Središnja medicinska knjižnica

Obesity and hypercholesterolemia in patients with prolactinomas: could DHEA-S and growth hormone be the missing link?

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Abstract

Purpose: Increasing evidence exists that hyperprolactinemia alters metabolic profile. The mechanism of this effect is unknown. We aimed to investigate differences between metabolic profile of patients with prolactinomas and nonfunctional pituitary adenomas and to evaluate the impact of other pituitary hormones on their metabolic profile.

Methods: Our retrospective study included 86 consecutive patients with prolactinomas and nonfunctional adenomas (29 prolactinomas and 57 adenomas). Body mass index (BMI), blood pressure, serum prolactin, growth hormone (GH), insulin-like growth factor I (IGF-I), adrenocorticotropic hormone (ACTH), cortisol, urinary free cortisol, triiodothyronine, thyroxine, thyroid-stimulating hormone (TSH), dehydroepiandrosterone-sulfate (DHEA-S), testosterone in men, triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, alanine-transaminase, aspartate-transaminase, fasting glucose and C-reactive protein were obtained for all patients. Regression analyses were performed on log-transformed data.

Results: After adjustment for age, gender and tumor size, prolactinomas were associated with higher BMI (OR 5.61, 95%CI 1.70–9.51, P=0.005), LDL cholesterol (OR 3.60, 95%CI 1.35-5.93, P=0.015), DHEA-S (OR 1.97, 95%CI 1.23-3.72, P=0.026) and lower GH levels (OR 0.43, 95%CI 0.03-0.84, P=0.037). In a linear multivariate regression, the association between DHEA-S, GH and prolactin remained significant even after adjustment for BMI. GH and IGF-I were associated with BMI and LDL cholesterol, but the association diminished after adjustment for serum prolactin.

Conclusions: Prevalence of obesity is four times higher in patients with prolactinomas than in patients with nonfunctional adenomas. Higher DHEA-S and lower GH levels in patients with prolactinomas may have an important role in prolactin-induced metabolic effects. Further studies are needed.

Introduction

Up till recently, prolactin has been associated almost exclusively with lactation and its effects on sex hormones. Nowadays, prolactin is linked with a number of various functions – from its role in the immune system where it induces cellular and humoral immunity to the nervous system where it acts as a kind of neurotransmitter and has an analgesic effect [1]. Bearing in mind the numerous effects of physiological concentrations of prolactin, we cannot ignore potential complications of hyperprolactinemia other than amenorrhea-galactorrhea syndrome.

Increasing evidence links hyperprolactinemia with insulin resistance, hyperinsulinemia, abnormal lipid and glucose metabolism and obesity [2-7]. Some studies associate hyperprolactinemia with proatherothrombotic state [8] that leads to microcirculatory disorders and endothelial dysfunction as the first sign of atherosclerotic events [6-8]. The majority of these studies were conducted on a small number of patients, and they mostly compared the metabolic profile and/or endothelial function before and after treatment with dopamine agonists. Both cabergoline and bromocriptine affect glucose metabolism regardless of the degree of reduction in prolactin levels [3,9]. A study by Inancli et al. showed that short-term treatment with cabergoline reduced body mass index (BMI), carotid intima media thickness, LDL cholesterol and C-reactive protein levels regardless of the decrease in prolactin levels [10]. Moreover, neither one study has taken into consideration the concentrations of other hormones of the anterior pituitary and their target glands, which may be altered in patients with a pituitary adenoma.

Therefore, we aimed to investigate differences in metabolic profile between patients with newly diagnosed prolactinomas and nonfunctional pituitary adenomas and to evaluate the impact of other pituitary hormones on metabolic profile.

Patients and methods

Study design

Our retrospective study included 86 consecutive patients with newly diagnosed pituitary adenomas. Twenty-nine patients were diagnosed with prolactinomas and 57 with nonfunctional adenomas. Prolactinomas were defined as pituitary adenomas with a diameter < 10 mm and serum prolactin level >70µg/L (microprolactinomas) and those with a diameter ≥1cm and serum prolactin >100µg/L (macroprolactinomas). The remaining patients were diagnosed with nonfunctional pituitary adenoma. Patients who met biochemical criteria for Cushing's disease (normal or elevated ACTH and cortisol > 50 nmol/L in 1 mg dexamethasone suppression test) and acromegaly (increased IGF-I and GH > 1 ng/ml during oral glucose tolerance test) were excluded from the analysis. Patients that had prior pituitary surgery and/or were taking dopamine agonists or hormone replacement therapy were also excluded.

