Increased serum prolactin levels in drug-naive first-episode male patients with schizophrenia

YAKUP ALBAYRAK, MURAT BEYAZYÜZ, ELMAS BEYAZYÜZ, MURAT KULOĞLU


Background: Prolactin is a hormone receiving considerable attention in psychiatry. Increased serum prolactin level is frequently associated with dopamine blocking antipsychotics. Furthermore, decreased prolactin level was considered a reflector of the effect of antipsychotics. However, there is restricted numbers of investigations that researched baseline prolactin levels in first-episode patients with schizophrenia. Aims: We purpose to investigate serum baseline prolactin levels in drug-naive first-episode patients with schizophrenia (FES) and to explore the differences in serum prolactin levels between FES, drug-free schizophrenic patients (DFS) and healthy controls (HC).

Material and Methods: The study was conducted in the Departments of Psychiatry, Gölbasi Hasvak and Kirklareli State Hospitals, Turkey. Thirty male FES, 41 male DFS and 32 male HC were included in study. All participants were clinically examined and individually interviewed. Before initiating any pharmacological treatment, 5 ml of venous blood was collected to measure serum prolactin levels between 08:00 and 10:00 h, which was determined by radioimmunoassay (RIA). Prolactin levels were also collected from the consenting HC using the same assay. Results: The mean age was higher in the DFS group. The mean score of Brief Psychiatric Rating Scale was higher in the FES group and mean score of Scale for the Assessment of Negative Symptoms was higher in the DFS group. The mean value of prolactin was higher in the FES group (34.1 ± 19.9 ng/dl) compared with DFS (17.9 ± 6.5 ng/dl) and HC (9.7 ± 2.3 ng/dl) (F = 35.5, P < 0.001). Additionally, the mean value of serum prolactin is higher in the DFS group compared with HC (P < 0.001). Conclusion: To our knowledge, this study is the first to demonstrate higher serum prolactin levels in male FES compared with male DFS and male HC. Prolactin might act as a protective factor while first episode of schizophrenia is experienced. Future studies are needed to provide the role of prolactin in schizophrenia.

• Drug-free, Drug-naive, First episode, Prolactin, Schizophrenia.

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Prolactin is a polypeptide hormone, which is secreted by the lactotroph cells of the anterior pituitary gland. Prolactin is released in a pulsatil manner and its half-life is approximately 50 min. The regulation of prolactin release is under the control of prolactin inhibitor factor (PIF) dopamine (DA) (1). The increased dopaminergic activity in mesolimbic dopaminergic pathway is the most widely accepted theory of symptomatology of schizophrenia and is commonly treated with antipsychotic drugs (2). Most of our knowledge concerning prolactin levels in schizophrenic patients has been gained from studies of patients treated with antipsychotic medications (3). Increased serum prolactin levels frequently are seen in patients treated with therapeutic doses of conventional antipsychotics, which block DA receptors (4, 5). Furthermore, elevated serum prolactin levels were considered a reflector of mesolimbic dopaminergic activity. According to this hypothesis, patients without exposure to any DA blocking antipsychotic agents have increased dopaminergic activity; thus decreased serum prolactin level might suggested to be associated with psychopathology (6, 7).

The most of studies that investigated serum prolactin levels in first-episode drug-naive patients with schizophrenia reported normal or lower serum prolactin levels (8–10). Some studies have demonstrated a relation between early relapse following neuroleptic withdrawal and low serum prolactin levels (11, 12). In a recent study, increased serum prolactin level was found to be inversely associated with severity of psychopathology in drug-naive patients with schizophrenia (13). Shrivastava et al. (7) reported increased serum prolactin levels in male drug-naive patients with schizophrenia in their
follow-up study (7). More recently, Riecher-Rössler et al. (14) reported hyperprolactinemia in antipsychotic naïve first-episode psychotic patients. Gender has a notable effect on serum prolactin level. Although the role of estrogens on prolactin secretion still remains unclear, long-term effects of estrogens regulate the prolactin secretion, which may explain the remarkable decrease in serum prolactin concentrations after menopause (15, 16). Thus, we think that investigating serum prolactin level in merely male gender might lead us to demonstrate more confident evidence in patients with schizophrenia and healthy individuals for understanding the baseline characteristic of serum prolactin level. In this study, we aimed to investigate whether there would be discrepancy in levels of prolactin in first-episode drug-naïve patients with schizophrenia (FES) compared with drug-free schizophrenic patients (DFS) and healthy controls (HC). We suggest that the dopaminergic activity in tuberoinfundibular pathway differs during the illness process and thus serum prolactin levels might differ between, FES, DFS and HC.

