The Influence of Hyperprolactinemia on Coagulation Parameters in Females with Prolactinomas

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Summary

Introduction Currently there is little information on the effects of prolactin (PRL) on the coagulation and fibrinolytic systems.

Objective The aim of this study was to evaluate the effects of hyperprolactinemia on the parameters of the hemostatic system and activation of the coagulation system.

Methods We studied PRL levels, body mass index (BMI), values of activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), D-dimer level, von Willebrand factor antigen (vWFAg) and fibrinogen in 15 young female patients with microprolactinomas before and after therapy and in 15 healthy female controls.

Results As expected, pretreatment PRL levels were significantly higher in patients than in controls (140.90±42.87 vs. 12.53±4.05 ng/ml; p<0.001). PT, although still in the normal range, was prolonged in patients with hyperprolactinemia as compared to the control group (13.55±1.39 vs. 12.65±0.53 s; p=0.03) and normalized after therapy (12.69±0.65 vs. 12.65±0.53 s; p=0.88). TT, although in normal range, was significantly shorter in the hyperprolactinemic patients than in the controls (14.34±4.52 vs. 17.21±1.35 s; p<0.025) and after treatment remained significantly shorter than in the controls (15.17±1.55 vs. 17.21±1.35 s; p<0.0001). D-dimer values before treatment in the patients with hyperprolactinemia were above the normal range (239.47±107.93 vs. 131.27±50.64 ng/ml, p=0.002) and decreased to normal values after therapy (239.47±107.93 vs. 146.60±39.15 ng/ml; p<0.001). D-dimer levels correlated with PRL (r=0.30) and the change in serum D-dimer values significantly correlated with the change in PRL levels during therapy (r=0.62). aPTT, vWFAg and fibrinogen were similar in patients and controls.

Conclusion In our study, increased thrombin generation that resulted in elevated D-dimer levels may be one of the contributing factors to the prethrombotic state in patients with hyperprolactinemia.

Keywords: hyperprolactinemia; hemostatic system; coagulation

INTRODUCTION

Changes in the hemostatic system activity that create a state of hypercoagulability, together with the presence of low grade chronic inflammation are involved in the pathogenesis of atherosclerosis/atherothrombosis and its various clinical manifestations, e.g. coronary artery disease, peripheral artery disease and ischemic stroke [1]. The association between atherosclerosis and venous thrombosis has recently been demonstrated [2]. Hemostasis is a complex biological process that maintains the integrity of a closed high-pressure circulatory system after vascular damage and prevents excessive bleeding or thrombotic events. The delicate hemostatic balance can be achieved and maintained by synchronized action of many factors that participate in this process of which the most important are the vessel (endothelial cells), platelets, coagulation and the fibrinolytic system [3]. A wide variety of endocrine disorders have been associated with disturbances in laboratory tests of coagulation, correlated with the occurrence of thrombotic or bleeding disorders [4].

Prolactinomas are the most common functionally pituitary tumors with prevalence of approximately 100 per 1 million people. The first line of treatment of macroprolactinomas and symptomatic microprolactinomas are dopamine agonists. These drugs lower prolactin (PRL) levels, decrease tumor size and restore gonadal function [5].

Hyperprolactinemia is found to be associated with a low grade chronic inflammation as well as endothelial dysfunction [6, 7]. The association between conditions with high levels of PRL (pregnancy, estrogen therapy, antipsychotic therapy, pituitary prolactin producing adenomas) and increased risk of venous thromboembolism (VTE) and atherothrombosis has been demonstrated [4, 8, 9]. Increased risk of VTE occurrence and higher incidence of coronary and peripheral artery disease and ischemic stroke in the individuals with hyper-
prolactinemia may be causative or simply a coincidence. Whether hyperprolactinemia increases ADP-induced platelet aggregation, not only in vitro but also in vivo, has yet to be confirmed by further investigation. To the best of our knowledge, the influence of hyperprolactinemia on coagulation system activation has not been thoroughly investigated. Under physiologic conditions, the coagulation system is composed of procoagulant factors which are balanced by naturally occurring anticoagulants (antithrombin and protein C). The basic laboratory tests of coagulation are the measurement of prothrombin time and activated partial-thromboplastin time.

**OBJECTIVE**

The aim of this study was to evaluate the possible effects of hyperprolactinemia on coagulation system activity and to investigate whether there is any difference in the activity of coagulation system parameters before and after the treatment of hyperprolactinemia.

