



Increased Lipid Levels Improves after Treatment with Cabergolin in Patients with Prolactinoma

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Abstract

It has been suggested that hyperprolactinemia may be associated with obesity and dyslipidemia. However it is not fully understood that dyslipidemia is occurs independently or due to obesity. The study was aimed to investigate lipid abnormalities and androgen hormone levels before and after cabergolin (CAB) treatment in non- obese premenopausal patients with prolactinoma. This study was a single-centre, prospective, case-control study, consisted of 53 patients with symptomatic prolactinoma (group 1) and 57 healthy women (group 3). All subjects underwent a physical examination, anthropometric measurement and a 12 hour fasting blood sample for fasting blood glucose and lipid levels. 49 patients with prolactinoma were reevaluated for metabolic parameters after one year of cabergolin treatment (group 2). The median age was 34 (24-38) in group 1, and 33 (27-41) in group 3 ($p=0.522$). The initially higher body mass index (BMI) in patients with prolactinoma became similar after one year of treatment those with control group ($p=0.475$). While LDL-C was significantly higher in group 1 than in controls, HDL was significantly lower in group 1. Also post- treatment values of LDL-C ($p=0.440$) and HDL-C ($p=0.612$) were not different from the control group. No correlation was found between baseline prolactin levels and FSH, LH, LDL-C, HDL-C ($p=0.129$, $p=0.658$, $p=0.817$, $p=0.760$ respectively). In conclusion, beneficial metabolic changes were seen in patients with prolactinoma after treatment with cabergoline. Thus considering the metabolic profile and an appropriate treatment goal is important in the clinical management of patients with prolactinoma.

Key words: Androgen hormones, lipid abnormalities, hyperprolactinemia, prolactinoma

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Introduction

Prolactinomas, derived from lactotroph cells, account for approximately 40% of all pituitary adenomas, with an estimated prevalence of 44 to 62 per 100,000 inhabitants and characterised by hypersecretion of prolactin (PRL) [1,2]. As prolactin may act as a hormone, and as a growth factor, neurotransmitter, or immunoregulator the primary action of prolactin is stimulation of lactation after delivery [3]. Whether the underlying mechanism is not fully understood hyperprolactinemia has been shown to be associated with abnormalities of carbohydrate and lipid metabolism as well as obesity [4,5]. Prolactin may have a direct effect on adipose tissue. Ling et al. demonstrated that, PRL increase triglyceride (TG) levels by reducing the lipoprotein lipase activity in adipose tissue [6]. Hyperprolactinaemia is associated with amenorrhoea and decreased estrogen concentration which may lead to the elevation in total cholesterol and low density lipoprotein cholesterol (LDL-C) and decrease in high density lipoprotein cholesterol (HDL-C) [7]. The aim of present study was to evaluate the metabolic parameters in non obese patients with prolactinoma and effect of cabergolin treatment on this parameters.

Materials and Methods

Subjects and Study Design: The study was a single-centre, case–control study conducted on patients with prolactinoma at Ankara Numune Research and Training Hospital between January 2012 and December 2013. Fifty-three nonobese, premenopausal women with newly diagnosed of hyperprolactinoma due to pituitary microadenoma (group 1) were recruited to our study. Cabergolin (CAB) treatment were given to all patients, started with 0.25 mcg/week and the dosage was titrated monthly until prolactin levels normalised. After one year of follow up, 49 patients could reevaluated for metabolic parameters (group 2). Fifty seven healthy subjects were included as a control group (group 3). The study was approved by the local ethical committee and written informed consent was obtained from all participants. Hypopituitarism was not exist in any of our patients except hypogonadotropic hypogonadism in 21 cases. The diagnosis of prolactinoma was based on the following: symptoms and signs of hyperprolactinemia; a PRL level higher than 100 ng/ml and a pituitary adenoma detection on enhanced magnetic resonance imaging or computed tomography [8]. Macroprolactinemia was excluded by the precipitation of serum with polyethylene glycol. The exclusion criteria

were; postmenopausal period, pregnancy, lactation, acute or chronic illness, obesity, and use of drugs that could increase PRL levels (neuroleptics, antidepressants, opiates, metpamid, and oral contraceptives), alcohol consumption, and smoking, thyroid dysfunctions. Medical history, blood pressure and anthropometric measurements were carefully evaluate by the same clinician. Body mass index (BMI) was calculated as weight (kg) / squared height (m²).