Blood pressure and BMI were measured at admission. All patients had undergone a biochemical and endocrinological evaluation as well. Endocrinological evaluation included serum prolactin, growth hormone (GH), insulin like growht factor-1 (IGF-I), adrenocorticotropic hormone (ACTH), morning cortisol, urinary free cortisol, dehydroepiandrosterone-sulfate (DHEA-S), triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH) and testosterone in men. Biochemical parameters included triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, alanine transaminase (ALT), aspartate transaminase (AST), fasting blood glucose and C-reactive protein (CRP). Patients were defined as overweight if their body mass index (BMI) was 25-30 kg/m^2 and as obese if BMI > 30 kg/m^2. Hypercholesterolemia was diagnosed in patients with LDL > 3,0

mmol/L, hypertriglyceridemia in patients with triglycerides > 1.7 mmol/L, diabetes in patients with fasting glucose >7.0 mmol/L.

Radiological evaluation

Magnetic resonance imaging (MRI) was performed in all patients using a 1.5 Tesla MRI according to the standard protocol. It included T1 and T2 - weighted sequences and dynamic T1 - weighted imaging after gadolinium-base contrast medium.

Laboratory methods

Quantitative measurements of TSH, T4, T3, IGF-1 and GH were made with CLIA - chemiluminescent immuno assay on the Imulite-1000 by Siemens. The normal ranges of their concentrations are as follow: TSH 0.4-4.0 mIJ/L, T4 60-165 nmol/L, T3 1.1-2.8 nmol/L, IGF-I 115-420 ng/mL, a GH 0-5 ng/mL. Quantitative measurements of cortisol, ACTH, DHEA-S and testosterone were made with ECLIA - electrochemiluminescent immuno assay on the autoanalizer Cobase 411 by Roche Diagnostics Gmbh. The normal range of their concentrations are as follow: morning cortisol 138 – 800 nmol/L, ACTH <10.1 pmol/L, DHEA-S 2.45 - 12.1 nmol/L and testosterone 10.5- 22.5 nmol/L . Urinary free cortisol was measured with ELISA – enzyme-linked immunosorbent assay with chemicals of the DRG Diagnostics Gmbh Company, with the normal concentration being between 54 and 319 nmol/24h. Quantitative measurement of prolactin was made with the DELFIA fluorescent method by the PerkinElmer Company. Normal range for women: 2.0 – 30.0 µg/L and for men: 2.0 – 20.0 µg/L.

Routine biochemical serum analyses (HDL, LDL, total cholesterol, triglycerides, AST, ALT, fasting blood glucose and CRP) were made with original chemicals (Beckman Coulter International S. A.) for all parameters. All analyses were made with the analytic system on the automatic analyzer AU 2700 (Beckman 40). The normal range of their concentrations are as follow: HDL for women >1.2mmol/l, HDL for men >1.0mmol/L, LDL 0-3mmol/L, total cholesterol for adults <5.0mmol/L, triglycerides 0-1.7mmol/L, AST for men 11-38 U/L, AST for women 8-30 U/L, ALT for men 12-48 U/L, ALT for women 10-36 U/L, fasting blood glucose 4.4-6.4 mmol/L, CRP <5.0 mg/L.

Statistical analyses

Patient characteristics were assessed using descriptive statistics presented as a median with interquartile range values. Independent continuous variables were compared using Mann-Whitney test and categorical variables were compared using Fisher's exact test. The majority of parameters did not follow normal distribution and therefore all continous variables were transformed by logarithm to base 10. Afterwards, we used two approaches to analyze the association between prolactin and other parameters. Firstly, we compared two groups by using binary logistic regression. Logistic regression was also used to adjust for age, gender, tumor size and other confounding factors. Secondly, we aimed to analyze the correlation between serum prolactin levels and other parameters in all patients, regardless of the tumor type. Spearman correlation was used to assess the association between prolactin and other variables. Linear regression was used to adjust other confounding factors. Our power analysis demonstrated a power of 88% for the lowest correlation coefficient (GH) and a power of 99% for the highest correlation coefficient (DHEA-S). Software *SPSS 20.0 for Windows* was used to perform all the analyses. *P* value <0.05 was considered significant.

Results

Patients characteristics

Patients had a median age of 33.0 years (27.0-41.0) and had a median tumor size of 9 mm (6-14.5). More female patients were diagnosed with nonfunctional adenomas (P=0.016). Patients with prolactinomas presented with larger tumors (P=0.017), but there was no difference in age between the groups. Two patients with prolactinomas and one patient with nonfunctional adenoma were taking statins, 7 patients with nonfunctional adenomas and 7 patients with prolactinomas were taking antihypertensive agents one patient with nonfunctional adenoma was taking metformin. Prevalence of obesity and hypercholesterolemia was higher in patients with prolactinomas (Table 1). Biochemical and endocrinological evaluation showed that patients with prolactinomas had higher total cholesterol, LDL cholesterol, CRP, DHEA-S and ACTH levels, but lower IGF-I and GH (Table 2). There were no significant differences in other parameters.

