THE FREQUENCY OF METABOLIC SYNDROME AND ITS INDIVIDUAL COMPONENTS IN WOMEN AGED 25–45 YEARS, DEPENDING ON THE LEVEL OF PROLACTIN

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BACKGROUND: Hyperprolactinemia is one of the most common hypothalamic-pituitary-endocrine disorders in women of reproductive age, with the highest frequency at the age of 25–44 years. In addition to influencing the reproductive system, it is important to study the effects of prolactin (PRL) on various metabolic links. Available data indicate that the effect of PRL on metabolism depends on its level. In this regard, the study of the relationship of different levels of PRL with anthropometric parameters, indicators of lipid and carbohydrate metabolism in young women is relevant.
AIM: To study the frequency of metabolic syndrome (MS) and its individual components in women aged 25–45 years with different levels of prolactin.
MATERIALS AND METHODS: Work design — cross-sectional research. A random population sample of women 25–45 aged- was examined. Pregnant and breastfeeding women with macroprolactinoma, and taking antipsychotics were excluded. Information was collected using a structured questionnaire, including, but not limited to, the presence of pregnancies, childbirth, menstrual irregularities, and a clinical examination, anthropometric measurements, biochemical and hormonal blood analyzes were performed. Statistical data processing was carried out.
RESULTS: According to the inclusion and exclusion criteria, this analysis presents data from 401 women, the average age of the examibed was 36.14±6.19 years. There was no difference in the levels of thyroid-stimulating hormone and prolactin (PRL) in the age groups of 25–34 and 35–45 years. According to the survey, the incidence of thyroid diseases in the studied groups is comparable. Every fifth woman indicated menstrual irregularities. Among women 25–45 years old, women with low-normal PRL values (Me = 4.49 [3.52; 5.41] ng/ml) have more unfavorable metabolic indicators. Metabolic syndrome (MS) was detected in 28%,with a predominant increase in the frequency of abdominal obesity — 55%, hypercholesterolemic LDL — 63%. Women with high PRL (Me = 41.35 [34.78; 45.88] ng / ml) also have an unfavorable metabolic profile: MS was detected in 47%, abdominal obesity — 56%, hypertension — 39%.
CONCLUSIONS: In women 25–45 years old, low and high PRL values are more often associated with metabolic ill health. PRL values are from 7.8 to 28 ng / ml, i.e. conditionally defined as normal, highly normal and at the level of moderate hyperprolactinemia contribute to the maintenance of a favorable metabolic profile. When deciding on the treatment of women with non-tumor etiology hyperprolactinemia, it is important to assess the metabolic status, expanding their understanding of PRL as a hormone associated only with lactation and with the pituitary-gonad axis.

KEYWORDS: prolactin; hyperprolactinemia; metabolic syndrome; obesity; lipids.

BACKGROUND

Hyperprolactinemia is one of the most common hypothalamic-pituitary-endocrine disorders in women of reproductive age. The PROLEARS research showed that women of 25-44 y.o. have the highest incidence of hyperprolactinemia [1]. In addition to influencing the reproductive system, it is important to study the effects of prolactin (PRL) on various metabolic links [2]. Extensive clinical and experimental data indicate that the effect of PRL on metabolism depends on its level. According to the majority of researchers, the pathologic hyperprolactinemia with extremely high values caused by prolactinoma is related to obesity, impaired glucose tolerance and insulin resistance both in men and women [36]. There are not so many studies researching the impact of PRL within or above the physiological threshold on the metabolic homeostasis. Few papers show that «higher» (within or above the physiological range of 25 μg/l or 525 mU/L) PRL levels promote favorable metabolic homeostasis in cases of diabetes and metabolic changes caused by obesity [7]. In different years several clinical and experimental papers showed that low PRL levels are related to unfavorable metabolic profile [8-10]. We should note that metabolic consequences of low-normal values and hyperprolactinemia in young women are mostly poorly known. There are no studies of the prevalence of the metabolic syndrome (MS) and its components in young women with different PRL levels with non-tumor etiology. That is why it is relevant to study the relationship of different levels of PRL with anthropometric parameters, indicators of lipid and carbohydrate metabolism in young women.

PURPOSE

To study the incidence of MS and its individual components in women aged 25-45 with different levels of prolactin.