**METHODS**

Fifteen non-obese female patients of mean age 31.07±6.69 years (range 22–40 years), body mass index (BMI) 25.25±4.00 kg/m² with newly diagnosed microprolactinomas were included in this prospective study. They were diagnosed at the outpatient clinic of the Clinical Center of Vojvodina, Novi Sad. Inclusion criteria were serum PRL level above 90 μg/ml, MRI evidence of pituitary microadenoma, normal basal level of cortisol, free thyroxin (FT4), insulin growth factor 1 (IGF 1), low or normal basal levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Patients with other causes of hyperprolactinemia were excluded from the study as well as women with hematologic, cardiovascular and autoimmune diseases, diabetes mellitus, alcohol abuse, pregnancy and current infection. The control group consisted of 15 age matched healthy women. All subjects were free of medications and estrogens prior to investigation.

The study was approved by the institutional Ethic Committee and all participants signed informed written consent to participate.

**Study protocol**

The study was designed as a prospective, case control clinical trial. Samples for PRL level (at 8 am and 11 am), activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), D-dimer level, von Willebrand factor antigen level (vWFAg) and fibrinogen were obtained at the time of diagnosis, before the commencement of the treatment of hyperprolactinemia. The second sampling time for all mentioned parameters was repeated after PRL level was normalized. All patients were treated with dopamine agonists (four with bromocriptine and 11 with cabergoline). The mean duration of treatment was 17.90±6.20 months (range 11.5 to 29.0 months). The same laboratory parameters were analyzed in the control group. BMI was calculated according to formula: body mass (kg)/(height (m))²×100.

**Laboratory measurements**

Plasma samples for hemostatic system investigation were obtained after venepuncture of the cubital vein, using trisodium citrate as an anticoagulant, after centrifugation at 2500 g for 15 minutes. aPTT, PT, TT, D-dimer level, vWFAg level and fibrinogen level were determined using Instrumentation Laboratory (IL, Milan, Italy) commercial kits. All coagulation tests were performed using an automated coagulometer ACL 9000, manufactured by IL, Milan, Italy. Fibrinogen level was determined according to Clauss, using IL reagent and coagulometer ACL 9000. D-dimer was determined using latex immunoassay (suspension of latex polystyrene particles coated with monoclonal antibodies MA-8D3), manufactured by IL, Milan, Italy, and vWFAg was determined using latex immunoassay HE-MOSIL vWF Antigen, manufactured by IL, Milan, Italy. Results of screening tests (aPTT, PT, TT) were compared to the results obtained from the samples of control normal plasma (IL, Milan, Italy) and expressed as ratio (R). The ratio between 0.85-1.29 for all three screening tests was considered to be normal. Reference values for D-dimer, vWFAg and fibrinogen were bellow 230 ng/ml, from 45% to 140% and from 2.2 to 3.9 g/l, respectively.

The blood samples for PRL level determination were taken by cubital vein venepuncture fasting at 8 am and 11 am (1 hour after meal) and the result was expressed as mean value of two determinations. Serum PRL levels were measured using ECLIA Elecsys Prolactin (Roche Diagnostics, Elecsys 2010 analyzer); reference range (non-pregnant women) were from 5.0 to 24.0 ng/ml. For 30.9 ng/ml, within-run precision, coefficient of variation (CV) was 2.5% and total CV was 4.1%.

All plasma samples were stored at -70°C.

**Statistical analysis**

Results are expressed as mean values, standard deviation (SD). Results of all investigated parameters in the study group before treatment and the control group were compared, as well as the results of the study group before and after treatment of hyperprolactinemia by using Student’s T test. The value of p<0.05 was considered to be statistically significant. The incidence of nonparametric variables was compared using Fisher’s Exact test. The correlation between PRL level and hemostatic parameter values as well as the correlation between BMI and hemostatic parameters values obtained before and after therapy were examined; the correlation coefficient r>0.3 either positive or negative was considered moderately and r>0.7 highly statistically significant.
RESULTS

Pretreatment PRL levels were significantly higher in patients than in controls (140.90±42.87 vs. 12.53±4.05 ng/ml; p<0.001) (Table 1). BMIs in the patients before treatment and controls were within the normal range, but significantly higher in the patients (25.25±4.00 vs. 21.06±1.99 kg/m²; p<0.001), (Table 1). We found no correlation between the level of PRL and BMI (r=0.21). There were no differences in age and smoking between the patients and controls. All participants had normal blood pressure, glucose levels and platelet count.

