

Insulin sensitivity and lipid profile in prolactinoma patients before and after normalization of prolactin by dopamine agonist therapy

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Abstract Hyperprolactinemia has been associated with impaired metabolism, including insulin resistance. However, the metabolic effects of elevated prolactin (PRL) levels are not completely clarified. The aim of this study was to obtain more insights of metabolic consequences in hyperprolactinemia patients. Fourteen consecutive patients, eight women and six men, aged 39.7 (± 13.7) years with prolactinomas (median PRL 72 [49–131] $\mu\text{g/L}$ in women and 1,260 [123–9,600] $\mu\text{g/L}$ in men) were included. Anthropometric data and metabolic values were studied before and after 2 and 6 months on DA agonists (Bromocriptine [5.7 (± 3.9) mg/day, $n = 13$] or Cabergoline [0.5 mg/week, $n = 1$]). Euglycemic hyperinsulinemic clamps were studied in six patients before and after 6 months of treatment. PRL normalized in all patients. Anthropometric data changed only in males with a significant decrease of median body weight (95.6 [80.7–110.1] to 83.4 [77.8–99.1] kg, $P = 0.046$), waist circumference and fat percentage after 6 months. LDL cholesterol was positively correlated to PRL at diagnosis ($r = 0.62$, $P = 0.025$) and decreased within 2 months (3.4 [± 0.9] to 2.9 [± 0.6] mmol/L, $P = 0.003$). Insulin, IGFBP-1 and total adiponectin levels did not change. Insulin sensitivity

tended to improve after 6 months; M-value from 5.7 (± 1.8) to 7.8 (± 2.6) mg/kg/min, $P = 0.083$ and per cent improvement in M-value was correlated to per cent reduction in PRL levels ($r = -0.85$, $P = 0.034$). In conclusion, beneficial metabolic changes were seen in prolactinoma patients after treatment with DA agonists, underscoring the importance of an active treatment approach and to consider the metabolic profile in the clinical management of hyperprolactinemia patients.

Keywords Hyperprolactinemia · Insulin resistance · Euglycemic clamp · LDL cholesterol · Dopamine agonist therapy

Introduction

Prolactin (PRL) is a multifunctional polypeptide hormone produced by the lactotrophs in the anterior pituitary as well as by different extrapituitary sites [1]. The main effect of PRL in humans is to regulate mammary gland development during pregnancy and to induce milk production. However, a wide variety of functions have been attributed to PRL [2].

For some years, PRL has attracted attention as a metabolic hormone. Hyperprolactinemia has been reported to be associated with abnormalities of carbohydrate and lipid metabolism [3]. In patients with elevated PRL levels reduced glucose tolerance and hyperinsulinemia have been demonstrated [4–6]. Moreover, increased insulin resistance using homeostasis model assessment (HOMA) index is described in patients with hyperprolactinemia [7, 8] and that insulin sensitivity index (ISI composite) is reduced in the hyperprolactinemic state, improving after normalization of PRL by dopamine (DA) agonist therapy [9]. Additionally, in a recent study hyperprolactinemic patients

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were more insulin resistant than controls, measured by a euglycemic hyperinsulinemic clamp [10]. Furthermore, treatment with Bromocriptine (BRC) in non-hyperprolactinemic obese humans or patients with diabetes mellitus (DM) type 2 improved lipid profile [11] and glycemic control [12], respectively.

Hyperprolactinemia has also been linked to hypercholesterolemia [13], with [14] or without [7] improvement after treatment with DA agonists. In humans, sustained hyperprolactinemia is often associated with weight gain and obesity [15, 16] with weight loss after normalization of PRL by DA agonists [15, 17], although some findings are conflicting and contradictory [7, 18]. The linkage between hyperprolactinemia and weight gain remains elusive; however, reduced central dopaminergic tone as a result of persistent hyperprolactinemia has been proposed as one possible mechanism [17]. Furthermore, endothelial dysfunction [9] and low-grade inflammation [7, 9] have been demonstrated in these patients. Thus, to some extent the metabolic consequences of hyperprolactinemia are similar to those of the metabolic syndrome. The aim of this study was to obtain more insight into the metabolic consequences of hyperprolactinemia by evaluating anthropometric data, blood lipids and insulin sensitivity before and after normalization of PRL by DA agonist therapy.