Biochemical Analyses: After overnight fasting, venous sample were taken for hormones including follicle-stimulating hormone (FSH), Luteinizing hormone (LH), estradiole (E2), total testosterone (TT), dehydroepiandrosterone-sulfate (DHEAS) and androstenedione (A) in the early follicular phase. All hormone levels were studied in specific labs using a Roche Hitachi Cobalt 600 device. FSH (mIU/ml), LH (mIU/ml), E2 (pg/ml), and prolactin (ng/ml) were studied using immune chemiluminescent method. A fasting lipid profile including HDL-C and triglycerides (TG) and Total- C/HDL-C were studied using a routine, automatic, standard enzymatic methods (Roche T800 Moduler analyser). LDL-C level was calculated by the Friedewald formula if triglyceride level was below 400 mg/dl.

Statistical Analyses: SPSS for Windows (vers.18.0) was used for statistical analysis. The Shapiro-Wilk and Kolmogorov Smirnov tests were performed to test for normal distribution of variables. In comparison of independent variables that were normally distributed, the student's t-test and analysis of variance were performed, and the variables were expressed as mean \pm standard deviation. The independent variables, which were non-normally distributed, were tested using Mann Whitney U and Kruskal Wallis tests. They were expressed with median and interquartile range. Moreover, PRL levels along with the correlation between the LH, Estradiol, LDL-C, HDL-C that differed between groups were assessed with simple correlation analysis. A p value of <0.05 was accepted as statistically significant.

Results

Our study population was consisted of 53 patients with prolactinoma and 57 healthy women, initially. The median age was 34 (24-38) in group 1, and 33 (27-41) in group 3 (p=0.522). Baseline characteristics of the participants are presented in the Table 1. Androstenedion, testosterone and DHEAS levels were not different between patients with prolactinoma and healthy subjects. While 60% of participants were eugonad, the remaining 40% were hypogonad at the time of diagnosis. All hypogonad participants became eugonad after 12 months of

treatment with cabergolin. Prolactin levels were higher in patients with hypogonadism than those with eugonadism ($p=0.021$).

The initially higher BMI in patients with prolactinoma became similar after one year of treatment those with control group ($p=0.475$). Also post- treatment values of LDL-C ($p=0.440$) and HDL-C ($p=0.612$) were not different from the control group.

Table 1. Clinical features, hormonal and metabolic parameters before and after 12 months of treatment with cabergoline and control groups (Data are given as median and interquartile range)

	Patients with prolactinoma		Healty subjects (Group 3, n=57)	p
	Baseline (group 1, n=53)	After treatment (group 2, n=49)		
Age (year)	34 (24-38)	35 (25-39)	33 (27-41)	0.693
BMI (kg/m ²)	26 (22- 29)*	24 (21-27)	23 (21-26)**	0.022
FBG (mg/dl)	88	91	87	0.124
Prolactin (ng/ml)	92 (64-123) *	5.1 (1.7-13)	17 (11-19) **	<0.01
Estradiol (ng/ml)	51 (22-90)*	59 (37-146)	77 (44-156)** ***	0.015
LDL-C (mg/dl)	107 (92-140)*	95 (77-116)	95 (80-111)**	0.025
Triglyseride (mg/dl)	89 (67-163)	80 (55-131)	123 (71-146)	0.474
HDL-C (mg/dl)	45 (41-57)*	50 (45-65)	51 (46-63)**	0.041
Total C /HDL-C	3.4 (2.8-3.5)	3.2 (2.4-4.3)	3.2 (2.8-3.9)	0.785
Tumour volume(cm ³)	5.4 (4-8)*	3.4 (0-6)	-	<0.01

BMI: Body Mass Index, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, FBG: Fasting blood glucose

* $p<0.05$, At diagnosis vs. after 12 months of cabergolin

** $p<0.05$, At diagnosis vs control group

*** $p<0.05$, After treatment vs control group

There was no significant difference between eugonad and hypogonad patients according to BMI, LDL-C, HDL-C, Total C/HDL-C and triglyseride (Table 2). No correlation was found between baseline prolactin levels and FSH, LH, LDL-C, HDL-C ($p=0.129$, $p=0.658$, $p=0.817$, $p=0.760$ respectively). There was a negative correlation between PRL and estradiol levels in patients with prolactinoma at baseline ($r=-0.319$, $p=0.008$).

