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FEATURES OF METABOLIC AND NEUROCOGNITIVE DISORDERS IN WOMEN WITH FUNCTIONAL HYPERPROLACTINEMIA IN PATIENTS WITH HYPERPROLACTINEMIA SYNDROME

Adlia Omonullaevna Kholikova
Head of the Department of Neuroendocrinology of the Republican Specialized Scientific - Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan named after acad. Y.H. Turakulov
Tashkent, Uzbekistan

Nargiza Yusufovna Khalimova
Independent competitorof the Republican Specialized Scientific - Practical Medical Center of Endocrinology of the Ministry of Health of the Republic of Uzbekistan named after acad. Y.H. Turakulov
Tashkent, Uzbekistan

Yulduz Makhkamovna Urmanova
Doctor of medical sciences, Associate Professor, Professor of the Department of Endocrinology with Pediatric Endocrinology, Tashkent Pediatric Medical Institute
Tashkent, Uzbekistan

Rovshanoy Turgunovna Khaidarova
Associate Professor of the Department of Endocrinology Center for the Development of Professional Qualifications of Medical Workers of the Ministry of Health of the Republic of Uzbekistan
Tashkent, Uzbekistan

ABSTRACT

The purpose of this study is to investigate the metabolic and neurocognitive abnormalities in women with functional hyperprolactinemia who present with hyperprolactinemia syndrome.

Materials and Methods. We conducted a comprehensive examination of 162 women of childbearing age diagnosed with hyperprolactinemia syndrome (HPRL) and who were under treatment at the Republican Specialized Scientific - Practical Medical Center of Endocrinology between 2021 and 2022.

Results. Our findings suggest that elevated prolactin levels have a significant impact on fat and carbohydrate metabolism and contribute to insulin resistance and an increased risk of atherosclerosis.

Our analysis of data from the 162 women with HPRL revealed a high prevalence of dyslipidemia (91.6%), characterized by elevated levels of triglycerides (79.2%), very-low-density lipoprotein (VLDL) (72.2%), and low-density lipoprotein (LDL) levels (57%), and an increase in cholesterol content (68.4%).

In summary, our study showed that women with HPRL are at higher risk of developing dyslipidemia (91.6%), with changes in triglyceride (79.2%), VLDL (72.2%), and LDL (57%) levels, and an increase in cholesterol (68.4%). Clinical manifestations of HPRL in the observed patients were diverse, ranging from characteristic mastalgia (46%), lactorrhoea (76%), NMC (83%), decreased libido (74%), to obesity with a BMI over 27-123 (76%), left ventricular hypertrophy -93(58%), increased blood pressure (76%), sleep apnea-55(34%) and snoring-66(41%). The heterogeneity of clinical symptoms can contribute to the delayed diagnosis and treatment of HPRL.

Conclusions. More than half of the women with HPRL in our study had a BMI greater than 25 kg/m2, with 29% being overweight, 20% having grade I obesity, and 27.4% having grade II obesity;Patients with HPRL presented with carbohydrate metabolism abnormalities, such as impaired fasting glycemia, elevated levels of insulin, glycated hemoglobin, and the HOMA index;Overweight or obese patients with HPRL had significantly elevated levels of total cholesterol and triglycerides in the blood serum.

KEYWORDS: hyperprolactinemia, obesity, metabolic syndrome, neurocognitive disorders

INTRODUCTION

According to various studies, to date, a positive relationship has been found between metabolic parameters such as increased arterial hypertension, waist circumference, aortic stiffness, mortality, and with pathologically high levels of PRL in the blood serum. . Meanwhile, other studies have shown an inverse relationship between PRL levelsin serum and metabolic parameters such as cardiovascular events, cardiac remodeling, diabetes, metabolic syndrome, HOMA index, and adverse lipid profiles. Based on this, the authors of the article conducted a study of carbohydrate and fat metabolism in patients with hyperprolactinemia syndrome and obtained data indicating the effect of an increased effect of prolactin on fat and carbohydrate metabolism. The factor of insulin resistance and an increased risk of atherosclerosis with this combination have been established.