MATERIALS AND METHODS

Site and time of the study

Study site. The study was conducted in the screening center of the Research Institute of Internal and Preventive Medicine,

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branch of the Federal Research Center of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences. The hormonal and biochemical blood tests are performed in the laboratory of clinical and biochemical studies of internal diseases of the Research Institute of Internal and Preventive Medicine, branch of the Federal Research Center of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, that has standardization of internal and external federal quality control. *Duration of the study.* The material was collected from 2013 to 2017.

Study populations (one or more)

One population was examined.

Inclusion criteria: women aged 25-45 were included in the study.

Exclusion criteria: pregnant and breastfeeding women, present of macroprolactinoma, and use of antipsychotics.

Sampling method from the study population (or several samples from several study populations)

This research is a case study of the random population of women aged 25-45 examined as part of the state-funded project «Epidemiological monitoring of public health and study of molecular and genetic mechanisms of development of common internal diseases in Siberia to improve strategies for their diagnosis, prevention and treatment». You can find the sampling description above [11]. We calculated the necessary sample volume taking into account the literature data on prevalence of hyperprolactinemia in young women [1]. The sample volume was calculated using the following formula [12]:

$$N = 15.4.(p.(1-p))/W2,$$

where: p — estimated random probability value of the event; W — width of the confidence interval for the probability value. According to this formula the minimum volume of studied subsample of young women was 246 people. The procedure of simple random subsampling was made with a random number generator.

Study design

We conducted a cross-sectional observational single-center study.

Description of the medical intervention

Information was collected using a structured questionnaire, including, but not limited to, the presence of pregnancies, child-birth, menstrual irregularities, smoking behavior. We took anthropometric measurements of all women (height, weight body mass index (BMI), waist circumference (WC)). The height measurements were performed in the upright position, without out wear and shoes, using the standard height meter with 0.5 cm accuracy. The body weight was determined without outwear and shows, using standard calibrated balance scales (the accuracy of measurement was 0.1 kg). Blood pressure was measured thrice. Blood was drawn from an ulnar vein in the morning after 12 h overnight fast. After the centrifuge ride, the serum was stored in a low-temperature chamber (70°C). The following parameters were determined in the blood serum: glucose, total cholesterol (TC), triglycerides (TG), High-density lipoprotein cholesterol (HDL-C), PRL and thyroid-stimulating hormone (TSH).

The essential study outcome

We studied the incidence of MS and its individual components in the representative sample of women aged 25-45 with different prolactin levels with non-tumor etiology.

Additional study outcomes

We analyzed the data on menstrual irregularities, presence of thyroid disorders, tobacco smoking and their association with PRL among the examined women. We studied PRL levels with different values of MS components and presence of MS in women aged 25-45.

Subgroup analysis

The study participants were split into two age groups of 25-34 and 35-45 y.o., with clinical and laboratory characteristics. Additionally, to study metabolic indicators we split into 4 subgroups with different PRL levels (25% in each).

The outcomes registration methods

The presence of menstrual irregularities, thyroid disorders in the past medical history, and smoking habit were assessed by analyzing the data of the structured questionnaire. The presence of MS was established based on the American guidance criteria, NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III, 2001) [13], and the Russian Society of cardiology (RSC, 2009, second revision) [14]. NCEP ATP III (2001) — three and more of the following components: WC over 88 cm in women, TG ≥1.7 mmol/L, HDL-C <1.3 mmol/L in women, BP ≥130/85 mm Hg, blood glucose level ≥6.1 mmol/L. RSC (2009) — WC over 80 cm in women plus two of the following criteria: BP ≥130/85 mm Hg, TG ≥1.7 mmol/L, HDL-C <1.2 mmol/L in women, LDL-C >3.0 mmol/L, plasma glucose ≥6.1 mmol/L.

