Turkish Journal of Endocrinology and Metabolism, (2003) 3 : 119-125 **ORIGINAL ARTICLE**

Psychological Status, Quality of Life in Hyperprolactinemic Premenopousal Women

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Objective: Hyperprolactinemia is a common and chronic disorder with metabolic and psychological consequences. The aim of this study is to evaluate depression levels and health status and it's relationship with insulin resistance in hyperprolactinemic premenapousal women. Design and patients: Nineteen hyperprolactinemic premenopausal women were enrolled in the study. All patients have a pituitary microadenoma. Twenty healthy women subjects matched in age were included as controls. All hyperprolactinemic patients were evaluated twice, before the study and after the suppression of prolactin levels. Patients were given bromocriptine (2,5- 20 mg /dL) and the dosage was titrated monthly until prolactin levels were lowered below 20 ng/dl All subjects evaluated for SF-36 Quality of Life Questionnaire, Symptom Check List-90-R (SCL-90-R), Beck Depression Inventory (BDI) and an oral glucose tolerance test was performed to evaluate insulin sensitivity before and after treatment. Results: Beck Depression inventory score was significantly higher in non-treated hyperprolactinemic patients compared with post-treatment levels ($p<0.05$) and healthy controls ($p<0.001$). In analysis of SCL-90 scales, hyperprolactinaemic patients were more depressive ($p<0.001$) hostile ($p<0.05$), anxious ($p<0.05$) and phobic ($p<0.05$) than the control subjects. Anxiety scale scores decreased after bromocriptine treatment ($p<0.05$). Insulin sensitivity index was significantly lower in non-treated hyperprolactinemic group compared with post-treatment calculations ($p<0.05$) and healthy controls ($p<0.01$) Conclusions: hyperprolactinemia is associated with depression, anxiety, phobia and hostility in women with prolactinomas. Bromocriptine treatment had beneficial effects on depression and anxiety. Increased insulin resistance, decreased estrogen or increased prolactine may take part in the mechanism of depression in hyperprolactinemic premenopausal women.

Key words: Prolactin insulin resistance depression bromocriptine quality of life

Introduction

Hyperprolactinemia is a common and chronic disorder in young women characterized with symptoms of galactorrhoea, menstrual irregularity or infertility (1). Most of the patients have a pituitary prolactin secreting tumor. Tumor progression is rare and prolonged clinical stability is the rule. The treatment aims to control the symptoms (2).

Hyperprolactinemia has metabolic and psychological consequences. Psychological abnormalities have been consistently described in patients with prolactinoma or idiopathic hyperprolactinoma. High prevalence of depressive disorders, hostility, depression and anxiety were more frequently reported in amenorrheic women with hyper-prolactinemia than amenorrheic normoprolactine-mic women (3,4).

Although sufficient data is not available, symptoms and signs of hyperprolactinemia such as rapid

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weight gain, amenorrhea, galactorrhea could be psychologically distressing and could also affect patients' quality of life.

The issue becomes even more complicated by the influence of increased prolactin on gonadal functions in patients with prolactinomas. It has been suggested that the psychological effects of hyperprolactinemia might be caused as a result of the interaction between prolactin and gonadal hormones (5). The long term hormonal effects of hyperprolactinemia are difficult to distinguish from those related to hypogonadism and to the effects of decreased estrogen on the central nervous system (6-8).

Apart from its psychological effects, recent studies also indicate that hyperprolactinemia is found to be diabetogenic (9-11). Studies in hyperprolactinemic patients with or without pituitary tumors have revealed hyperinsulinemia and reduced glucose tolerance which might indicate that hyperprolactinemia causes insulin resistance and atherogenic state (9,10).

Insulin resistance has been shown to be associated with major depression (12). Furthermore, depressive disorders are common psychological sequela of diseases associated with insulin resistance such as type 2 diabetes mellitus, coronary artery disease and obesity (13-14).

The prevalence rates of depression in diabetes mellitus are at least 3 times higher than that of the prevalence rate of major depression in general population (15). It would be interesting to evaluate whether there is an association between depression and insulin resistance in hyperprolactinemic state.