Materials and Methods

Participants

The study was conducted in the Departments of Psychiatry, Gölbüş Hasvak and Kirklareli State Hospitals, Turkey, between the October 2011 and October 2012. Among patients who were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, text revision (DSM-IV-TR) (17) and who were admitted or followed up at inpatient clinics, outpatient clinics and community health services, 72 were suitable for inclusion in the present study (14). The diagnoses were made by trained interviewers (YA and MB) using the Structured Clinical Interview for DSM-IV Axis I (18, 19). Thirty patients were experiencing their first episode of schizophrenia and had never previously been exposed to any antipsychotic drug. Another 41 patients had suffered from schizophrenia for at least 2 years and all of them were drug free for at least 4 weeks in the case of oral antipsychotics and 6 weeks for long-acting injectable antipsychotics because of non-adherence. Additionally, 32 male healthy subjects who were willing to participate in the study were selected by clinicians (YA and MB) and provided blood samples.

All subjects provided written informed consent for participation in the study after the procedure had been fully explained. The exclusion criteria were as follows: 1) female gender; 2) presence of any other psychiatric morbidity, such as alcohol or substance dependence, which is likely to interfere with diagnosis; 3) presence of any concurrent medical or endocrine disorder; 4) administration of other medications that are likely to alter prolactin levels.

Procedure

All patients were clinically examined and individually interviewed. In order to obtain an objective history of the patients, accompanying close relatives were interviewed. The socio-demographic and clinical data includes age, marital status, employment status, length of education, living place and duration of treatment. The patients were rated with the Scale for the Assessment of Negative Symptoms (SANS) (20), the Scale for the Assessment of Positive Symptoms (SAPS) (21) and the Brief Psychiatric Rating Scale (BPRS) (22). Before initiating any pharmacological treatment, 5 ml of venous blood was collected to measure serum prolactin levels between 08:00 and 10:00 h, which was determined by radioimmunoassay (RIA). Prolactin levels were also collected from the consenting healthy subjects using the same assay.

Psychopathological assessment in patients

Instruments

The Structured Clinical Interview for DSM-IV Axis I (SCID-I) is a semi-structured interview for making the major DSM-IV Axis I diagnoses. The instrument is designed to be administered by a clinician or trained mental health professional. It was developed by First et al. (19) and the Turkish version was reported to be reliable by Corapcioğlu et al. (18).

The SANS assesses five symptom complexes to obtain clinical ratings of negative symptoms in patients with schizophrenia. They are: affective blunting; alogia (impoverished thinking); avolition/apathy; anhedonia/ asociality; and disturbance of attention. The final symptom complexes seem to have less obvious relevance to negative symptoms than the other four complexes. Assessments are conducted on a 6-point scale (0 = not at all to 5 = severe). It was developed by Andreasen (20). The Turkish version was reported to be reliable by Erkoç et al. (23).

The SAPS is designed to assess positive symptoms, principally those that occur in schizophrenia. It is intended to serve as a complementary instrument to SANS. These positive symptoms include hallucinations, delusions, bizarre behavior and positive formal thought disorder. SAPS was developed by Andreasen (21). The Turkish version reported to be reliable by Erkoç et al. (24).

The BPRS is a rating scale that a clinician or researcher may use to measure psychiatric symptoms such as depression, anxiety, hallucinations and unusual behavior. Each symptom is rated 1–7 and depending on the version a total of 18–24 symptoms are scored. The BPRS was developed by Overall & Gorham (22) and its Turkish translation is available.

Statistical methods

Data were analyzed using the Statistical Package for the Social Sciences, PC version 16.0 (SPSS, Chicago, IL). A
confidence interval (CI) of 95% and a two-tailed P-value < 0.05 were considered statistically significant for all analyses. Variables were tested for homogeneity of variance using the Levene test and for normality of distribution by utilizing the Kolmogorov–Smirnov test. Differences between ages and serum prolactin levels were tested with a series of one-way analyses of variance (ANOVAs), whereas differences in marital status, employment status, length of education and living place were assessed by a χ² test. Tukey’s HSD was applied in post hoc analysis for the multiple comparisons of the three groups. Because the distribution of scores in the SANS, SAPS and BPRS were parametric and homogeneous, the Student t-test was used for comparing the scores of the SANS, SAPS and BPRS between FES and DFS.

Results
The mean ages of FES, DFS and HC were respectively 25.7 ± 5.4, 35.3 ± 10.1 and 26.4 ± 6.5 years. There was a significant difference between groups in terms of age (F = 8.2, P = 0.001). The DFS group was older than compared with the FES and HC groups (respectively P = 0.001 and P = 0.005). The duration of illness in the DFS group was 7.21 ± 4.74 years. After extracting the duration of illness in each subject from DFS, the mean ages of FES, DFS and HC were respectively 25.7 ± 5.4, 24.1 ± 3.6 and 26.4 ± 6.5 years, and there was no significant differences between groups (F = 1.94, P = 0.15). The numbers of individuals in employment and married were significantly higher in the HC group compared with both patient groups (respectively; χ² = 55.16, P < 0.001; χ² = 13.61, P = 0.009). The percentage of participants who were educated for 8 years and above were higher in HC (χ² = 21.56, P < 0.001). All participants were likely to live in rural areas (P > 0.05) (Table 1).