Statistical analysis

Methods for statistical data analysis. The findings were statistically processed using the SPSS program for Windows (v.13), automated verification of the data base and statistical analysis are performed. The Kolmogorov-Smirnov test was used to assess continuous distributions. The assessment indicates that all have continuous non-normal distributions ($p>0.05$). The data are presented as absolute (n) and relative values (%) and as M±SD, where M is the arithmetic mean, SD is the Standard Deviation, Me (25; 75), where Me is the median, 25th and 75th percentiles. The studied data is presented in PRL quartiles. We compared continuous non-normal distributions in two independent groups using the Mann–Whitney U-test, intragroup attribute correlations were assessed while calculating Spearman's rank correlation coefficient. Attribute associations were assessed with the univariable analysis using cross tables; we also assessed odds ratio (OR) with confidence interval (CI). Fractional difference of characteristics was calculated with the Pearson's chi-squared test. The differences were considered statistically significant with $p<0.05$.

Ethical expert review

The study is approved by the local ethical committee of the Research Institute of Internal and Preventive Medicine, branch of the Federal Research Center of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, protocol № 10 of January 21,

2014. Before the beginning of the study all participants signed an informed consent.

RESULTS

Subjects (participants) of the study

Taking into account inclusion and exclusion criteria, this analysis presents data on 401 women, the average age of the participants is 36.14±6.19, the median is 36.25 [30.88; 41.54] y.o.

The study primary results

The main characteristics of the examined women are presented in tables 1, 2. In older women (the 2nd age group as against the 1st group) we observe statistically significant increase of weight, BMI, WC, TC, LDL-C, TG, fasting plasma glucose, systolic and diastolic blood pressure. The 2nd age group has higher incidence of overweight and obesity, abdominal obesity (AO), hypertension (HT), hypercholesterolemia and increased level of LDL-C (hyper-LDL-C), fasting hyperglycemia; statistically significant increase of MS incidence is noted independent of the used criterion.

Then the analysis of MS incidence definitions and MS in PRL value quartiles was conducted. Women with TSH levels going beyond the reference range were excluded from the analysis as it was earlier shown that lipid spectrum proatherogenic changes appear already with subclinical hypothyroidism; the concept is being developed about the TSH level increase as MS component with the key role of insulin resistance [15, 16]. All PRL quartiles have the same MS incidence. There is no difference in HT and hyperglycemia incidence in PRL quartiles. Although most women with WC of over 80 cm are found in PRL Q1 vs Q4: 55.3 vs 36.2%, p=0.009 (OR=2.18; 95% CI 1.22–3.92), as well as with hyper-LDL-C in PRL Q1 vs Q4: 62.6 vs 48.9%, p=0.063, though the difference has not reached the statistical significance. On the contrary, PRL increase is associated with the increased incidence of hypo-HDL-C: PRL Q2 vs Q4: 16.3 vs 32.6%, p=0.011 (OR=2.48; 95% CI 1.23–5.02); PRL Q2 vs Q4: 27.2 vs 46.7%, p=0.007 (OR=2.35; 95% CI 1.27–4.35) respectively (table 3). When analyzing the percentage of MS components in PRL quartiles in women with hyperprolactinemia (over 19.5 ng/ml) (n=74), we found out that PRL Q4 (Me=41.35 [34.78; 45.88]) has most women with WC of over 80 cm — 56%, with BP≥130/85 mm Hg — 39%, with MS — 47 and 39% (table 4). Thus, women with low-normal PRL values (Me=4.49 [3.52; 5.41] ng/ml) have poorer metabolic characteristics. MS is identified in 28%, with prevailing incidence increase of AO — 55%, with hyper-LDL-C — 63%. Women with high PRL levels (Me=41.35 [34.78; 45.88] ng/ml) also have poor metabolic profile: MS was detected in 47%, AO — 56%, HT — 39%.

Additional study results

There were more smoking women in the younger age group, each third woman indicated that she currently smokes; most women with BMI <18.5 kg/m2. According to the survey data the incidence of AIT (autoimmune thyroiditis), GD (Graves' disease), thyroid structural problems is comparable in studied age groups. Each fifth woman in both groups indicated menstrual irregularities. As the PRL and TSH values are comparable in 25-34 and 35-45 age groups, the further analysis was conducted in the joint group of women aged 25-45. Spearman correlation found association of PRL with menstrual irregularities (r=0.230, p=0.001); weak positive correlation with TSH (r=0.100, p=0.046). We studied PRL values with absence/presence of MS and its components in women aged 25-45 (table 5). Women with TSH levels going beyond the reference range were excluded from the analysis. It was found that PRL mean values did not differ in women with and without MS and when analyzing MS individual components.