The aim of this study is to evaluate depression levels and health status and their relationship with insulin sensitivity in hyperprolactinemic premenopausal women. Also effects of bromocriptine treatment were evaluated for the same parameters

Methods

Patients: Nineteen hyperprolactinemic premenopausal women (Group P) were enrolled in the study after giving written informed consent. The protocol was approved by the local ethics committee of the Marmara University Hospital. Twenty healthy subjects matched in age and sex were included as controls (Group C).

A diagnosis of pituitary microadenoma was made by either Magnetic Resonance Imaging (MRI) scan in all hyperprolactinemic patients. Macroprolactinemia was excluded with polyethylene glycol (PEG) test.

Formal tests of hypothalamic-pituitary function and pelvic ultrasonographic examination were normal. None of the patients had any illness other than hyperprolactinemia and none of the participants was a smoker or on any medication at the time of the study.

All hyperprolactinemic patients were evaluated twice, before the study and after the suppression of prolactin levels. Serum prolactin levels were measured twice at baseline and once every 3 weeks period until reached target prolactin levels. Patients were given bromocriptine (2,5- 12 mg /d) and the dosage was titrated monthly until prolactin levels were lowered below 20 ng/dl. Controls and post-treatment hyperprolactinemic patients were studied 2 months after reaching target prolactin levels. All evaluations were done in the early follicular phase. All measurements except oral glucose tolerance test (OGTT) were reevaluated in controls with a similar time delay.

For the psychological evaluation following questionnaires were used:

Symptom Check List-90-R (SCL-90-R): The SCL-90-R is designed to reflect the psychological symptom patterns of the respondents in both clinical and research situations. It is a self report instrument that contains 90 items and 10 subscales. Each item is rated on a 5-point scale of distress ranging from "not at all" to "extremely". The questions should be answered in terms of symptoms or feelings "over the last week, including today". The nine primary symptom dimensions are labeled as: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. There are three global indices: Global severity index (GSI), positive symptom distress index (PSDI) and positive symptom total (PST).The reliability and validity of the scale in Turkish population has been tested (16).

Beck Depression Inventory (BDI): The BDI is a 21 item self-report rating inventory measuring

emotional, cognitive, somatic and motivational signs of depression. Scores higher than nine indicate the presence of depression. The reliability and validity of the scale in Turkish population has been tested.

SF-36 Quality of Life Questionnaire: SF-36 is designed for use to survey health status in clinical practice and research and in the general population. The SF-36 includes one multi-item scale that assesses eight health concepts: Limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health (psychological distress and well-being) limitations in usual role activities because of emotional problems; vitality (energy and fatigue); and general health perceptions. The reliability and validity in Turkish population has been researched (17). A scale between 0-100 can be obtained on each item and 100 indicates good while 0 indicates poor health.

All three scales mentioned above, were delivered twice, once before the bromocriptine treatment and once after the serum prolactin levels reached below 20 ng/dL .

Insulin sensitivity was determined by an oral glucose tolerance test (OGTT) based on the formula described by Matsuda and De Fronzo and named as insulin sensitivity index composite (ISI Composite) (18). Whole-body insulin sensitivity during the OGTT was calculated by the following formula: ISI Composite =[10000/ √ (fasting plasma glucose x fasting plasma insulin) x (mean OGTT glucose concentration x mean OGTT insulin concentration)]. After an overnight fast oral glucose tolerance tests (75 g glucose) were performed between 8 and 9 a.m. Blood samples were taken just before (0 min) and 30,60,90 and 120 min after the administration of glucose for the measurement of serum glucose and insulin concentrations.

The HOMA formula was used for homeostatic model assessment ($HOMA_{IR}$) (19).

Area under the curve calculations were done according to tropezoid rule.

Assays: Serum prolactin levels were measured by an electrochemiluminescence immunoassay (Roche Elecsys 2010, Roche Diagnostics GmbH, Mannheim). The inter and intraassay coefficients of variations were 2.8% and 3.4 %, for a measurement range of 72±2- 2332±78.6 mg /dl, respectively.