One of the multifunctional pituitary hormones involved in lactation, reproduction, metabolism, immune regulation is prolactin (PRL) (1,2,3,4). Physiological hyperprolactinemia (HPRL) is observed during pregnancy, breastfeeding, physical activity and stress (5). Accumulating experimental evidence suggests that prolactin can stimulate beta cell proliferation and improve insulin secretion and sensitivity (1,6,7,8). It also functions as an adipokine to regulate adipogenesis, lipid metabolism and inflammation (1,5).

PRL, through inhibition of adiponectin and IL-6 production in adipose tissue, has been shown to influence food intake, weight gain, and insulin resistance, which may lead to type 2 diabetes (9,10). Several studies have found a positive association between metabolic parameters such as elevated hypertension, waist circumference, aortic stiffness, mortality, and abnormally high serum levels of PRL (11,12,13,14). In addition, dopamine agonists have been shown to be effective in improving insulin sensitivity and bromocriptine has been approved for the treatment of type 2 diabetes mellitus in the United States (15). In contrast, other studies have shown an inverse relationship between serum PRL levels and metabolic parameters such as cardiovascular events, cardiac remodeling, diabetes, metabolic syndrome, HOMA index, and adverse lipid profiles (16,17,18,19,20). Therefore, the relationship between serum PRL levels and metabolic parameters in HPRL requires further evaluation.

In connection with the above, the purpose of this work was to study the state of carbohydrate and fat metabolism in patients with hyperprolactinemia syndrome.

The purpose of the study is to studyfeatures of metabolic and neurocognitive disorders in women with functional hyperprolactinemia in patients with hyperprolactinemia syndrome

MATERIALS AND METHODS

We examined 162 patients of childbearing age with hyperprolactinemia syndrome (HPRL), who were observed at the RSNPMCCE for the period 2021-2022. The age of the patients ranged from 25 to 45 years and averaged 34±6.5 years. The control group consisted of 25 practically healthy women, the average age was 31.8±1.7 years. This group included women who did not have any complaints, diseases of the endocrine system and somatic pathology.

All subjects underwent general clinical, anthropometric, biochemical research methods. Assessment of hormonal status by determining the levels of prolactin (PRL), luteinized (LH), follicle-stimulating hormones (FSH), estrodiol (E-2), testosterone (T), thyroid-stimulating hormone (TSH). Hormone studies were carried out by IHLA and ELISA methods.

Anthropometric studies included the determination of height, weight and the calculation of body mass index (BMI = weight (kg) / height (m2)), the degree of obesity was assessed according to the WHO classification (1997).

Assessment of carbohydrate metabolism was carried out by the content of fasting blood glucose and the level of glycated hemoglobin in blood plasma. Insulin resistance (IR) was determined by the index HOMA-IR - the ratio of basal insulin to the content of fasting glycemia, normally up to 2.77.

Lipid metabolism was assessed by the level of total cholesterol (Cholesterol), triglycerides (TG), low and very low-density lipoproteins (LDL and VLDL), high density lipoproteins (HDL), followed by calculation of the atherogenic index (AI).

The analysis of cognitive functions (memory, orientation, reading, writing, thinking) was performed according to the MMSE - minimental state examination questionnaires.
Brief mental status rating scaleMMSE- This is a short questionnaire of 30 items, widely used for the initial assessment of the state of cognitive functions and screening for their disorders, including dementia. MMSE is also used to assess the dynamics of cognitive functions during therapy.
The scale was developed in 1975 (Folstein MF, Folstein SE, McHugh PR (1975). Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. Journal of psychiatric research 12 (3): 189-98.), and later underwent a number of changes ..The test result is obtained by summing the results for each of the items. The maximum you can score in this test is 30 points, which corresponds to the highest cognitive abilities. The lower the test result, the more pronounced the cognitive deficit.
Any score over 27(out of 30) is an effective normal. The normal value is also adjusted according to the degree of training and ageor mild (19–23 points) cognitive impairment. The raw score also needs to be adjusted for education and age.
Statistical analysis of the obtained results was carried out using Statistica 6.0 statistical programs from StatSoftInc (USA). The results are presented as a sample mean and its error (M±m). Statistically significant differences were determined using the Kruskal-Wallis and Mann-Whitney (ANOVA) criteria. In all types of analysis, the significance was taken as significant at $p<0.05$.