Adverse events

During the study adverse events were not registered

DISCUSSION

This study was performed in Novosibirsk which is a typical large industrial center in Siberia. We examined women living in the Oktyabrskiy district, typical for Novosibirsk in terms of industrial, social, population-demographic, ans transportation structures as well as the level of population migration. The representative sampling of women aged 25-45 was formed using random number tables based on lists of candidates. The subsample volume is determined with a random number generator. The forgoing helps extrapolate the findings to the target population.

Study primary result summary

The findings indicate that low and high PRL levels with non-tumor etiology are related to the aggravation of metabolic characteristics in young women. Women with normal and high-normal PRL levels and moderate hyperprolactinemia have a favorable metabolic profile. At present, when examining patients with hyper-PRL it is necessary to take into account PRL pleiotropic action.

Discussion of the study primary result

Over recent years we have been accumulating more and more information on the fact that besides weight increase the pathologic hyperprolactinemia comes with hyperinsulinemia, insulin resistance, HT, dyslipidemia, endothelial dysfunction, activation of indolent inflammation [2-5]. As many authors note, metabolic consequences of hyperprolactinemia with non-tumor etiology have not been given proper attention for many years.

In the examined sample of women the incidence of obesity was 20%, AO — 47%, hyper-LDL-C — 54%, hypo-HDL-C — 23%, HT — 21%, hyperglycemia — 17%, hyper-TG — 10%. MS incidence (RSC, 2009) — 23.5%, according to NCEP ATP (2001) — 16.5%. 26% currently smoke. Our data is comparable with the results earlier presented by Yul. Ragino et al. with a bigger sample which had adverse prognostic factors in terms of cardiovascular abnormalities among young women of Novosibirsk [17].

According to the survey data, the incidence of AIT, GD, thyroid structural problems in the studied age groups of women did not vary. Each fifth woman in both groups indicated menstrual irregularities. As the PRL and TSH mean values and median are comparable in 25-34 and 35-45 age groups, the further analysis of metabolic characteristics was conducted in the joint group of women aged 25-45. To assess the metabolic condition of the patient

Table 1. Clinical and laboratory characteristics of women aged 25-45 (M±SD and Me (25; 75))