Patients and methods

Patients

Fifteen consecutive patients with newly diagnosed hyperprolactinemia, referred to the outpatient clinic at the Department of Endocrinology, Metabolism and Diabetology, Karolinska University Hospital, Stockholm, Sweden, were included in the study. One woman was excluded because of pregnancy. Thus, the final sample consisted of fourteen patients (eight women and six men). The study was approved by the Stockholm Regional Ethical Review Board and informed written consent was obtained from all patients.

Inclusion criteria were elevated PRL levels found on at least two occasions and magnetic resonance imaging of the hypothalamic-pituitary region confirming a prolactinoma. Exclusion criteria were combined hormone-producing pituitary tumors, secondary causes of hyperprolactinemia, pregnancy or patients on medication for hyperlipidemia and DM.

Baseline characteristics of the study subjects at diagnosis are presented in Table 1. Male patients had higher PRL levels ($P = 0.004$) and larger tumors than females. One woman was postmenopausal receiving low-dose estrogens at study entry. Her initially low gonadotrophins

Table 1 Baseline characteristics of study subjects. Quantitative data are shown as mean \pm SD if normally distributed or as median and range if not normally distributed

| | Women ($n = 8$) | Men ($n = 6$) |
|---------------------------|---------------------|--------------------|
| Age at diagnosis (years) | 36.1 (± 16.3) | 44.5 (± 8.4) |
| Microadenoma (n) | 8 | 0 |
| Macroadenoma (n) | 0 | 6 |
| S-PRL ($\mu\text{g/L}$) | 72 (49–131) | 1,260 (123–9,600) |
| Blood pressure | | |
| Systolic (mmHg) | 119 (± 22) | 127 (± 15) |
| Diastolic (mmHg) | 73 (± 9) | 80 (± 8) |

rose to normal postmenopausal levels after normalization of PRL. The other seven women were premenopausal: four of them were on hormonal contraceptives both at diagnosis and throughout the study period. In the other three women, two had secondary amenorrhea and one had oligomenorrhea. Two male patients had testosterone substitution already at referral to our clinic, which was kept unchanged during the study period. The other four men had hypogonadotropic hypogonadism with testosterone levels below normal range together with low or normal levels of gonadotrophins. One male patient had secondary hypothyroidism at diagnosis and received substitution with 100 μg levothyroxine per day. This patient did not participate in the clamp and was excluded from the analysis of thyroid hormones and lipids. Apart from this, all patients were without medications and were non-smokers.

Study protocol

Patients were examined at base line (t_0) and after 2 (t_2) and 6 (t_6) months of DA agonist therapy (BRC or Cabergoline [CAB]). Anthropometric data and laboratory measurements were studied at t_0 , t_2 and t_6 . Blood samples were obtained in the morning after an overnight fast for measurements of hormones (PRL, TSH, fT_4 , testosterone, GH, IGF-I, IGF-binding protein-1 [IGFBP-1]), metabolic variables (glucose, hemoglobin A_{1c} [HbA $_{1c}$], insulin, C-peptide, lipid profile, leptin, adiponectin) and inflammatory markers (high sensitive CRP [hsCRP], tumor necrosis factor alpha [TNF- α]). Peripheral insulin sensitivity was determined using the euglycemic hyperinsulinemic clamp (clamp) technique at t_0 and t_6 in six patients (four women and two men). The other patients did not accept the clamp procedure for different reasons. We also assessed insulin resistance in all patients using HOMA and the insulin resistance index (HOMA-IR) was calculated (fasting plasma glucose [mmol/L] * fasting serum insulin [$\mu\text{U/mL}$]/22.5) [19]. To convert insulin from SI units to conventional unit values were divided by 6.945.

Thirteen patients were treated with BRC (mean dose 5.7 [± 3.9] mg per day [range 1.25–15 mg]) and one patient was treated with CAB (0.5 mg per week) because of side effects of BRC. To normalize PRL the male patients required significantly higher doses of BRC than the females (8.5 [± 4.1] mg vs. 3.2 [± 1.2] mg) ($P = 0.007$).