The mean score of the BPRS in the DFS group (34.9 ± 9.5) was higher than score of the FES group (29.3 ± 7.5) (F = 0.17, P = 0.008). The mean score of the SANS in the DFS group (37.8 ± 15.4) was also higher than score of the FES group (27.1 ± 9.4) (F = 5.78, P = 0.001). The mean scores of the SAPS were similar between groups (scores of DFS and FES respectively; 34.3 ± 15.1, 33.6 ± 17.2; P > 0.05) (Table 2).

The mean value of serum prolactin levels were found to be significantly different between groups (F = 35.5, P < 0.001). Post hoc analysis of Tukey HSD revealed that the serum prolactin level was higher in the FES group (34.1 ± 19.9 ng/dl) compared with the DFS (17.9 ± 6.5 ng/dl) and HC (9.7 ± 2.3 ng/dl) (respectively P < 0.001 and P < 0.001). The mean serum prolactin level in the DFS group level was higher than in the HC (P < 0.001) (Table 2). In correlation analysis, there were no significant associations between serum prolactin levels and scores of SANS, SAPS and BPRS (respectively r = 0.19, r = −0.105, r = −0.64, P > 0.05).

Discussion
Prolactin is a hormone receiving considerable attention in psychiatry and there have been numerous studies that investigated serum prolactin levels in many psychiatric disorders such as schizophrenia, bipolar disorder and anxiety disorders (7, 25–27). Serum prolactin levels were reported to be reduced or normal in FES in most of previous studies (8–10). Elevated serum prolactin levels were frequently associated with dopaminergic blockage in the tuberoinfundibular pathway by antipsychotics.

Table 1. Socio-demographic characteristics of participants.

<table>
<thead>
<tr>
<th></th>
<th>FES (n = 30)</th>
<th>DFS (n = 41)</th>
<th>HC (n = 32)</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.7 ± 5.4</td>
<td>35.3 ± 10.1</td>
<td>26.4 ± 6.5</td>
<td>F = 8.2, DFS&amp;FES:</td>
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<tr>
<td></td>
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<td>P = 0.001; DFS&amp;HC:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.005</td>
</tr>
<tr>
<td>Family status</td>
<td></td>
<td></td>
<td></td>
<td>χ² = 13.61, P = 0.009</td>
</tr>
<tr>
<td>Single</td>
<td>24 (80%)</td>
<td>30 (73.2%)</td>
<td>3 (9.4%)</td>
<td>χ² = 55.16, P &lt; 0.001</td>
</tr>
<tr>
<td>Married</td>
<td>6 (20%)</td>
<td>11 (26.8%)</td>
<td>29 (90.6%)</td>
<td>χ² = 21.56, P &lt; 0.001</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Works regularly</td>
<td>8 (26.7%)</td>
<td>3 (7.8%)</td>
<td>3 (9.4%)</td>
<td></td>
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<tr>
<td>Unemployed</td>
<td>22 (73.3%)</td>
<td>38 (92.7%)</td>
<td>29 (90.6%)</td>
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<tr>
<td>Education</td>
<td></td>
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<tr>
<td>0–7 years</td>
<td>7 (23.3%)</td>
<td>10 (24.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>7–11 years</td>
<td>15 (50%)</td>
<td>23 (56.1%)</td>
<td>11 (34.4%)</td>
<td></td>
</tr>
<tr>
<td>Above 11 years</td>
<td>8 (29.3%)</td>
<td>8 (26.7%)</td>
<td>21 (65.6%)</td>
<td></td>
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<tr>
<td>Living place</td>
<td></td>
<td></td>
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<tr>
<td>Rural</td>
<td>18 (60%)</td>
<td>29 (70.7%)</td>
<td>21 (65.6%)</td>
<td></td>
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<tr>
<td>Urban</td>
<td>12 (40%)</td>
<td>12 (29.3%)</td>
<td>11 (34.4%)</td>
<td></td>
</tr>
</tbody>
</table>