To estimate the concentration of macroprolactin present, specimens were assayed for prolactin after treatment with PEG 8000. The difference between the prolactin concentrations in the untreated and the PEG-treated sera provided a measure of the macroprolactin concentration (20)

Insulin levels were detected by an immunometric assay (immulite, DPC, CA). Within run precision ranged between 3.8% to 4.8% for a mean range of 10.7-439 ıu/ml. The total precision ranged between 4.8-5.8 % for the same mean range.

Plasma glucose levels were determined by the glycoxidase method. The within run cv was 0.9% for a mean concentration of 116 mg/dl and between day cv was 1.8 % for a mean concentration of 123±2.2 mg/dl.

Statistical Analysis: All calculations and statistical analysis were performed with the statistical package for social sciences for IBM-PC (SPSS. inc.). Comparisons between the groups were done using the paired t test and student's t test where appropriate. Correlation analyses were determined by Pearson test. Area under the curves was calculated according to the trapezoid rule. Levels of statistical significance were set at p less than 0.05. The results are expressed as mean ± SD.

Results

All patients completed the study. Demographic characteristics of study groups are shown in Table 1. There is no statistically significant difference between the demographic characteristics of hyperprolactinemic and Control group . BMI were 26.8±4.6 kg/m^2 and 26.0±3.8 kg/m^2 for before and after treatment in hyperprolactinemic group and it was not statistically significant.

Table 1. Demographic characteristic of the study groups

	Group P (n=19)	Group C (n=19)
Age (yrs)	32.7±9.3	33.0±7.9
Duration of symptoms (mo)	15±5	-
Amennorhea and or galactorrea	15/19	0/19
BMI (kg/m^2)	26.8±4.6	25.9±2.5

BMI: Body mass index

Beck depression scale scores were 13.9±6.5, 8.6±4.6 and 6.1±4.4, 6.6±3.9 for baseline and final evaluation in hyperprolactinemic and Control groups respectively. It was significantly higher in non-treated hyperprolactinemic patients compared with post-treatment levels ($p<0.05$) and healthy controls ($p<0.001$) (Figure 1).

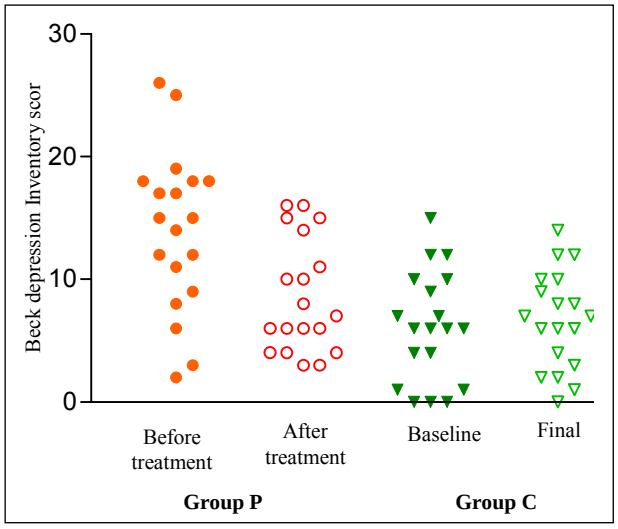

Figure 1. Beck depression scale scores were significantly higher in baseline than post-treatment evaluation in Group P ($p<0.05$) and Group C ($p<0.001$).

In analysis of SCL-90 scales, hyperprolactinemic patients were more depressive ($p<0.001$) hostile ($p<0.05$), anxious ($p<0.05$) and phobic ($p<0.05$) than the control subjects (Table 2). Anxiety scale scores decreased after bromocriptine treatment ($p<0.05$). Somatization scale score of the post-treatment group were higher than the non-treated patients ($p<0.05$). General symptom index score of the prolactin group was higher than healthy controls.

Scores of SF-36 Questionnaire are shown in table 3. There was no difference between the groups.