Anthropometric data

Physical examination included measurements of height, weight, waist and hip. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2). Waist and hip circumference were measured to calculate waist-hip ratio (WHR). Total body fat, fat free mass (FFM) and total body water were determined by bioelectrical impedance [20] using a body composition analyzer (Tanita, TBF-300).

Euglycemic hyperinsulinemic clamp

A clamp was performed according to De Fronzo et al. [21]. In brief, intravenous catheters were inserted into the right arm for substrate (insulin/glucose) infusion. A superficial dorsal hand vein was cannulated in retrograde fashion with a 21-gauge butterfly needle and kept patent by a slow saline infusion. The hand was kept warm by an electric device for intermittent sampling of arterialized venous blood. During the 120 min of the test, insulin (Actrapid [40 mU * $\text{m}^2(-1)$ * min^{-1}], NovoNordisk A/S, Copenhagen, Denmark) was infused together with 20% dextrose (Fresenius Kabi, Stockholm, Sweden). The rate of dextrose infusion was adjusted to achieve a blood glucose level of 5.0 mmol/L based on arterialized samples withdrawn every 5th min from an ipsilateral dorsal hand vein (heated air box set at 55°C, University of Nottingham, U.K.). Whole-body insulin sensitivity (M-value) was calculated from the amount of glucose infused during the last 30 min of the clamp divided by body weight (kg) and period (min) and expressed as mg/kg/min.

Biochemical assays

Serum PRL was measured using commercial chemiluminescence immunoassay (Beckman Coulter Unicel, DXI), normal range: 3–27 $\mu\text{g}/\text{L}$ (women <50 years); 3–20 $\mu\text{g}/\text{L}$ (women ≥ 50 years); 3–13 $\mu\text{g}/\text{L}$ (men). The sera were not screened for macroprolactin due to the specificity of the PRL method. In-house RIAs were used for IGF-I and IGF-BP-1 with individual serum samples from the different investigations in the same assay. IGF-I was measured after ethanol extraction and cryoprecipitation and using des (1–3) IGF-I as ligand [22]. The intra- and inter-assay CV were 4 and 11%, respectively. The standard deviation (SD) scores of IGF-I were calculated from the regression of healthy

adult subjects [23]. The RIA for IGF-BP-1 was performed according to Póvoa et al. [24] with intra- and inter-assays CV 3 and 10%, respectively. The geometrical means and 95% confidence interval (CI) of IGF-BP-1 in 595 non diabetic middle-aged women and men are 41 (95% CI; 39–44) and 19 (95% CI; 18–20) $\mu\text{g}/\text{L}$, respectively [25]. Plasma total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured by automated colorimetric methods (UniCel DXC800, Beckman Coulter, Fullerton, CA, USA). Low-density lipoprotein (LDL) cholesterol was calculated according to the formula suggested by Friedewald et al. [26]. The upper normal limit in reference population for fasting total cholesterol was 6.1 mmol/L (<31 years), 6.9 mmol/L (<51 years) and 7.8 mmol/L (≥ 51 years); the corresponding values for LDL cholesterol were 4.3, 4.7 and 5.3 mmol/L, respectively. The normal range for fasting triglycerides was 0.45–2.6 mmol/L. Commercial kits were used for the following factors: S-insulin and S-C-peptide by electrochemiluminescence immunoassays (Roche Diagnostics GmbH, Mannheim) (reference range for fasting values 18–173 pmol/L and 0.25–1.0 nmol/L, respectively), S-total adiponectin and S-leptin by RIA kit (Millipore Corporation, Linco Research, Inc, USA), S-TNF- α by chemiluminescent immunometric assay (Immulite, Siemens, Gwynedd, Great Britain) and P-hsCRP by an automated immunoturbidimetric assay (Beckman Coulter, Fullerton, CA, USA) with the lower detection limit 0.2 mg/L and reference range <3.0 mg/L. HbA1c was measured by cat-ion exchange chromatography (MonoS column) with HPLC (Bio-Rad) (reference range 3.9–5.3%). S-TSH (reference range 0.4–3.5 mE/L), S-free T₄ (reference range 8–14 pmol/L), S-testosterone (reference range in men, 10–30 nmol/L), P-glucose (reference range for fasting values 4.0–6.0 mmol/L) and S-GH were all measured using routine assays.