RESULTS AND DISCUSSION

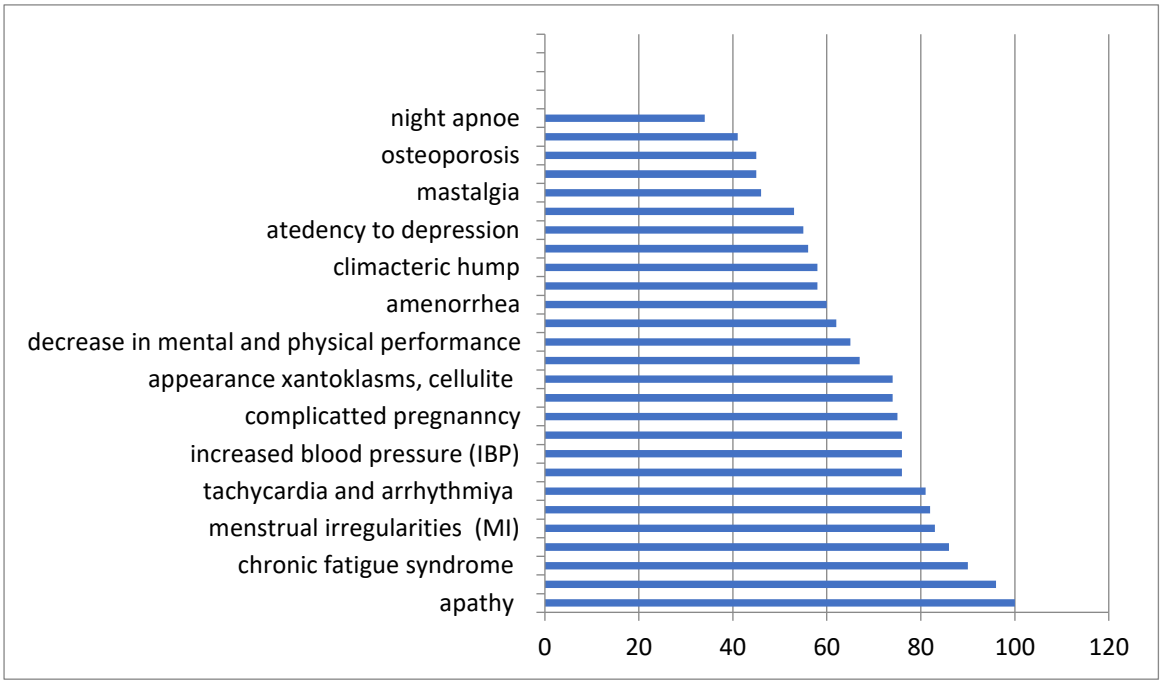
To assess the general condition of patients with HPRL, we examined the complaints of patients with whom they turned to doctors (table 1).

Table 1
The main complaints of patients with HPRL

No.	Complaints	Quantity	
		abs.	%
1	Edema	74	45.8
2	Shortness of breath during exercise	35	21.6
3	Lack of air	15	9.2
4	increased appetite	92	56.7
5	Elevated blood sugar	thirty	18.5
6	Rapid weight gain	90	55.5
7	Fast fatiguability	107	66.4
8	Frequent headaches	86	53.1
9	Drowsiness	88	54.3
10	Decreased memory	82	50.6
11	Thirst	42	25.9
12	Decreased ability to work	88	54.3
13	Decreased sex drive	85	52.6
14	Menstrual irregularities (MI)	87	53.7
15	Absence of pregnancy	12	7.4
16	Increased blood pressure (IBP)	78	48.1
17	Tearfulness	120	74.0
18	Tendency to depression	100	67.2
19	Pain in bones and joints	35	21.6

An analysis of the complaints of our patients proves that the most frequent complaints were overweight (55.5%), fatigue (66.4%), increased appetite (56.7%), decreased ability to work (54.3%), MI (53 .7%), tearfulness (74%) and depression (67.2%). With these complaints, they are observed by therapists, nutritionists, cardiologists and otolaryngologists.