Parameters		The whole sampling (n=401)	Age group, y.o.		P
			25–34 (n=177)	35–44 (n=224)	
Age, years		36.14±6.19 36.25 (30.88; 41.54)	30.15±2.96 30.25 (28; 32.67)	40.88±3.28 41.17(38.02; 43.58)	<0.001
Height, cm		164.66±6.20 164.51 (160.0; 168.55)	165.21±5.95 165.52 (161.25; 170.01)	164.23±6.38 164.01(160.02; 168.03)	0.116 0.073
Weight, kg		69.65±16.81 65.95 (57.55; 76.95)	67.51±17.46 64.20 (55.20; 72.75)	71.35±16.11 68.20(59.50; 79.0)	**0.023** **0.002**
BMI, kg/m^2		25.67±5.98 24.29(21.63; 28.34)	24.69±6.04 23.43 (20,45; 27.0)	26.45±5.82 25.33 (22.21; 29.27)	<0.001
BMI, n/%	<18.5 kg/m^2	17/4.3	16/9.0	1/0.4	<0.001
	18.5–24.9 kg/m^2	202/50.5	96/54.2	106/47.5	0.170
	≥25 kg/m^2	181/45.3	65/36.7	116/52.0	**0.002**
	≥30 kg/m^2	78/19.5	27/15.3	51/22.9	0.056
WC, cm		81.71±13.45 78.9 (72.0; 89.7)	78.86±13.23 76.0 (69.0; 86.3)	83.97±13.22 81.0 (74.3; 92.0)	<0.001
WC ≥80 cm, n/%		189/47.3	66/37.3	123/55.2	<0.001
WC ≥88 cm, n/%		110/27.5	36/20.3	74/33.2	**0.004**
SBP, mm Hg		115.96±14.68 114.0 (106.5; 122.5)	112.60±11.00 112.5 (105.3; 120.5)	118.61±16.59 116.5 (108.0; 126.4)	<0.001
DBP, mm Hg		75.79±10.17	73.39±8.73 73.0 (66.5; 79.5)	77.69±10.82 76.5 (70.0; 84.9)	<0.001
HT ≥140/90 mm Hg, n/%		44/11.0	9/5.1	35/15.6	0.001
HT ≥130/85 mm Hg, n/%		86/21.4	21/11.9	65/29.0	<0.001
Biochemical indicators, mmol/L					
FPG		5.61±0.64 5.52 (5.20; 5.94)	5.48±0.60 5.41 (5.10; 5.83)	5.71±0.66 5.62 (5.31; 6.04)	<0.001
TC		4.50±0.87 4.91 (4.39; 5.50)	4.85±0.80 4.75 (4.27; 5.27)	5.10±0.91 5.01 (4.53; 5.65)	**0.004** **0.002**
HDL-C		1.42±0.29 1.37 (1.21; 1.60)	1.43±0.27 1.39 (1.26; 1.60)	1.41±0.30 1.37 (1.21; 1.57)	0.651 0.312
LDL-C		3.10±0.81 3.08 (2.51; 3.59)	2.96±0.75 2.90 (2.40; 3.47)	3.20±0.83 3.19 (2.63; 3.65)	**0.003** **0.003**
TG		1.01±0.707 0.85 (0.63; 1.18)	0.95±0.88 0.76 (0.60; 1.08)	1.05±0.55 0.93 (0.69; 1.29)	0.168 **0.001**
Biochemical indicatorrs, n/%					
FPG 6.1–6.9 mmol/L		68/17.0	22/12.5	46/20.5	**0.032**
FPG 5.6–6.9 mmol/L		190/47.5	72/40.7	118/52.7	**0.017**
FPG ≥7.0 mmol/L		6/1.5	2/1.1	4/1.8	0.591
TC ≥5.0 mmol/L		185/46.3	69/39.2	116/51.8	**0.012**
TG ≥1.7 mmol/L		39/10.1	12/7.4	27/12.1	0.131
LDL-C ≥3.0 mmol/L		207/53.8	74/45.7	133/59.6	**0.007**
HDL-C <1.2 mmol/L		90/23.4	35/21.6	55/24.7	0.484
HDL-C <1.3 mmol/L		139/36.1	51/31.5	88/39.5	0.108
MS is diagnosed based on 2009 RSC criteria		91(388)/23.5	21(166)/12.7	70(222)/31.5	<0.001
MS is diagnosed based on 2001 NCEP ATP criteria		64(389)/16.5	15(166)/9.0	49(223)/22.0	**0.001**

Note. BMI — body mass index, WC — waist circumference, SBP — systolic blood pressure, DBP — diastolic blood pressure, FPG — fasting plasma glucose, TC — total cholesterol, HDL-C — high-density lipoprotein cholesterol, LDL-C — low-density lipoprotein cholesterol, TG — triglycerides, MS — metabolic syndrome. Values were considered statistically significant with p<0.05.

Table 2. Clinical and laboratory characteristics of women aged 25-45 (M±SD and Me (25; 75))

Parameters	The whole sampling (n=401)	Age group, y.o.		P
		25–34 (n=177)	35–44 (n=224)	
TSH, IU/ml	1.897±2.165 1.48 (0.99; 2.19)	1.97±2.88 1.42 (0.99; 2.05)	1.84±1.36 1.52 (0.98; 2.28)	0.568 0.371
PRL, ng/ml	13.62±9.60 11.86 (6.61; 17.85)	13.14±9.39 11.28 (6.16; 17.64)	14.00±9.76 12.02 (6.85; 17.88)	0.373 0.434
		n/%		
TSH >4.0 IU/ml	23/5.8	11/6.3	12/5.4	0.712
TSH >6.1 IU/ml	8/2.0	4/2.3	4/1.8	0.736
TSH >10.0 IU/ml	2/0.5	2/1.1	0	–
PRL ≥19.5 ng/ml	80/20	33/18.6	47/21	0.561
Menstrual irregularities	75 (390)/19.2	36 (173)/20.8	39 (217)/18.0	0.480
Smokes	104/25.9	57/32.2	47/21.0	0.011
Stopped smoking	94/23.4	46/26.0	48/21.4	0.285
Doesn't smoke	203/50.6	74/41.8	129/57.6	0.002
AIT	25/6.2	8/4.5	17/7.6	0.208
Goiter and/or THY focal lesions	47/11.7	21/11.9	26/11.6	0.937
GD	5/1,2	2/1.1	3/1.3	0.851
THY surgery	2/0.5	0	2/0.9	–