Statistical analysis

Normally distributed data are presented as mean (\pm SD), otherwise as median and range (min–max). Differences between women and men were analyzed with unpaired Student's t test when data or log-transformed data were normally distributed. The Mann–Whitney rank sum test was used if the distribution was not normal. For comparison between repeated measurements in the same patients, one way repeated measures analysis of variance (ANOVA) was used and if significance followed by Tukey post-hoc test, in non normally distributed data Friedman ANOVA was used followed by Wilcoxon signed rank test. Correlation analyses were performed using linear regression with log-transformed data when required or Spearman Rank order correlation test. Per cent change in M-value was calculated as M-value ($[\text{t6-t0}]/\text{t0}$) * 100 and per cent change in S-PRL

as S-PRL ($([t6-t0]/t0) * 100$). Statistical analyses were performed using Statistica StatSoft version 9.0 (Tulsa, OK, USA). A two-sided p -value < 0.05 was considered statistically significant.

Results

The main reduction of serum PRL occurred after 2 months of DA agonist treatment in both women and men (Fig. 1). Median PRL level in women decreased from 72 (49–131) to 11 (1.0–17) $\mu\text{g/L}$ at 2 months ($P = 0.012$) and remained within normal range at 6 months, 9.3 (2.9–20) $\mu\text{g/L}$. In the six men, the corresponding values were 1,260 (123–9,600), 51 (3.8–77) and 11 (3.1–13) $\mu\text{g/L}$, respectively.

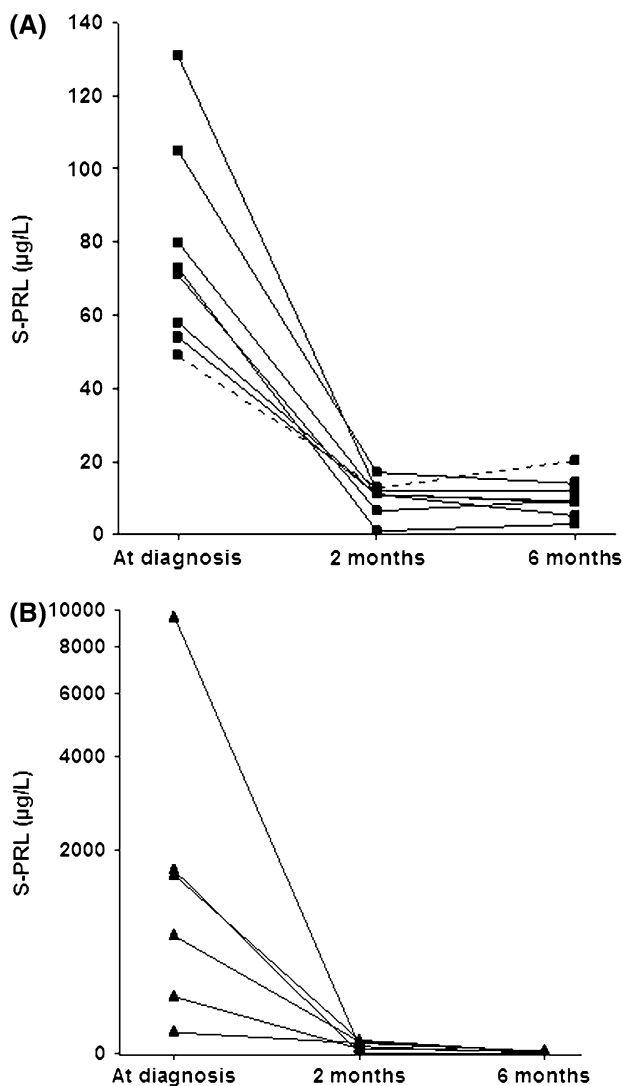


Fig. 1 S-PRL levels at diagnosis and after 2 and 6 months of DA agonist therapy in women (a) and men (b) with prolactinomas. Dotted line indicates Case 4 (Fig. 1a)

Anthropometric variables

Data on body composition before and after DA agonist therapy are presented in Table 2. None of the women had a BMI $\geq 30 \text{ kg/m}^2$ at diagnosis, whereas three out of six men were obese (BMI $\geq 30 \text{ kg/m}^2$). However, no significant difference in BMI was observed between women and men ($P = 0.228$). No significant changes in anthropometric variables were observed in women after DA agonist treatment. In men no changes in body composition were demonstrated after 2 months, but after 6 months there was a significant decrease in body weight, BMI, waist circumference and body fat % ($P < 0.05$) (Table 2).