Table 2. Comparison of metabolic parameters between hypogonad and eugonad patients (Datas are given as median and interquartile range)

	Eugonad (N=32)	Hypogonad (N=21)	p
Age (year)	33 (24-38)	34 (23-39)	0,838
BMI (kg/m ²)	24 (22-29)	26 (22-28)	0,995
LDL-C (mg/dl)	102 (89-126)	112 (101-156)	0,299
HDL-C (mg/dl)	55 (42-60)	43 (40-50)	0,121
Triglyceride (mg/dl)	98 (56-144)	89 (67-195)	0,558
Total C/HDL-C	3,4 (2,8-4,18)	3,1 (2,8-4,1)	0,221

Discussion

The relationship between hyperprolactinaemia and oligoamenorea, galactorea and impaired reproductive function are well known for a long time [9]. But the metabolic abnormalities such as obesity, dyslipidemia and insulin resistance, which was shown to be associated with hyperprolactinemia, are ignored. It was shown that hyperprolactinemia may leads to weight gain in human studies [5,10,11]. In a recent study, a higher prevalence of obesity/overweight was found in patients with prolactinoma than in general population [12]. However, in that study, BMI was not correlate with PRL levels. As obesity is a confounding factor on lipids our study cohort were consisted of non- obese patients. We observed a higher BMI in patients with prolactinoma than those healty subjects which was comparable with controls at the 12th month of treatment with CAB. No correlation was observed between prolactin and BMI in our study; as previously mentioned study. It is suggested that obesity is occurs secondary to the changing in hypothalamic energy metabolism [13]. But, direct relationship between high prolactin and BMI is not clear [14]. A reduction in dopaminergic tone [5,15]; leptin resistance [5]; decreased adiponectin levels [16] and hypogonadism [17] are also hypothesized to be contributing factors on weight gain in patients with prolactinoma. Therefore we assesed whether hypogonadism was a determinant factor for obesity in our population. Although patients with hypogonadism had higher PRL levels than those with eugonadism, we did not find a significant difference in terms of BMI and lipid profile between two groups.

Lipid abnormalities such as, hypercholesterolemia, hypertriglyceridemia and normal lipid profiles are reported in prolactinoma patients [14,18,19]. Some studies have suggested the

influence of hyperprolactinemia on the lipid profile but the mechanism is not well established. Hyperprolactinemia leads to a reduction in estrogen levels by inhibiting the gonadotropin releasing hormone secretion, which may lead to an elevation in total and LDL-C and decrease in HDL-C [7]. Total C/ HDL C ratio, which has been approved as a new atherosclerotic risk marker for endothelial dysfunction in AACE 2012 Lipid and Atherosclerosis guidelines [20], were similar between three groups. Hypercholesterolemia may improve (21) or not [14] after treatment with DA agonists. As previously demonstrated [22-24], it was supported in our study that CAB therapy reduce LDL-C and increase HDL-C. Our study cohort was consisted of young, non- obese and premenopausal women without traditional cardiovascular risk factors. The other strengths of our study were a prospective design, relatively high volume of participants and the presence of results of treatment affect. In conclusion, our study revealed a possible association of prolactinoma with increased BMI, and LDL-C and low HDL-C, independently with gonadal status. Additionally, CAB treatment may be effective in improving metabolic parameters in patients with prolactinoma.

Author contributions: BAD led the conception and design. MMT participated in design and coordination of the study, and drafted the manuscript. MNB gave the concept of the research paper. AA helped to perform the Statistical Analyses, DB and SG reviewed the manuscript. All authors read and approved the manuscript.

Conflict of interest: The authors declare no conflict of interest.

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