Note. TSH — thyroid stimulating hormone; PRL — prolactin, AIT — autoimmune thyroiditis, GD — Graves' disease, THY — thyroid gland. Values were considered statistically significant with $p<0.05$.

depending on the PRL level. Yazmin Macotela et al. (2020) propose to assess the metabolic state of the patient depending on the level of PRL based on the quartile distribution of the hormone, and not on the generally accepted "normoprolactinemic range"[18]. In the whole sample of women the biggest MS incidence (RSC, 2009), 28%, is defined in the low-normal PRL range in Q1 (4.39±1.22 ng/ml (min 1.49; max 6.51 ng/ml; Me 4.49 (3.52; 5.41) ng/ml) with predominant increase of incidence of hyper-LDL-C — 63%, AO — 55%. Earlier we showed that women with low-normal PRL values have poorer metabolic characteristics [19]. Our data is comparable with the literature data where in studies with various designs researchers show that the low PRL level (below 7 ng/ml) negatively affects metabolism. Two of them are big cohort studies in adults showing the inverse correlation between PRL levels and prevalence of type 2 diabetes and IGT (impaired glucose tolerance) [20, 21]. These studies were extended and confirmed in various populations [22-25]. The third study was in children (the average age was 10.7 years) and it found that the low PRL levels were present in cases of obesity and were a risk factor for MS development independently of other factors [26]. The concept of low level circulating PRL as a clinical syndrome first appeared in 2009 when studying sexual dysfunction. Male patients with serum PRL levels below 5 ng/ml had a higher risk of developing MS [27]. Lower PRL levels are detected in female patients with polycystic ovarian syndrome (PCOS) in comparison with female patients without this syndrome. In women with PCOS PRL is negatively associated with such MS components as WC, hyper-TG and LDL-C and with insulin resistance (HOMA-IR), there was found a positive correlation with HDL-C [28, 29]. Men and women with non-alcoholic fatty liver disease had lower PRL levels than control subjects; and patients with severe hepatic steatosis had lower levels than patients with moderate disease [30]. Furthermore, low PRL levels during pregnancy independently predict the higher risk of developing post-partum pre-diabetes/diabetes [30]. Among examined women the MS incidence according to RSC (2009) criteria in PRL Q2-Q4 (8-28 ng/ml) was 21-22%, according to NCEP ATP (2001) criteria — 15-17%. As we showed earlier, women with PRL level in Q2-Q4 do not have differences in fasting plasma glucose, TC, TG, HDL-C, LDL-C, BMI, WC, SBP, DBP and the mean values of studied characteristics are within their reference ranges [19]. Few studies showed that "higher" PRL concentrations (within or above the physiological range of 25 μg/l or 525 mU/L), but not extremely high, promote favorable metabolic homeostasis [18].

The findings we got in our study are comparable with the findings from the Framingham Heart Study where participants were selected from the third generation cohort to study the associations between PRL within the normal range, changes in body composition and CVD risk factors. After selection with inclusion/exclusion criteria the studied subgroup had 832 participants (335 women and 497 men). The average age of women was 40.2±8.7 years, mean PRL levels was 11.9 ±5.2 mg/dL. MS incidence based on 2001 NCEP ATP criteria — 14%. After two examinations with the interval of 6 years and exclusion of people with increased PRL (>30 mg/dL for women, >20 mg/dL for men) the researchers showed that PRL level was not linked to the probability of developing hypercholesterolemia, hypertriglyceridemia or MS in women. In multivariate adjusted logistic regression models in women for each 5-mg/dL increment in PRL, was observed increased odds of low HDL-C at follow-up (odds ratio 1.50, 95% CI

Table 3. The percentage of metabolic syndrome components in prolactin quartiles in women in the 25-45 y.o. population sample