Hormonal and metabolic variables

The hormonal and metabolic levels are shown in Table 3. Apart from the patient with TSH deficiency, the thyroid hormone levels were within the normal range before and after treatment. Serum testosterone levels increased significantly after 6 months in the four men without testosterone replacement therapy ($P = 0.002$) (Table 3). Total IGF-I levels in relation to age were within normal range and did not change during therapy in the whole group. Leptin values decreased significantly after 6 months of DA agonist therapy only in men, which was probably due to the close positive correlation between percent change in leptin and body fat% ($r = 0.89$, $P < 0.05$).

A positive association between LDL cholesterol and serum PRL levels at diagnosis was demonstrated ($r = 0.62$, $P = 0.025$) (Fig. 2). Total and LDL cholesterol decreased significantly already after 2 months of DA agonist treatment. No correlations between LDL cholesterol and dose of BRC at 2 and 6 months, respectively, were seen ($r = 0.02$, $P = 0.958$ and $r = 0.04$, $P = 0.901$). Further, no detectable changes were observed in HDL cholesterol, triglycerides, hsCRP or TNF- α between the hyperprolactinemic and normalized state (Table 3).

IGFBP-1 and adiponectin levels were not altered during therapy in the whole sample or in men and women analyzed separately. There was no significant correlation between total adiponectin and PRL levels at diagnosis or after 2 and 6 months, respectively ($r = -0.43$, $P = 0.123$; $r = -0.43$, $P = 0.122$; $r = 0.15$, $P = 0.599$). Fasting glucose, HbA_{1c}, insulin, C-peptide levels and HOMA-IR did not change after treatment (Table 3). After inclusion in the study, DM type 2 was diagnosed in one male patient with fP-glucose 12 mmol/L and HbA_{1c} 8.2% which improved after 6 months (6.7 mmol/L and 5.6%, respectively), without glucose lowering treatment. This patient did not participate in the clamp.

Table 2 Anthropometric data in eight women and six men with hyperprolactinemia at diagnosis and after 2 and 6 months on DA agonist treatment

| | Baseline | DA agonist treatment | | <i>P</i> value |
|--------------------------|-------------------|----------------------|------------------|--------------------|
| | | 2 months | 6 months | |
| Body weight (kg) | | | | |
| Women | 67.6 (45.5–82.1) | 67.5 (45.6–81.2) | 67.9 (47.6–81.6) | NS |
| Men | 95.6 (80.7–110.1) | 93.7 (82.2–103.4) | 83.4 (77.8–99.1) | 0.046 ^a |
| BMI (kg/m ²) | | | | |
| Women | 25.1 (17.8–29.2) | 25.0 (17.8–29.1) | 25.3 (18.6–30.4) | NS |
| Men | 27.6 (23.4–32.9) | 26.7 (23.4–30.9) | 25.4 (22.8–29.6) | 0.046 ^a |
| Waist (cm) | | | | |
| Women | 83 (63–98) | 78 (64–94) | 84 (66–94) | NS |
| Men | 101 (91–113) | 99 (92–107) | 95 (89–102) | 0.028 ^a |
| Waist Hip-ratio | | | | |
| Women | 0.82 (0.69–0.91) | 0.78 (0.71–0.93) | 0.81 (0.73–0.93) | NS |
| Men | 0.95 (0.86–1.0) | 0.96 (0.87–0.98) | 0.94 (0.87–0.96) | NS |
| Body fat (%) | | | | |
| Women | 33.4 (13.3–39.8) | 34.0 (12.8–41.3) | 33.6 (20.4–41.6) | NS |
| Men | 21.9 (17.6–31.9) | 20.3 (16.4–28.5) | 18.3 (15.6–28.0) | 0.028 ^a |
| Fat free mass(kg) | | | | |
| Women | 44.3 (39.0–48.8) | 44.8 (39.3–47.7) | 44.3 (37.5–47.9) | NS |
| Men | 73.4 (65.0–74.6) | 71.5 (66.4–75.6) | 68.4 (65.1–76.1) | NS |