Regression analysis between patients with prolactinomas and nonfunctional adenomas

Logistic regression was performed in order to closely examine these associations and to adjust for of other varables. Patients with prolactinomas had 4-fold higher risk for obesity (relative risk 3.93, 95%CI 1.92 − 8.05). Accordingly, univariate analysis confirmed that patients with prolactinomas had significantly higher BMI. This positive correlation remained significant after adjustment for age, gender and tumor size (OR 5.61, 95%CI 1.70 − 9.51, P = 0.005). Binary logistic regression confirmed that patients with prolactinomas had higher total cholesterol (OR 1.99, 95% CI 1.09-3.65, P = 0.016) and LDL (OR 2.83, 95% CI 1.35 - 5.93, P = 0.002). After adjustment for age, gender and tumor size, the difference in total cholesterol was not significant (P = 0.088), but for LDL the difference was still evident (OR 3.60, 95%

CI 1.35-5.93, P = 0.015). However, the association between LDL and prolactinomas diminished after adjustment for BMI. The association between prolactinomas and CRP was significant in univariate binary logistic regression, but diminished after adjustment for age and gender. Although patients with prolactinomas had significantly higher CRP and ACTH (Mann-Whitney test), we found no significant correlations after univariate nor multivariate analysis.

After adjustment for age, gender and tumor size, patients with prolactinomas had lower GH (OR 0.43, 95%CI 0.03 - 0.84, P=0.037). However, after adjustment for BMI this association was no longer statistically significant. Patients with prolactinomas did have significantly lower age-adjusted IGF-I, but the association diminished after adjustment for gender, and remained insignificant in multivariate model with the rest of variables.

Positive association of DHEA-S and prolactinomas was confirmed in binary logistic regression and remained significant after adjustment for age, gender and tumor size (OR 1.97, 95% CI 1.23-3.72, P = 0.026). However, after including BMI into a multivariate model, this association became insignificant.

Correlation of prolactin levels and variables within the study population

Serum prolactin correlated inversely with T4, IGF-I and GH and positively with BMI, DHEAS, LDL and CRP. The association remained significant only for BMI, GH and DHEA-S after adjustment for age, gender and tumor size (Table 3). In a subgroup analysis of male patients, we found negative correlation between prolactin and testosterone (ρ = -0.479) but it did not reach statistical significance (P = 0.07). On the other hand, we observed strong negative correlation between DHEA-S and prolactin (ρ = 0.721, P = 0.019). There was no significant correlation between testosterone and DHEA-S.

DHEA-S correlated positively with CRP, but this correlation diminished after adjustment for serum prolactin. We found no correlation between serum DHEA-S and BMI or LDL cholesterol. On the other hand, both serum IGF-I and GH were inversely associated with BMI, CRP, LDL and triglycerides, but positively associated with HDL cholesterol. After adjustment for serum prolactin, only positive correlation between GH and HDL cholesterol (r = 0.315, P = 0.04) and negative correlation between IGF-I and CRP (r = -0.356, P = 0.019), LDL (r = -0.366, P = 0.031) remained significant.

Discussion

Prolactinomas represent 40% of all pituitary tumors. They are classified according to their size as macroprolactinomas (≥10 mm) or microprolactinomas (<10 mm). Patients are diagnosed with prolactinomas if they harbor macroadenoma with prolactin levels > 100 µg/L /L, or microadenoma with increased prolactin levels. Typically, young females with microadenomas represent the vast majority of patients with prolactinomas [11]. In our study, young females were mostly diagnosed with nonfunctional adenoma since we used a prolactin > 70 mcg/L cutoff to diagnose patients with prolactinomas [11]. This was necessary in order to insure that all patients in prolactinoma group really do have primary hyperprolactinemia. This is rather important, since approximately 64% of patients with polycystic ovary syndrome have secondary hyperprolactinemia and often have nonfunctional microadenomas, misdiagnosed as microprolactinomas [12]. However, due to atypical diagnostic criteria for prolactinomas, linear regression models were conducted on the entire study population regardless of the prolactin cut-off value used for the diagnosis of prolactinoma. We obtained similar results after conducting two different approaches of statistical analyses. This brings

additional power to our conclusions and reduces the possibility of a bias due to criteria used for the diagnosis of prolactinomas.