Next, we studied the clinical features of HPRL in the patients we studied (Pict. 1.) As the results showed, the clinical manifestations of HPRL in the patients we observed were very diverse: from characteristic mastalgia (46%), lactorrhea (76%), NMC (83%) , decrease in libido (74%) to obesity \ BMI over 27\-123 (76%), left ventricular hypertrophy -93 (58%), increased blood pressure (76%), sleep apnea - 55 (34%) and snoring - 66 (41%). The variety of clinical symptoms contributed to the occurrence of HPRL under the guise of such diseases as hypertension, obesity, infertility of various origins, and depression. Allthisledtodelayeddiagnosisanddelayedtreatment.



Pict. 1. Clinical features of HPRL.

Anthropometric studies of patients with HPRL showed that 52.7% (58 patients) had a weight within the normal range (table 2.)

Table 2.
BMI indicators in patients with HPRL

kg/m2	BMI 18-24.9	BMI 25-29.9	BMI 30-34.9	BMI 35-39.9
Number of patients	48 (43.6%)	32 (29.0%)	22 (20%)	8 (7.4%)

As can be seen from the table2, 56.4% of women had a BMI above 25 kg / m2, while 29% were overweight, 20% had degree I obesity, 2 7.4% had degree II obesity.

For patients with initial hyperinsulinemia, as well as for patients with hyperinsulinemia and hyperglycemia, an increase in the atherogenic potential of the blood is characteristic, which is manifested by an increase in the concentration of low density lipoproteins (LDL) and very low density (VLDL), as well as a decrease in the content of high density lipoproteins (HDL) (10) . Changes in the lipid spectrum of the blood have 62% of patients with GP in reproductive age and 76% in perimenopause (3.19). For patients with HPRL, hyperlipidemia IIa, IIc and IV types are most characteristic. It is important to note that if at the reproductive age in patients with HPRL, type IIa and IIc dyslipidemias were predominant, then at the perimenopausal age this ratio shifts towards type IV dyslipidemia (11,16). Thus, the insulin resistance and hyperinsulinemia present in HPRL lead to the development of hyperlipoproteinemia and obesity (9). Based on this, we studied the biochemical and hormonal composition of the blood of these patients.

Next, we assessed carbohydrate and lipid metabolism in the group of patients with HPRL and overweight, compared with the control group.

We assessed carbohydrate metabolism by the levels of fasting glycemia, insulin andglycosylated hemoglobin, as well as the HOMA index (table 3).

Table 3
Indicators of carbohydrate metabolism in women with hyperprolactinemia

Indicators	ExcessBMI n=32	Obesity, n=30	Control, n=25
Fasting glycemia (mmol/l)	5.46±0.3*	6.7±0.5*	4.4±1.1
Insulin (MKed/ml)	19.2±1.3***	25.9±1.5***	9.1±1.2
HbA1(%)	5.5±0.6	5.9±0.9	4.9±0.2
HOMA index	4.2±0.5**	7.8±1.8***	1.6±0.4

Note: statistical significance of the difference in indicators compared to control: *- p<0.05; ** - p<0.01; ***p<0.001

As the results showed, in the group of patients with HPRL and overweight, there were significantly high levels of fasting glucose (5.46 ± 0.3 mmol/l, p < 0.05) and glycosylated hemoglobin (5.5 ± 0.6%) compared with the control group. The average level of insulin in patients with HPRL and overweight also significantly exceeded compared with the control (19.2±1.3, mcU/ml, p<0.001). Calculation of the HOMA index showed a significant increase in patients with GPRL who are overweight (4.2±0.5, p<0.001) and obese (7.8±1.8, p<0.001), which indicates the presence of insulin resistance in surveyed patients with HPRL.