Data are shown as median and range

^a At diagnosis vs. 6 months. NS non-significant (using non parametric ANOVA)

Insulin sensitivity determined by clamp

No obvious differences were observed between the six patients who accepted to perform the clamp and the whole patient group (Table 4). A tendency of improvement in insulin sensitivity after normalization of PRL by DA agonist therapy was demonstrated: the M-value at baseline was 5.7 (± 1.8) and at 6 months 7.8 (± 2.6) mg/kg/min, $P = 0.083$ (Fig. 3). All patients, except one female (case 4), improved their insulin sensitivity as assessed by the clamp. Per cent change in insulin sensitivity was correlated to per cent reduction in PRL levels at 6 months ($r = -0.85$, $P = 0.034$) (Fig 4). In the five patients treated with BRC who performed the clamp; percent change in insulin sensitivity was correlated to per cent reduction in PRL levels ($r = -0.89$, $P = 0.042$) but also to BRC dose ($r = 0.92$, $P = 0.029$), which, in addition, was associated with the reduction in PRL levels ($r = -0.90$, $P = 0.035$). No correlation was found between per cent change in M-value and adiponectin levels ($r = 0.37$, $P = ns$) or change in body fat% ($r = -0.49$, $P = ns$).

Discussion

In the present study of women and men with prolactinomas total and LDL cholesterol decreased significantly after

reduction of PRL by DA agonist treatment. Furthermore, insulin sensitivity tended to improve and there was a correlation between improvement in insulin sensitivity and reduction in PRL levels.

Hypercholesterolemia has been linked to patients with hyperprolactinemia [13]. In a recent study total and LDL cholesterol were higher in patients with prolactinomas than controls [27], while in other studies no differences in lipoprotein profile have been reported [7, 9]. Treatment with BRC in obese non-diabetic women [11] and in patients with DM type 2 [12] has been shown to reduce both PRL and total cholesterol, while another study showed no changes in total cholesterol in patients with DM type 2 after BRC therapy [28]. In our cohort, LDL cholesterol correlated positively to PRL levels at diagnosis and total and LDL cholesterol decreased significantly already after 2 months on DA agonists. The reduction in LDL cholesterol was seen in women despite no change in weight and was evident in men before their weight loss. Furthermore, we found no correlation between reduction in LDL cholesterol and BRC dosage. Hypogonadism could be a confounding factor considering the levels of LDL cholesterol, but the majority of our female patients were on hormonal contraceptives from study start without any change in this medication during the study. In the four men without testosterone replacement the increase in testosterone levels

Table 3 Hormonal and metabolic values in 14 patients with hyperprolactinemia at diagnosis and after 2 and 6 months on DA agonist treatment