Serum prolactin levels were significantly higher ($p<0.001$) and estrogen levels were lower ($p<0.01$) in hyperprolactinemic patients than healthy controls. Serum prolactin levels decreased ($p<0.001$) and serum estrogen levels ($p<0.01$) increased after treatment in group P (Table 4).

Baseline insulin sensitivity index was significantly lower compared with post-treatment calculations ($p<0.05$) in group P and group C ($p<0.01$) (Table 4). Although $HOMA_{IR}$ levels were not over 2.5, $HOMA_{IR}$ was higher in non-treated hyperprolactinemic group ($p<0.01$) than healthy controls and post-treatment values.

Basal serum glucose and insulin levels were not different both of the groups. Glucose and insulin area under the curve calculations during OGTT were significantly higher in baseline measurements of hyperprolactinemic group ($p<0.05$).

Table 2. Results of SCL-90-R in hyperprolactinemic and control groups.

	Group P		Group C	
	Before treatment	*After treatment*	Baseline	Final
Global symptom index	0.79±0.4*	0.66±0.4	0.42±0.3	0.45±0.3
Somatisation	0.95±0.8	1.22±0.96*	0.51±0.66	0.54±0.6
Obsessive-compulsive	1.0±0.5	1.02±0.7	0.8±0.6	0.86±0.6
interpersonal sensitivity	0.77±0.4	0.7±0.5	0.53±0.3	0.53±0.3
Depression	0.87±0.5**	0.83±0.5**	0.59±0.4	0.53±0.4
Anxiety	0.94±0.8*	0.76±0.6*, †	0.32±0.3	0.34±0.3
Hostility	0.80±0.5*	0.60±0.5	0.35±0.3	0.38±0.3
Phobic anxiety	0.47±0.4*	0.40±0.4*	0.19±0.2	0.16±0.2
Paranoid	0.93±0.60	0.85±0.67	0.48±0.50	0.47±0.4
Psychotic	0.38±0.30	0.39±0.34	0.25±0.26	0.24±0.2

* $p<0.05$ vs control group
** $p<0.01$ vs control group
† $p<0.05$ vs before treatment

Table 3. Results of SF-36 quality of life questionnaire in control and hyperprolactinemic group.

	Group P		Group C	
	Before treatment	*After treatment*	Baseline	Final
Limitations in physical activities	73.1±26.6	82.2±20	88.1±19.5	88.5±20
Limitation in usual role activities because of physical health problems	75±35	71.8±40.6	84.2±22	83.8±34
Bodily pain	71.2±21.3	61.8±40.6	69.8±31.6	66.3±30
General health perceptions	51.5±23.2	52.2±18.5	73.9±18.8	72.7±19
Vitality	60.1±20.2	57.1±15.2	64.2±14.8	63.8±15
Limitations in social activities	72.8±23.7	67.5±28.5	84.2±16	83.3±17
Limitations in usual role activities because of emotional problems	66.6±38.4	71.3±40.1	75.4±34.8	74.4±36
General mental health limitations	61.0±19.7	63.2±11.4	69.4±16.9	68.9±16

Table 4. Serum prolactin, estrogen levels and Insulin sensitivity indices, serum glucose and insulin levels and area under the curve calculations during oral glucose tolerance test of all study groups

	Group P		Group C	
	Before treatment	*After treatment*	*Baseline*	*Final*
Prolactin (ng/mL)	200.5±42	5.37±5.3*	17.1±8.3	15.8±7.4
Estrogen (ng/mL)	77.0±50**	138.5±72.3	127.2±33	132±60
$HOMA_{IR}$	2.41±1.0	1.61±0.4***	1.44±0.4	1.35±0.4
Insulin sensitivity index	1.75±0.5†	1.89±0.4	2.2±0.6	-
Serum glucose AUC (mg.h/dl)	103±58†	61±51	64±49	-
Serum insulin (mıu.h/ml)	92±36†	59±24	54±36	-
Basal glucose (mg/dl)	90±11	76±9	74±8	-
Basal insulin (mıu/ml)	11.0±5	8.9±2	8.5±2	-

* p<0.001 vs before treatment
** p<0.01 vs after treatment and control group
***p<0.01 vs before treatment
† p<0.05 vs after treatment and control group

Beck Depression Index scores found to be positi-vely correlated with serum prolactin levels (r=0.32, p<0.01) and negatively correlated with serum estrogen levels (r = -0.34, p<0.05) and insulin sensitivity index (r = -0.44, p<0.005) in hyperprolactinemic group (Figure 2). SCL-90 scores were not found significantly correlated with prolactin and insulin sensitivity levels. There were no significant correlations between questionnaires scores and other OGTT based on parameters.