Our study showed that patients with prolactinomas have higher BMI and LDL levels than patients with nonfunctional pituitary adenomas. This observation is in accordance with previous studies that reported a decrease in BMI and total cholesterol after treatment with dopamine agonists [2,3,10,13]. However, our study is the first to report that patients with prolactinomas have higher BMI and LDL cholesterol, independently of dopamine agonists. This is important since dopamine agonists may affect metabolic profile regardless of the degree of reduction in prolactin levels [3,9,10]. Additional new information is that hypercholesterolemia is simply the consequence of obesity, rather than directly associated with hyperprolactinemia. This can be concluded from the fact that the association between hypercholesterolemia and hyperprolactinemia was lost after adjustment for BMI. Previous studies have also emphasized the role of insulin resistance in alteration of metabolic profile in patients with hyperprolactinemia. However, patients with hyperprolactinemia in those studies had baseline HOMA-IR of only 1.5, which could hardly be defined as insulin resistance [3]. Some evidence exists that morbidly obese subjects have low levels of serum prolactin [14], along with the strong negative correlation between prolactin and insulin resistance [14]. Hence, it is highly unlikely that insulin resistance could explain hyperprolactinemia-induced alterations in metabolic profile. Unfortunately, since this is a retrospective study, we can't provide information on insulin resistance in our patients. However, there was a trend of lower fasting glucose levels and lower prevalence of diabetes in patients with prolactinomas. Despite the limitations, our study suggests that higher levels of DHEA-S and lower GH levels may explain the metabolic effects associated with hyperprolactinemia.

Few small and clearly forgotten studies published three decades ago, reported that patients with hyperprolactinemia have higher levels of DHEA-S [15-17]. Using monolayer cultures of

human adrenal cells, the authors showed direct stimulatory effect of prolactin on DHEA and DHEA-S secretion [16]. Unfortunately, these studies haven't analyzed the metabolic profile of patients and therefore could not elucidate the true impact of DHEA-S. However, previous epidemiological studies on healthy individuals, reported positive correlation between DHEA-S and BMI, LDL cholesterol and cardiovascular risk [18]. Additionally, DHEA-S had no effect on insulin resistance [19]. Patients with prolactinomas in our study had higher levels of DHEA-S, BMI and LDL cholesterol. Moreover, there was a strong positive correlation between serum prolactin level and BMI, but also between serum prolactin and DHEA-S. The correlation between prolactin and DHEA-S was not influenced by BMI, which suggests that prolactin directly stimulates DHEA-S secretion. Similar inverse association was found for GH and prolactin. Although obese individuals tend to have lower GH and IGF-I levels due to hyperinsulinemia, the correlation between prolactin and GH remained significant even after adjustment for BMI. We found no significant correlations between the DHEA-S and metabolic syndrome components. However, this is a subgroup analysis and the conclusions must be drawn carefully, since the sample size may not be sufficient to detect those associations, which were clearly evident in previously mentioned studies. But on the other hand, GH and IGF-I were associated with BMI and several other components of metabolic syndrome. The majority of these associations diminished after adjustment for prolactin levels, indicating that GH effects may be mediated by hyperprolactinemia. To our knowledge, neither one study has previously found similar association between GH and prolactin. Bearing in mind the common embryological origin of lactotropic and somatotropic cells, we suggest that there is a possibility that chronic hyperprolactinemia may suppress GH secretion. On the other hand, there is some evidence that IGF-1 gene therapy reverses morphological changes and reduces hyperprolactinemia in rats with prolactinomas [20].

In conclusion, patients with prolactinomas have higher BMI, LDL cholesterol, DHEA-S and lower GH levels than patients with nonfunctional adenomas. The association between hypercholesterolemia and hyperprolactinemia was lost after adjustment for BMI, which suggests that hypercholesterolemia is simply the consequence of obesity, rather than directly associated with hyperprolactinemia. We found strong positive correlation between prolactin and DHEA-S and negative correlation between serum prolactin and GH, which was independent of BMI. We found no correlation between DHEA-S and BMI, but GH and IGF-I were associated with obesity and several components of metabolic syndrome. Interestingly, these associations diminished after adjustment for prolactin levels, indicating that GH effects are mediated by hyperprolactinemia. Higher DHEA-S and lower GH levels in patients with prolactinomas may have an important role in prolactin-induced metabolic effects. Further studies in this field are needed.

Conflicts of interest statement

Ethical approval

The ethics committee of the University Hospital Center "Sestre Milosrdnice" in Zagreb, Croatia approved this study (EC number: EP-4532/14-6)

Informed consent was not required for our retrospective observational study.