Before treatment of hyperprolactinemia, aPTT was within normal range and with no difference between the patients and controls (26.31±3.29 vs. 25.29±1.81 s; p=0.30), (Table 2).

Pretreatment values of PT in the patients and controls were within referent ranges, but significantly prolonged in the patients compared to controls (13.53±1.39 vs. 12.65±0.53 s; p=0.03), (Table 2). No correlation between PT and PRL (r=-0.21) was found. TT was significantly shorter in the hyperprolactinemic patients than in controls (14.34±4.52 vs. 17.21±1.35 s; p=0.025), (Table 2). The correlation between TT and PRL was positive and slightly significant (r=0.47). No correlation between TT and BMI was found (r=0.01).

Mean D-dimer values in the hyperprolactinemic patients before treatment with dopamine agonists were above normal range and significantly higher than in the controls (239.47±107.93 vs. 131.27±50.64 ng/ml, p=0.002), (Table 2). The values of D-dimer and PRL showed positive correlation (r=0.30).

The values of vWFAg in the hyperprolactinemic patients were not significantly different from the control group (100.93±31.46% vs. 97.20±22.05%; p=0.71), (Table 2). There was no correlation between vWFAg and PRL (r=-0.04).

The mean values of fibrinogen in the patients before treatment and controls were within the normal range, and were not different between the patients and controls (3.20±1.41 vs. 2.94±1.15 g/l, p=0.15), (Table 2).

Elevated PRL levels before therapy normalized after treatment (140.90±42.87 vs. 16.14±12.36 ng/ml; p<0.001), (Table 2). After treatment, BMI in the patients was decreased significantly (25.25±4.00 vs. 24.72±4.06 kg/m²; p<0.02), (Table 2). BMI in the patients after therapy and controls was similar (24.72±4.06 vs. 21.06±1.99 kg/m²; p=0.29), (Table 2). There was no difference in aPTT values neither before (26.31±3.29 vs. 25.25±3.08 s; p=0.146) nor after treatment (25.25±3.08 vs. 25.29±1.81 s; p=0.96), (Table 2) as compared to the controls.

PT was statistically significantly shorter after therapy (13.53±1.39 vs. 12.69±0.65 s; p<0.02), (Table 2). Changes in PT values did not correlate with changes in PRL levels (r=-0.068) nor with changes in BMI values (r=-0.25).

PT values in the patients after therapy and controls were similar (12.69±0.65 vs. 12.65±0.53 s; p=0.88), (Table 2). TT did not differ before and after treatment (14.34±4.52 vs. 15.17±1.55 s; p=0.48), (Table 2). TT values did not correlate with changes in PRL levels during therapy (r=-0.094) nor with changes in BMI values (r=-0.001). Although TT was in the normal range in the patients after therapy it remained significantly shorter than in the controls (15.17±1.55 vs. 17.21±1.35 s; p<0.0001), (Table 2).

Mean D-dimer values were above the normal range and they significantly decreased after therapy (239.47±107.93 vs. 146.60±39.15 ng/ml; p<0.001), (Table 2). The change in D-dimer values significantly correlated with the change in PRL levels after therapy (r=0.62), (Graph 1), but not with changes in BMI (r=-0.09). No difference was found

Table 1. Clinical characteristics of patients with hyperprolactinemia before therapy and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (n=15)</th>
<th>Controls (n=15)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before therapy</td>
<td>After therapy</td>
<td></td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td>140.90±42.87</td>
<td>12.53±4.05</td>
<td>0.001**</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.25±4.00</td>
<td>21.06±1.99</td>
<td>0.001**</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>26.31±3.29</td>
<td>25.25±3.08</td>
<td>0.878</td>
</tr>
<tr>
<td>PT (s)</td>
<td>13.53±1.39</td>
<td>12.69±0.65</td>
<td>0.019**</td>
</tr>
<tr>
<td>TT (s)</td>
<td>14.34±4.52</td>
<td>17.21±1.35</td>
<td>0.300</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>239.47±107.93</td>
<td>16.14±12.36</td>
<td>0.004**</td>
</tr>
<tr>
<td>vWFAg (%)</td>
<td>100.93±31.46</td>
<td>93.87±22.63</td>
<td>0.280</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>3.20±1.41</td>
<td>3.49±0.83</td>
<td>0.500</td>
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</tbody>
</table>

Table 2. Prolactin, BMI and hemostatic system values (mean±SD) in hyperprolactinemic patients before and after therapy with dopamine agonists and controls