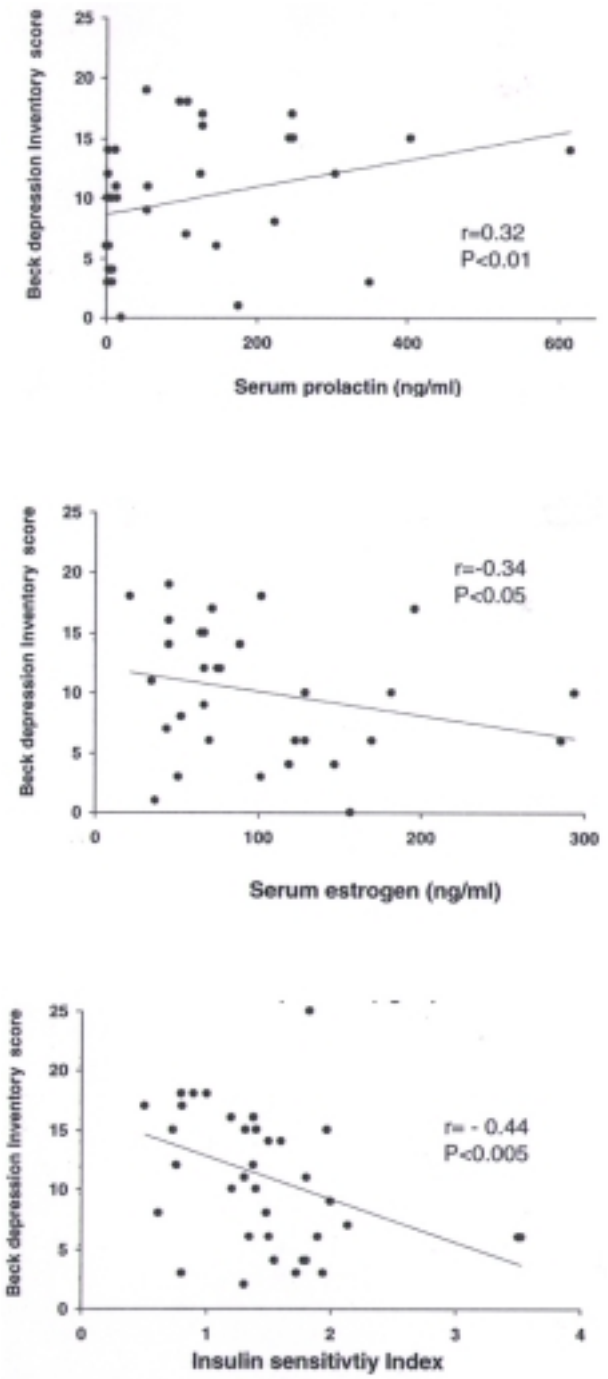

Figure 2. Beck depression Inventory score was positively correlated with serum prolactin and negatively correlated with serum estrogen levels and insulin sensitivity index in hyperprolactinemic patients.

Discussion

Our results indicate that hyperprolactinemic premenopousal women with microprolactinomas are more depressive, hostile, phobic and anxious than healthy women. After bromocriptine treatment depression scores and the anxiety score was decreased in the hyperprolactinemic patients. Our results are in concordance with those done previously in which women with hyperprolactinemia have been found more depressed, hostile and anxious than the controls. Fava et al compared 10 women with hyperprolactinemic amenorrhea, 10 women with amenorrhea who had normal prolactin levels and 10 normal female employees (3). The hyperprolactinemic patients had significantly higher Symptom Questionnaire scores on hostility, anxiety and depression than the other two groups. Kellner et al. investigated psychological aspects of hyperprolactinemic patients (21). The scores of 14 women with hyperprolactinemia on the Symptom Rating Test and the Symptom Questionnaire were compared with those of nonpsychotic women attending a psychiatric clinic, women