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Table 1. Anthropometric parameters of the study population divided based on tumor type

	Prolactinoma N=29	Nonfunctional adenoma N=57	P value
Gender			
Male No (%)	10 (34%)	6 (11%)	**0.016**
Age (years)	34.0 (29.5-49.8)	32.0 (26.8-40.0)	0.246
Tumor size (cm)	1.0 (0.7-2.0)	0.8 (0.5-1.3)	**0.017**
BMI (kg/m^2)	31.0 (24.6-34.6)	21.5 (19.9-23.9)	**<0.001**
Systolic pressure (mmHg)	125 (120-140)	120 (110-130)	0.087
Diastolic pressure (mmHg)	80 (70-85)	80 (75-90)	>0.3
Overweight No (%)	4 (13.8)	10 (17.5)	>0.3
Obesety No (%)	17 (59)	10 (17.5)	**<0.001**
Diabetes No (%)	0 (0)	7 (12.3)	0.090
Hypercholesterolemia No (%)	25 (86.2)	22 (38.6)	**<0.001**
Hypertryglyceridemia No (%)	12 (41.4)	15 (26.3)	0.220

Table 2. Biochemical parameters of the study population divided based on tumor type

	Prolactinoma N=29	Nonfunctional adenoma N=57	P value
LDL (mmol/L)	3.90 (3.43-4.33)	2.75 (2.30-3.78)	**0.004**
HDL (mmol/L)	1.28 (1.07-1.49)	1.21 (1.03-1.50)	>0.3
Total cholesterol (mmol/L)	5.94 (5.08-6.42)	4.65 (4.24-5.52)	**0.005**
Triglycerides (mmol/L)	1.66 (0.94-2.03)	1.21 (0.97-1.53)	0.184
AST (U/L)	17.0 (11.8-23.0)	17.0 (12.0-22.0)	>0.3
ALT (U/L)	18.0 (15.0-23.3)	20.0 (16.5-23.0)	>0.3
Glucose (mmol/L)	5.1 (4.7-5.5)	4.9 (4.6-5.4)	>0.3
CRP (mg/L)	2.1 (1.1-6.1)	0.8 (0.5-2.1)	**0.002**
Prolactin (μg/L)	148.6 (103.8-625.5)	22.7 (10.7-51.4)	**<0.001**
Cortisol (nmol/L)	487.0 (346.8-552.5)	458.0 (317.0-557.5)	>0.3
ACTH (pmol/L)	8.92 (6.64-9.86)	6.65 (4.01-9.24)	**0.035**
DHEA-S (nmol/L)	7.58 (5.32-8.91)	4.43 (2.17-7.06)	**0.039**
Urinary cortisol (nmol/24h)	120.5 (90.0-244.0)	148.0 (98.0-223.0)	0.300
T4 (nmol/L)	90.2 (74.2-105.3)	94.4 (80.2-106.5)	>0.3
T3 (nmol/L)	1.6 (1.3-1.8)	1.6 (1.3-1.8)	>0.3
TSH (mIU/L)	2.33 (1.51-2.88)	1.98 (1.17-2.71)	0.235
Testosterone in men (nmol/L)	5.1 (1.1-7.4)	7.2 (5.05-15.8)	0.175
Growth hormone (ng/ml)	0.14 (0.06-0.40)	0.32 (0.11-0.92)	**0.021**
IGF-I (ng/ml)	157.0 (127.5-201.0)	193.0 (150.5-254.5)	**0.020**

Table 3. Correlation coefficients and p values showing the association between serum prolactin and other parameters.

	BMI	T4	IGF-I	GH	DHEA-S	CRP	LDL
Unadjusted (ρ)	.394	-.322	-.309	-.296	.489	.328	.324
P value	.005	.005	.015	.015	.002	.008	.034
Adjusted for age (r)	0.477	-.341	-.357	-.298	.619	.266	.357
P value	.002	.003	.012	.014	.000	.037	.031
Adjusted for age and gender (r)	.385	-.221	-.277	-.256	.487	.176	.295
P value	.013	.046	.034	.022	.001	.172	.045
Multivariable model including tumor size[a] (r)	.327	-.154	-.230	-.273	.522	.161	.221
P value	.046	0.200	.086	.017	.001	.191	.152
Multivariable model including BMI[b] (r)	NA	-.050	-.261	-.347	.600	.172	.074
P value	NA	>.3	.102	.015	.002	>.3	>.3

[a] multivariable model including age, gender and tumor size, [b] multivariable model including age, gender, tumor size and BMI; NA – not analyzed