<table>
<thead>
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<th>Variable</th>
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<th>Controls (n=15)</th>
<th>p#</th>
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<tr>
<td>Prolactin (ng/ml)</td>
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<td>BMI (kg/m²)</td>
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<tr>
<td>aPTT (s)</td>
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<td>25.25±3.08</td>
<td>0.878</td>
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<td>0.878</td>
</tr>
<tr>
<td>TT (s)</td>
<td>14.34±4.52</td>
<td>17.21±1.35</td>
<td>0.001**</td>
<td>0.360</td>
</tr>
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<td>D-dimer (ng/ml)</td>
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<tr>
<td>vWFAg (%)</td>
<td>100.93±31.46</td>
<td>3.49±0.83</td>
<td>0.500</td>
<td></td>
</tr>
</tbody>
</table>

Values are expressed as mean value ± standard deviation and as number of patients with percent.

* p<0.05 compared patients and controls
** p<0.01 compared patients and controls
# Fisher’s Exact test
n – number of subjects; BMI – Body Mass Index; BP – blood pressure

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Increased risk of VTE and coronary and peripheral arterial disease and stroke co-exist in hyperprolactinemic conditions [4, 9]. Wallaschofski et al. [10, 11] have described the association between hyperprolactinemic conditions such as pregnancy, prolactinomas and antipsychotic therapy with increased risk of VTE. The same group has also demonstrated that PRL levels are increased in patients with idiopathic thrombosis [12]. Increased values of PRL in patients with stroke and myocardial infarction have also been found [13, 14]. Platelet activation is involved in the pathogenesis of atherosclerosis and VTE, and might be a possible link between these two entities. Platelets under normal condition adhere to damaged vessel walls through interaction with vWFAg promoting aggregation and formation of hemostatic plug. Platelets also support thrombin generation by assembling activated coagulation factors on their surfaces. Several studies showed that PRL may be a novel potent co-factor for platelet aggregation [10, 15-18]. On the other hand, Atmaca et al. [19] investigated whether platelet activity is increased by hyperprolactinemia during pregnancy as reflected by β-thromboglobulin level. They found that platelet activity during pregnancy was comparable to non-pregnant state, therefore no significant effect of PRL on platelet function in vivo was observed. Mon SY et al. [20] did not find a significant rate of deep vein thrombosis, pulmonary embolism and cerebrovascular accidents in prolactinoma patients. According to these results they concluded that hyperprolactinemia per se did not appear to predispose to hypercoagulable state. Unfortunately, this study had some limitations and further examinations are needed.

A recently published study suggest that hyperprolactinemia presents proinflammatory and procoagulant state [21].

As previously stated, a direct effects of PRL on coagulation has not been investigated thoroughly [4, 9]. Study of Erem et al. [22] suggested a potential mechanism for hypercoagulability in patients with hyperprolactinemia. They found that platelets, fibrinogen, antithrombin III, plasminogen activator inhibitor and the ratio of plasminogen activator inhibitor to tissue plasminogen activator were significantly increased in patients with prolactinoma. However, there are some data on the possible indirect impact of high PRL on the parameters of the hemostatic system. Hyperprolactinemia stimulates hematopoiesis [23-26] and has an impact on growth factors, for example vascular endothelial growth factor (VEGF) [27]. Furthermore, it is known that hyperprolactinemia is associated with a low level of inflammation, dyslipidemia, endothelial dysfunction [7, 8, 21] as well as some disturbances in glucose metabolism [28] all of which indirectly effect the hemostatic system. When studying coagulations in patients treated with dopamine agonists, then the inhibitory effects of bromocriptine on vascular smooth muscle cell proliferation as well as the effect of cabergoline on vascular permeability controlling the secretion of VEGF must be taken into account [29, 30]. The effects of dopamine agonists on the vascular system in prolactinomas have not been systematically studied. Mon et al. [20] did not find significant differences in throm-

In our study we showed that D-dimer values were elevated in the patients with hyperprolactinemia and decreased with normalization of PRL levels. A positive correlation was found between PRL changes and D-dimer changes during therapy with dopamine agonists. Elevated D-dimer levels indicate increased coagulation activation, with consecutively increased fibrinolytic system activity, which may represent a factor for thrombotic disease. This may suggest that PRL per se may have impact on the coagulation activity.

We also found that PT was significantly prolonged in patients with hyperprolactinemia in comparison with healthy controls and that with normalization of PRL with dopamine agonists, it shortened. However, the absence of correlation between PRL level and PT before therapy, and between changes of PRL levels and changes of PT did not favor the role of high PRL on PT.