attending a family practice clinic and healthy female subjects. They found that hyperprolactinemic patients were significantly more hostile, depressed and anxious than family practice patients and healthy subjects. The Symptom Questionnaire scores of the hyperprolactinemic patients and the psychiatric patients were found to be similar. In another study hyperprolactinemic patients had higher scores compared with postpartum patients and controls. (22).

Depression and anxiety was improved after bromocriptine treatment in hyperprolactinemic patients. Decreased prolactin levels and/or restored gonadal functions may have played a role in these improvements however, this study was not design to distinguish their precise effects on mood.

It is widely accepted that depression is associated with hyperprolactinemic state but the mechanism needs to be clarified. Hyperprolactinemia itself seems to be the major candidate for depression. But changes in gonadal steroid concentrations may contribute to depressive symptoms in hyperprolactinemic patients. A negative correlation between depression scores and estrogen levels in hyperprolactinemic patients implicates that decreased estrogen may play role on mood in hyperprolactinemic women as previously suggested (5,23).

Hyperprolactinemia was found to be associated with decreased estrogen. By means of multitude of mechanisms, estrogens triggers the increase of the concentration and availability of serotonin in the brain. It may influence serotonin activity via decreasing plasma monoaminoxidase (MAO) activity. Since MAO is the enzyme that catabolise serotonin, the net effect of estrogen administration would be to maintain higher brain serotonin levels (24,25). In accordance with biogenic amin hypothesis of depression, a decrease in serotonin level may precipitate depression (24).

This study is one of the first case control studies which compares a homogenous hyperprolactinemic group with carefully matched and reevaluated control group. But direct effects of bromocriptine on depression was not addressed in the study. Gastrointestinal side effects and dizziness could negatively affect quality of life but in our study they are well tolerated and none of the patients quit the treatment during the study. Beneficial effects of bromocriptine treatment on mood in hyper-proalctinemic patients were reported previously. Double blind placebo-controlled crossover studies were shown that bromocriptine diminished depression, anxiety and hostility in hyperprolactinemic patients while decreasing serum prolactin concentrations (26,21).

Furthermore our results suggest another factor, insulin resistance which is a central component of cardiovascular risk factors, may take part in mood problems in hyperprolactinemia.

Although data is not clear insulin resistance may contribute to the pathophysiology of depressive disorder. A high proportion of patients with depression develop glucose tolerance accompanied by hyperinsulinemia, suggestive of reduced insulin sensitivity (27,28). In a study a significant improvement of insulin sensitivity after treatment of depression was observed (28).

In our study insulin sensitivity index which is an indirect marker of insulin resistance have been found to be decreased in hyperprolactinemic women than healthy controls in this study. Improvement of insulin sensitivity index after bromocriptine treatment was observed. The negative correlation between insulin sensitivity index and scores of Beck Depression inventory may indicate a possible relationship between insulin sensitivity and depressive symptoms in our group.

Calculated insulin sensitivity index strongly correlated with hyperglyceamic euglyceamic clamp technique than HOMA calculations (19) Although $HOMA_{IR}$ results were not to reach cut off levels in hyperprolactinemic group, ISI calculations which is more sensitive than $HOMA_{IR}$ calculations was found to be decreased in hyperprolactinemic group.

Increasing subject number may help to clarify the relationship between $HOMA_{IR}$ calculations and mood in hyperprolactinemic patients.

In conclusion hyperprolactinemia is associated with depression, anxiety, phobia and hostility in women with prolactinomas. Bromocriptine treatment had beneficial effects on depression and anxiety. Increased insulin resistance, decreased estrogen or increased prolactin may take part in the mechanism of depression in hyperprolactinemic premenopausal women. Further studies are needed to clarify the relationship between insulin resistance and mood problems in both man and women hyperprolactinemic patients.

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