Parameters	Prolactin quartiles, Me (25; 75) ng/ml							
	1 (n=94) 35.5±5.8 years 4.49 [3.52; 5.41]		2 (n=95) 36.0±6.3 years 9.11 [7.84; 10.63]		3 (n=95) 36.4±6.5 years 14.36 [12.92; 15.79]		4 (n=95) 36.8±6.4 years 22.71 [19.64; 28.03]	
	n	%	n	%	n	%	n	%
WC ≥80 cm (RSC, 2009)	52	55.3	44	46.3	48	50.5	34	36.2*
WC ≥88 cm (NCEP ATP, 2001)	25	26.6	30	31.6	26	27.4	20	21.3
Triglycerides ≥1.7 mmol/L	9	9.9	11	12.0	8	9.0	8	8.7
HDL-C <1.2 mmol/L (RSC, 2009)	23	25.3	15	16.3	16	18.0	30	32.6#
HDL-C <1.3 mmol/L (NCEP ATP, 2001)	36	39.6	25	27.2	26	29.2	43	46.7**
LDL-C >3.0 mmol/L (RSC, 2009)	57	62.6	46	50.0	46	51.7	45	48.9^
BP ≥130/85 mm Hg	22	23.4	26	27.4	15	15.8	19	20.0
Fasting plasma glucose ≥6.1 mmol/L	15	16.1	13	14.1	17	17.9	18	18.9
MS is diagnosed based on 2009 RSC criteria	26	28.3	19	20.7	20	22.0	19	20.9
MS is diagnosed based on 2001 NCEP ATP criteria	14	15.2	16	14.4	14	15.4	16	17.2

Note. WC — waist circumference, BP — blood pressure, TC — total cholesterol, HDL-C — high-density lipoprotein cholesterol, LDL-C — low-density lipoprotein cholesterol, MS — metabolic syndrome. Values were considered statistically significant with p<0.05.

*$p_{WC\geq80\ cm}$ = 0.009, the level of statistical significance is between 1 and 4 quartiles.
#$p_{HDL\text{-}C\ <1.2\ mmol/L}$ = 0.011, the level of statistical significance is between 2 and 4 quartiles.
**$p_{HDL\text{-}C\ <1.3\ mmol/L}$ = 0.007, the level of statistical significance is between 2 and 4 quartiles.
^$p_{LDL\text{-}C\ >3.0\ mmol/L}$ = 0.063, the level of statistical significance is between 1 and 4 quartiles.

Table 4. The percentage of metabolic syndrome components in prolactin quartiles in women aged 25-45 with hyperprolactinemia

Parameters	Prolactin quartiles, Me (25; 75), ng/ml								p_{1-4}
	1 35.6±5.3 20.52 [19.81; 21.33]		2 38.2±6.8 23.24 [22.35; 23.78]		3 36.3±6.7 26.84 [25.45; 28.44]		4 38.0±6.9 41.35 [34.78; 45.88]		
	n	%	n	%	n	%	n	%	
WC >80 cm (RSC, 2009)	4	22.2	8	42.1	8	42.1	10	55.6*	0.040
WC >88 cm (NCEP ATP, 2001)	2	11.1	7	36.8	3	15.8	5	27.8	0.238
Triglycerides ≥1.7 mmol/L	0	-	0	-	3	15.8	5	29.4	-
HDL-C <1.2 mmol/L (RSC, 2009)	5	27.8	7	41.2	4	21.1	6	35.3	0.586
HDL-C <1.3 mmol/L (NCEP ATP, 2001)	5	27.8	10	58.8	8	42.1	8	47.1	0.316
LDL-C >3.0 mmol/L (RSC, 2009)	8	44.4	12	70.6	10	52.6	7	41.2	0.312
BP ≥ 130/85 mm Hg	1	5.6	5	26.3	5	26.3	11	38.9#	0.016
Fasting plasma glucose ≥6.1 mmol/L	2	11.1	4	21.1	3	15.8	3	16.7	0.878
MS is diagnosed based on 2009 RSC criteria	1	5.6	5	29.4	4	21.1	8	47.1^	0.005
MS is diagnosed based on 2001 NCEPATP III criteria	1	5.6	4	23.5	3	15.8	7	38.9##	0.022

Note. WC — waist circumference, BP — blood pressure, TC — total cholesterol, HDL-C — high-density lipoprotein cholesterol, LDL-C — low-density lipoprotein cholesterol, MS — metabolic syndrome. Values were considered statistically significant with p<0.05.