Shorter TT in the studied group may contribute to the increased risk for the occurrence of thrombotic complication. After normalization of PRL levels with dopamine agonist therapy, TT did not reach values as in the control group.

No difference in the aPTT values between the patients before and after treatment and healthy controls was found. The levels of vWFAg and fibrinogen were similar in patients and controls and did not change after therapy with dopamine agonists.

DISCUSSION

In D-dimer levels between the study group after treatment and controls (146.60±39.15 vs. 131.27±50.64 s, p=0.36), (Table 2).

The level of vWFAg remained unaffected by treatment (100.93±31.46 vs. 93.87±23.63%; p=0.28), (Table 2) and was not different compared to the control group (93.87±23.63 vs. 97.20±22.05 %; p=0.69), (Table 2).

Fibrinogen level in the patients after therapy remained within the normal range (3.20±1.41 vs. 3.49±0.83 g/l; p=0.50), (Table 2) with no significant difference between the two groups (3.49±0.83 vs. 2.94±1.15 g/l; p=0.15), (Table 2).

Graph 1. The regression curve (∆ D-dimer=1.38+0.02x ∆ PRL), (solid line) and 95% confidence interval (dotted line) presents the correlation between changes in D-dimer (∆ D-dimer) and changes in PRL (∆ PRL) in patients with prolactinomas after dopamine agonists therapy.
boembolic events between prolactinoma patients treated by dopamine agonists or surgery. According to that finding, any influence of dopaminergic therapy on the risk of thromboembolic events was excluded, but further studies are needed.

CONCLUSION

Prethrombotic state in patients with hyperprolactinemia is of complex origin, with increased level of thrombin generation determined by elevated D-dimer levels, along with endothelial dysfunction and increased platelet reactivity. Possible effects of dopamine agonists themselves have remained unsolved. Furthermore, the role of anticoagulants in the prothrombotic state of hyperprolactinemia needs to be addressed in future studies.

ACKNOWLEDGMENT

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Утицај хиперпролактинемије на параметре коагулатије код жена са пролактиномом

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КРАТАК САДРЖАЈ
Увод Утицај пролактина на коагулатиони и фибринолитички систем је мало проучаван досад.
Циљ рада Циљ ове студије је био да испита утицај хиперпролактинемије на параметре хемостатног система и активације коагулатионог система.
Методе рада Одређивали смо ниво пролактина у сееруму и вредности активисаног парцијалног тромбопластинског времена (aPTT), протромбинског времена (PT) и тромбинског времена (TT), ниво D-димера, антиген Фон Вилебранд-вовг (von Willebrand) фактора (vWFAg) и фибриногена у сееруму 15 младих жена с пролактиномом пре и после лечења хиперпролактинемије и 15 здравих жена контролне групе.
Резултати Као што се и очекивало, ниво пролактина пре лечења су код истипанца с хиперпролактинемијом биле статистички значајно више него код истипанца контролне групе (140±42,87 према 12,53±0,51 ng/ml; p<0,001). PT, мада и даље у оквиру нормалних вредности, било је продужено код жена с хиперпролактинемијом у поређењу с контролном групом (13,53±1,39 према 12,65±0,53 s; p=0,03), али се нормализовало после лечења (12,69±0,65 према 12,65±0,53 s; p=0,88). Иако у оквиру референтних вредности, TT је било статистички значајно краће код жена с хиперпролактинемијом него код истипанца контролне групе, како пре терапије (14,34±4,52 према 17,21±1,35 s; p<0,025), тако и после ње (15,17±1,55 према 17,21±1,35 s; p=0,0001). Вредности D-димера су пре лечења код жена с хиперпролактинемијом биле изнад горње границе нормалних вредности (239,47±107,93 према 131,27±50,64 ng/ml; p=0,002), а нормализовале су се после терапије (239,47±107,93 према 146,60±39,15 ng/ml; p<0,001). Између нивоа D-димера и пролактина уочена је позитивна корелација (r=0.30), а промене нивоа D-димера у сееруму имале су статистички значајану, позитивну корелацију с променама пролактина у сееруму током лечења жене од хиперпролактинемије (r=0.62). Вредности aPTT, vWFAg и фибриногена биле су сличне код болесница и здравих истипанца. Закључак Повећано стварање тромбина уочено у нашем испитивању, које се огледало у повишењим вредностима D-димера, могло би бити фактор који доприноси протромбинозном стању жена с хиперпролактинемијом.
Клучне речи: хиперпролактинемија; хемостатски систем; коагулатија

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