The study of lipid metabolism showed that in patients with HPRL and with a BMI of 25.0 kg/m2, changes in the lipid spectrum were detected (table 4).

Table 4
Lipid spectrum parameters in women with hyperprolactinemia

Indicators	Excess MT n=32	Obesity, n=30	Control, n=25
total cholesterol, mmol/l	5.4±0.4*	5.6±0.3*	4.4±0.3
TG, mmol/l	3.8±0.3***	3.1±0.6***	1.2±0.1
LDL, mmol/l	3.7±0.5***	4.1±0.8***	2.2±0.2
VLDL, mmol/l	0.9±0.03	1.1±0.02	0.65±0.03
HDL, mmol/l	1.1±0.002*	0.91±0.003**	1.5±0.05
IA	4.1±0.3*	4.7±0.7**	2.1±0.2

Note: statistical significance of the difference in indicators compared to control: *- p<0.05; ** - p<0.01; ***p<0.001

As can be seen from Table 4, high levels of total cholesterol (1gr-5.4±0.4mmol/l,p<0.05; 2gr-5.6±0.3mmol/l,p<0.05) and triglycerides (1g-3.8±0.3mmol/l,p<0.001; 2gr-3.1±0.6mmol/l,p<0.001), compared with the control group. HDL levels were significantly reduced in the studied overweight women (1.1±0.002,mmol/l,p<0.05) and obesity compared to the control group (0.91±0.003,mmol/l,p<0.01).

A study of such indicators of the lipid spectrum as LDL and VLDL showed an increase in their level in 16.9% of patients with obesity and overweight, compared with the control group.

The study of the coefficient of atherogenicity in the studied groups showed its significant increase in patients with overweight (4.1±0.3,p<0.05) and obese (4.7±0.7,p<0.05).
So, the results of the study indicate the effect of elevated prolactin levels on the indicators of fat and carbohydrate metabolism. The factor of insulin resistance and an increased risk of atherosclerosis with this combination have been established.
The next stage of the research was the study of neurocognitive disorders in the study group of patients (Table 5).

Table 5
Questionnaire results of test MMSE

N of group	**Total**	**Test MMSE**		
1	n=162	19±2.7 n=22	24 ± 3.8 n=36	27 ± 3.4 n=104
Control	n=25	30±4.6		

Data from 162 women with HPRL showed dyslipidaemia (91.6%) characterized by elevated levels of triglycerides (79.2%), very-low-density lipoprotein (VLDL) (72.2%), and low-density lipoprotein (LDL) levels (57 %), an increase in the content of cholesterol (CHC) (68.4%).
Thus, our studies have shown that women with HPRL more often develop dyslipidemia (91.6%), characterized by changes in the levels of triglycerides (79.2%), VLDL (72.2%) and LDL (57%), an increase in cholesterol (68.4%). At the same time, the clinical manifestations of HPRL in the patients we observed were very diverse: from characteristic mastalgia (46%), lactorrhoea (76%), MI (83%), decreased libido (74%) to obesity \ BMI over 27\-123 (76%), left ventricular hypertrophy -93(58%), increased blood pressure (76%), sleep apnea-55(34%) and snoring-66(41%). The variety of clinical symptoms contributed to the occurrence of HPRL under the guise of other diseases, delayed diagnosis and delayed treatment.
The above circumstances increase the number of patients with cardiovascular diseases and complicate the condition of patients at a younger fertile age, cause reproductive dysfunction and a decrease in the quality of life of women.

CONCLUSION

1) 56.4% of women with HPRL had a BMI above 25 kg/m2, while 29% were overweight, 20% had grade I obesity, 2 7.4% had grade II obesity;
2) Patients with HPRL were found to have disorders of carbohydrate metabolism in the form of impaired fasting glycemia, increased levels of insulin, glycated hemoglobin, and the HOMA index;
3) Patients with HPRL who are overweight or obese have high levels of total cholesterol and triglycerides in the blood serum

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