Table 5. PRL values with absence/presence of MS and its components in women aged 25-45

Parameters	PRL (M±SD)	p
WC ≥80 cm (RSC, 2009) WC <80 cm	12.78±9.48 14.17±9.29	0.154
WC ≥88 cm (NCEP ATP, 2001) WC <88 cm	12.87±8.89 13.75±9.58	0.420
Triglycerides ≥1.7 mmol/L Triglycerides <1.7 mmol/L	14.57±11.22 13.39±9.14	0.473
HDL-C <1.2 mmol/L (RSC, 2009) HDL-C ≥1.2 mmol/L	14.73±10.56 13.14±8.95	0.172
HDL-C <1.3 mmol/L (NCEPATP, 2001) HDL-C ≥1.3 mmol/L	14.34±10.08 13.05±8.92	0.209
BP ≥130/85 mm Hg BP <130/85 mm Hg	13.77±10.71 13.46±9.01	0.793
Fasting plasma glucose ≥6.1 mmol/L Fasting plasma glucose <6.1 mmol/L	14,06±9,43 13,49±9,43	0.663
LDL-C ≥3.0 mmol/L (RCS, 2009) LDL-C <3.0 mmol/L	13.04±9.66 14.05±8.99	0.304
MS according to RSC criteria, 2009 People without MS	13.98±11.30 1333±8.69	0.577
MS based on 2001 NCEP ATP criteria People without MS	15.12±11.00 13.28±9.12	0.168

Note. WC — waist circumference, BP — blood pressure, TC — total cholesterol, HDL-C — high-density lipoprotein cholesterol, LDL-C — low-density lipoprotein cholesterol, MS — metabolic syndrome. The values were considered statistically significant with p<0.05

1.18-1.91, p=0.001), that persisted after adjustment for BMI (p=0.001). In women only, baseline PRL was positively associated with change in TC (r=0.05, *P*<0.05), though no connection was observed between PRL and hypertension as one of MS components (OR 0.99; 95% CI 0.65-1.49; p=0.91) [32].

Recent large study with the participation of over 8000 women (Nurses' Health Study (NHS), where participated women aged 30-55 and 43-70; in NHS II — 25-42 and 32-54 y.o.) showed that higher, but physiologically normal PRL concentrations were linked to the lower risk of developing type 2 diabetes mellitus within two decades after the assessment and adjustment for numerous risk factors [22]. The findings different from previous publications were received in the Study of Health in Pomerania (SHIP) which found the independent positive correlation between PRL within the physiological range and Me=6.4 (4,5; 9.3) (people with PRL above 30 μg/l were excluded) and total mortality and cardiovascular mortality. The women age median in this study was 49.2 (35.9; 62.3) years and was higher than in our study and Framingham Heart Study. Women with PRL concentrations in the highest tertile (when compared with lowest PRL tertile) experienced the highest mortality risk (HR 1.66: 95% CI 1.08-2,56), with a significant trend across PRL tertiles (p for trend <0.05) [33]. In our study almost half the women with high PRL levels, Me=41.35 [34.78; 45.88], but not extremely high, have MS — 47%, AO — 56%, HT — 39% that indicates metabolic ill-health and poor prognosis regarding cardiovascular diseases.

Study limitations

The limitation of this study is one time determination of serum PRL level in the examined women. The presence of prolactinoma in women with high PRL levels was determined based on the structured questionnaire data and analysis of source medical records.

CONCLUSION

PRL values from 7.8 to 28 ng/ml, i.e. conditionally defined as normal, highly normal and at the level of moderate hyperprolactinemia contribute to the maintenance of a favorable metabolic profile. In young women low and high PRL levels are more often related to metabolic ill-health. Over half the women with low and low-normal PRL values have increase of LDL-C (63%) and AO (55%). Every second woman with high PRL levels with non-tumor etiology has MS (47%), AO (56%), HT 39%. Our findings indicate that it is advisable to determine PRL in young women with MS having MS individual components like AO, HT and LDL-C increase for further follow-up and pharmacological treatment. Conversely, when thinking about how to treat young women with hyperprolactinemia with non-tumor etiology,

it is important to assess their metabolic status and extend our notion of PRL as a hormone only related to lactation and pituitary-gonad axis.

ADDITIONAL INFORMATION

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