| | Baseline | DA agonist treatment | | P value |
|---|-------------------|----------------------|-------------------|---------------------------------------|
| | | 2 months | 6 months | |
| S-PRL ($\mu\text{g/L}$) | 114 (49–9600) | 12.5 (1.0–77) | 9.3 (2.9–20) | <0.001 ^{c,d} |
| S-TSH (mE/L) ^a | 2.1 (\pm 1.1) | 2.2 (\pm 1.1) | 2.2 (\pm 0.9) | NS |
| S-fT4 (pmol/L) ^a | 9.4 (\pm 1.9) | 9.7 (\pm 1.4) | 10.0 (\pm 0.9) | NS |
| S-Testosterone (nmol/L) ^b | 4.6 (\pm 2.3) | 6.2 (\pm 1.7) | 8.8 (\pm 1.7) | 0.002 ^d |
| S-GH ($\mu\text{g/L}$) | 0.71 (0.02–13.0) | 2.45 (0.06–8.9) | 1.16 (0.04–14.6) | NS |
| S-IGF-I (SD-score) | 0.04 (\pm 1.3) | 0.3 (\pm 1.2) | 0.4 (\pm 1.2) | NS |
| S-IGFBP-1 ($\mu\text{g/L}$) | 32 (8–97) | 35 (12–84) | 36 (7–95) | NS |
| S-Leptin ($\mu\text{g/L}$) | 8.8 (2.1–33.3) | 6.9 (2.0–37.5) | 10.6 (1.4–39.4) | NS |
| S-Adiponectin (mg/L) | 6.3 (3.8–14.0) | 6.7 (3.2–11.0) | 6.2 (3.4–12.0) | NS |
| P-hsCRP (mg/L) | 1.4 (0.2–11.5) | 1.2 (0.2–13.8) | 0.7 (0.2–13.0) | NS |
| S-TNF- α (pg/mL) | 8.1 (3.3–17.0) | 8.8 (2.9–22.3) | 7.6 (4.8–16.9) | NS |
| P-Glucose (mmol/L) | 4.7 (4.5–12.0) | 5.0 (4.6–6.9) | 4.8 (4.5–6.7) | NS |
| B-HbA _{1c} (%) | 4.5 (3.9–8.2) | 4.4 (3.7–6.2) | 4.5 (3.7–5.6) | NS |
| S-Insulin (pmol/L) | 47 (19–127) | 50 (21–136) | 57 (21–114) | NS |
| S-C-peptide (nmol/L) | 0.59 (0.41–1.30) | 0.64 (0.45–1.00) | 0.60 (0.42–0.94) | NS |
| HOMA-IR | 1.4 (0.6–9.8) | 1.6 (0.7–4.2) | 2.1 (0.8–3.5) | NS |
| P-Total cholesterol (mmol/L) ^a | 5.4 (\pm 1.0) | 4.8 (\pm 0.7) | 4.8 (\pm 0.8) | 0.002 ^{c,d} |
| P-LDL cholesterol (mmol/L) ^a | 3.4 (\pm 0.9) | 2.9 (\pm 0.6) | 2.9 (\pm 0.6) | 0.003 ^c 0.002 ^d |
| P-HDL cholesterol (mmol/L) ^a | 1.3 (\pm 0.3) | 1.3 (\pm 0.4) | 1.4 (\pm 0.4) | NS |
| P-Triglycerides (mmol/L) ^a | 1.7 (\pm 1.9) | 1.2 (\pm 0.8) | 1.2 (\pm 0.8) | NS |

Data are shown as mean \pm SD if normally distributed or as median and range if not normally distributed

NS non-significant (using parametric or non-parametric ANOVA)

^a Exclusion of a male with TSH deficiency at diagnosis

^b In men without testosterone replacement, $n = 4$

^c At diagnosis vs. 2 months

^d At diagnosis vs. 6 months

were not clinically significant until after 6 months of treatment. Our results, may suggest a direct relation between LDL cholesterol and PRL levels. Its homologue GH induces the expression of hepatic LDL receptors, which is accompanied by a decrease in serum cholesterol [29] and it can be speculated that PRL may act in a similar way as GH in the liver.

In the present study, only six of the 14 patients participated in the clamp, reducing the power in this part of the study. However, five of these six patients showed a considerable improvement of peripheral insulin sensitivity. The woman in whom the M-value did not increase (case 4), had only slightly elevated PRL levels at diagnosis (49 $\mu\text{g/L}$) and also the highest PRL level within normal range at 6 months (20 $\mu\text{g/L}$). A significant correlation was found between per cent increase in M-value and reduction in PRL levels as well as to BRC dosage, which in turn correlated to decrease in PRL levels. Thus, the improvement in insulin sensitivity could be attributed to the decrease in PRL levels, BRC treatment, or a combination of these factors. In a

previous study, BRC treatment of non-diabetic females did not change plasma insulin levels or the ability of insulin to mediate glucose disposal [11]. In contrast, in a clamp study of obese type 2 diabetics, BRC therapy improved insulin sensitivity [28]. Recently, insulin sensitivity, evaluated by clamp, was shown to be significantly lower in 16 hyperprolactinemia patients than controls [10] and in another study that HOMA-IR improved after DA agonist treatment [30]. Results from clamp studies evaluating insulin sensitivity in prolactinoma patients after DA agonist therapy has not been published before.