FES, drug-naive first-episode patients with schizophrenia; DFS, drug-free schizophrenic patients; HC, healthy controls; NS, not significant. Significant P-values in bold.
The primary physiological role of prolactin is the induction of lactation. Secretion from lactotrophs is controlled by stimulatory and inhibitory inputs supplied by neurosecretory cells in the hypothalamus by the portal vessel system (31, 32). The prolactin-inhibiting factor is DA, and this plays the most important role in prolactin secretion (33). It is released by three hypothalamic neural populations such as periventricular hypothalamic dopaminergic neurons, tuberohypophyseal neurons and tuberoinfundibular neurons of the arcuate nucleus (32). Prolactin in turn feeds back time delayed DA neurons stimulating DA synthesis and secretion. Thus, prolactin causes activation of DA neurons that suppress their own prolactin level (34). There are studies that demonstrated increased pituitary volumes in FES (35, 36). This might indicate an increased pituitary activity associated with prolactin production (37). Moreover, Mondelli et al. (38) reported enlarged pituitary volumes in unaffected relatives of patients with schizophrenia. Regarding increased dopaminergic transmission in schizophrenia and the reciprocal relationship between DA and prolactin, it would be plausible that stress-induced hyperprolactinemia might be downregulated with DA increase (29). We suggest that this protective mechanism of prolactin might work in a first episode but not in subsequent episodes of schizophrenia.

Prolactin, in addition to its role during lactation, may influence both emotional responses and hypothalamic–pituitary–adrenal axis activity. The neurobiological basis of anxiety-related behavior includes various neuropeptidergic systems such as corticotropin-releasing hormone (39), neuropeptide Y (40), substance P (41) and vasopressin (42). Under pathological conditions of hyperanxiety (43) or in rats displaying high anxiety-related behavior (44), an increased hyperactivity of the hypothalamic–pituitary–adrenal axis has been described. A possible involvement of prolactin in stress response mechanisms is suggested by the findings as: 1) prolactin is released into the blood from pituitary lactotroph cells in response to exposure to different stressors (45,46), 2) chronic stress leaded the expression of the long form of the prolactin receptors in choroid plexus cells (47), and 3) administration of prolactin into the cerebral ventricles prevented the stress-related formation of gastric ulcers and showed antidepressant effects during forced swimming.

Table 2. Comparisons of Scale for the Assessment of Negative Symptoms (SANS), the Scale for the Assessment of Positive Symptoms (SAPS), the Brief Psychiatric Rating Scale (BPRS) and mean values of serum prolactin.

<table>
<thead>
<tr>
<th></th>
<th>FES (n = 30)</th>
<th>DFS (n = 41)</th>
<th>HC (n = 32)</th>
<th>Statistic</th>
</tr>
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<tbody>
<tr>
<td>BPRS</td>
<td>29.3 ± 7.5</td>
<td>34.9 ± 9.5</td>
<td></td>
<td>F = 0.17, P = 0.008</td>
</tr>
<tr>
<td>SANS</td>
<td>27.1 ± 9.4</td>
<td>37.8 ± 15.4</td>
<td></td>
<td>F = 5.78, P = 0.001</td>
</tr>
<tr>
<td>SAPS</td>
<td>33.6 ± 17.2</td>
<td>34.3 ± 15.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin value (ng/dl)</td>
<td>34.1 ± 19.9</td>
<td>17.9 ± 6.5</td>
<td>9.7 ± 2.3</td>
<td>F = 35.5, P &lt; 0.001; FES&amp;DFS: P &lt; 0.001; FES&amp;HC: P &lt; 0.001; DFS&amp;HC: P &lt; 0.001</td>
</tr>
</tbody>
</table>

FES, drug-naive first-episode patients with schizophrenia; DFS, drug-free schizophrenic patients; HC, healthy controls; NS, not significant. Significant P-values in bold.
(48, 49). Furthermore, neuroendocrine stress responses were found to be attenuated in states of hyperprolactinemia. In an animal study, prolactin was reported to have anxiolytic and antistress effects in male and female rats (50). It has also been proposed that prolactin secretion patterns differ in acute states of psychosis (51) where marginal or significant increases in prolactin levels may be expected due primarily to "non-dopaminergic excitatory factors" of prolactin secretion (52). We suggest that these non-dopaminergic factors might be another mechanism for explaining hyperprolactinemia during a first episode of schizophrenia.

We think that investigating serum prolactin levels in only male gender, comparing serum prolactin levels between FES, DFS and HC and the results of increased serum prolactin level in FES compared with DFS and HC are the strengths of our study.

Our study has some limitations. The design of our study is cross-sectional; however, we suggest that a follow-up study might provide stronger evidence for alterations in serum prolactin level during the illness period. Unsurprisingly, the mean age of the DFS group was higher than other groups; this might be considered a limitation. The small sample sizes of groups are limitations for making a general conclusion.

Conclusion
In the present study, we demonstrated that serum prolactin level increased in FES compared with DFS and HC. This might be a valuable and helpful biomarker for psychotic attack with clinical signs. Nevertheless future, this might be a valuable and helpful biomarker for psychotic attack with clinical signs. Nevertheless future, future, future (53). We did not include patients whose BMI is greater than 30 and we could not demonstrate the data of BMIs of subjects in the present study; that is another limitation. The small sample sizes of groups are limitations for making a general conclusion.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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