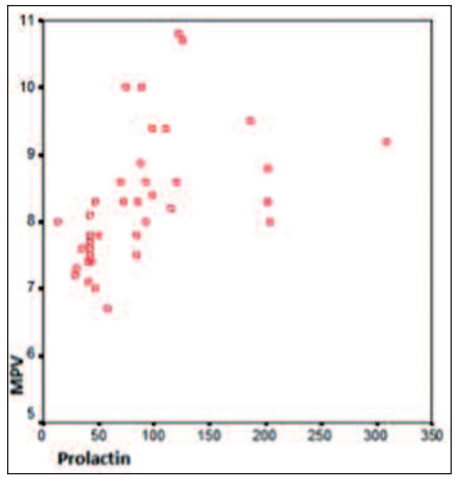

FIGURE 2: Relationship between Prolactin and MPV in prolactinoma group.

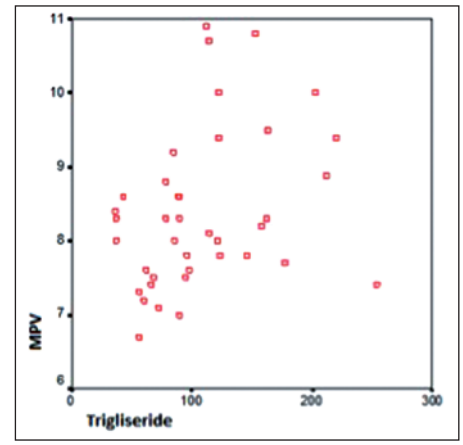

FIGURE 3: Relationship between Triglyceride and MPV in prolactinoma group.

(SPSS, version 11.5) software was used for the analyses. We used paired and unpaired student-t test, where necessary, to compare groups. Correlation analyses were performed according to Spearman co-efficient as appropriate. A two-tailed p value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic and clinical features of the participants. There were no significant differences between prolactinoma and control groups with regard to age, BMI, and waist cir-

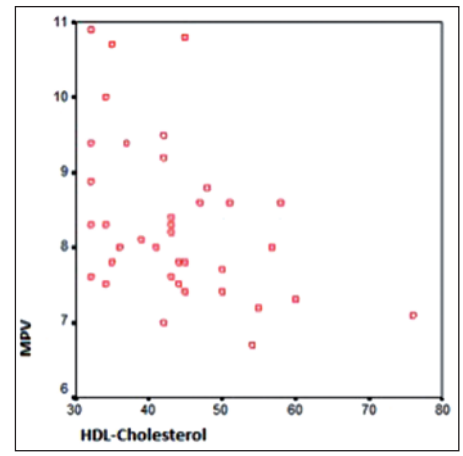

FIGURE 4: Relationship between HDL-Cholesterol and MPV in prolactinoma group.

TABLE 3: Correlations between MPV and hormones and metabolic measurements in the prolactinoma group.

Variables	Correlation Coefficient	p
Prolactin, ng/ml	0.727	<0.001
Androstenedione, ng/ml	0.024	0.883
DHEAS, µg /dl	0.095	0.564
Total Testosterone, ng/ml	-0.125	0.450
Free Testosterone, ng/ml	0.301	0.063
LDL -C, mg/dl	0.179	0.275
HDL -C, mg/dl	-0.437	0.005
Triglyceride, mg/dl	0.357	0.026
VLDL -C, mg/dl	-0.197	0.368

DHEAS: Dehiydroepiandrotenedione-sulphate; LDL: Low density lipoprotein; HDL: High density lipoprotein; VLDL-C: Very low density lipoprotein.

DISCUSSION

Hyperprolactinemia has been related to impaired metabolism, including dyslipidemia, hypercoagulability, impaired endothelial function, and decreased insulin sensitivity.[1-3] However, the metabolic effects of elevated prolactin levels are not completely understood. It has been shown that prolactin induces glucose intolerance, hyperinsulinemia and insulin resistance in prolactinoma patients.[2-4] Additionally, the relationship between disturbed glucose tolerance and high prolactin level in patients with/without prolactinoma has been shown.[2-5] Morover, it is hypothesized that hyperprolactinemia causes obesity by changing the hypothalamic energy metabolism.[10,11] But, direct interaction between high prolactin and BMIs is uncertain.[12] Because of these reports, we involved non-obese patients without insulin resistance in the present study.

Reuwer et al. reported some alterations in levels of plasma thrombotic factors in prolactinoma patients.[13] Plasma prothrombin, endogenous thrombin, IL-6, and hsCRP concentrations were found to be higher in prolactinoma patient in that study. Supporting these results, Wallaschofski et al. demostrated an increase in frequency of thrombosis in prolactinoma patients.[6] The authors also showed elevated prolactin levels in some atherosclerotic diseases. In accordance, patients with prolactinoma have found to higher platelet count, fibrinogen, and tissue plasminogen activator inhibitor-1 levels compared to healthy controls in a study by Erem et al.[7] On the other hand, results from studies showing elevated values of antithrombin in prolactinoma patients indicate that anticoagulant activity is also enhanced in these population.[14] All these data show that the relationship between prolactin and cardiovascular risk is not completely understood. Also, the underlying mechanisms of thrombosis in prolactinoma patients are still unclear.

Mean platelet volume, the most commonly used measure of platelet size, is a potential marker of platelet reactivity. Larger platelets are metabolically and enzymatically more active and have greater prothrombotic potential.[15,16] Our study showed that MPV in women with prolactinoma was higher than in healthy controls. Moreover, we also identified a positive correlation between MPV and prolactin levels. Based on these findings, we suggest that besides other thrombotic factors, elevated MPV may have an impact on atherothrombosis in patients with prolactinoma.

Regarding lipid levels, studies of prolactinoma patients reported conflicting results. While some studies showed increased cholesterol and triglyceride levels, others showed a normal lipid profile.[1,17] It was suggested that elevated prolactin levels may be responsible for the lipid abnormalities in prolactinoma patients, but the mechanism is not well understood yet. Inhibition of gonadotropin releasing hormone secretion by prolactin leads to hypoestrogenism, which results in increased total cholesterol and LDL-C and reduced HDL-C.[14] Moreover, Ogawa et al. showed the lipolytic effect of bovine prolactin in the goldfish Carassius auratus.[18] Nonetheless, the direct effect of prolactin on plasma lipids is difficult to establish since many factors influencing lipid metabolism are altered during hyperprolactinemia. In our study, although lipid levels were similar between prolactinoma patients and control group we detected a positive correlation between LDL-C and MPV and a negative correlation between HDL-C and MPV values, which suggests that interactions between lipid abnor-

malities and MPV may contribute to systemic inflammation in prolactinoma patients.[19]

CONCLUSION

Hyperprolactinemia and hypertriglyceridemia may cause platelet reactivity through elevating MPV values and therefore contribute to the pathogenesis of atherothrombosis in patients with prolactinoma. Similarly, high HDL-C may be protective from atherosclerosis by lowering MPV in prolactinoma patients.

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