PRL has been shown to inhibit secretion of adiponectin from human adipose tissue in vitro [31] and suppression of adiponectin levels may be one factor that increases insulin resistance in hyperprolactinemic patients [32]. However, neither PRL levels nor the improvement in insulin sensitivity was correlated to total adiponectin levels in our study. Similar to adiponectin, IGFBP-1 levels did not change during DA agonist therapy, indicating no alterations in hepatic insulin sensitivity [33]. We did not find any

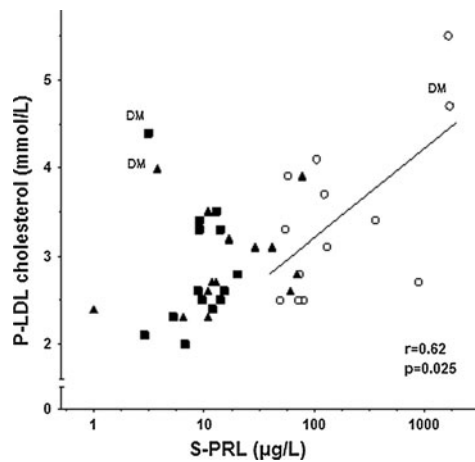


Fig. 2 The relation between P-LDL cholesterol and S-PRL in hyperprolactinemia patients at diagnosis (*circle*) and after 2 (*filled triangle*) and 6 (*filled square*) months of DA agonist therapy. The regression line for the correlation between P-LDL cholesterol and S-PRL at diagnosis (*circle*) is presented. The patient with diabetes mellitus at diagnosis is marked (DM)

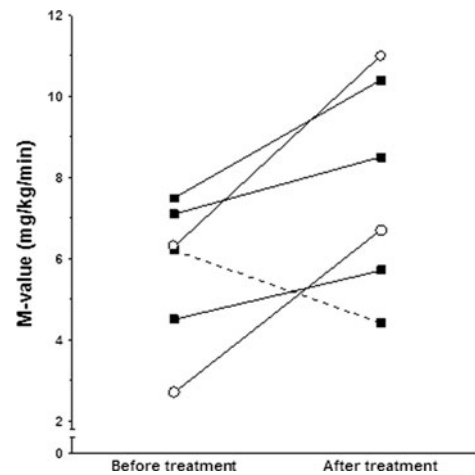


Fig. 3 M-value in four women (*filled square*) and two men (*circle*) with hyperprolactinemia at diagnosis and at normalized PRL levels after 6 months of DA agonist treatment ($P = 0.083$). *Dotted line* indicates Case 4

Table 4 Anthropometric data and hormonal and metabolic values in six hyperprolactinemic patients who performed the clamp at diagnosis and after 6 months of DA agonist treatment

| | Baseline | 6 months | <i>P</i> value |
|--------------------------|------------------|------------------|----------------|
| Body weight (kg) | 72.3 (45.5–96.3) | 73.9 (47.6–83.3) | NS |
| BMI (kg/m ²) | 25.0 (17.8–29.7) | 24.8 (18.6–30.4) | NS |
| Waist (cm) | 91 (63–104) | 89 (66–95) | NS |
| Waist Hip-ratio | 0.84 (0.69–0.98) | 0.85 (0.73–0.94) | NS |
| Body fat (%) | 26.1 (13.3–35.4) | 26.3 (15.8–38.4) | NS |
| Fat free mass (kg) | 46.4 (39.0–73.2) | 46.4 (37.5–67.3) | NS |
| S-PRL (µg/L) | 69 (49–1630) | 9.1 (5.2–20) | 0.028 |
| S-TSH (mE/L) | 1.6 (0.8–3.0) | 2.5 (0.7–3.5) | NS |
| S-IGF-I (SD-score) | −0.3 (−1.7–2.0) | 0.3 (−1.4–1.1) | NS |
| S-IGFBP-1 (µg/L) | 37 (8–77) | 42 (7–95) | NS |
| P-Glucose (mmol/L) | 4.7 (4.5–5.0) | 4.8 (4.5–5.5) | NS |
| B-HbA1c (%) | 4.2 (3.9–5.3) | 4.5 (3.7–4.6) | NS |
| S-Insulin (pmol/L) | 50 (19–104) | 75 (26–114) | NS |
| S-C-peptide (nmol/L) | 0.56 (0.44–0.88) | 0.79 (0.54–0.94) | NS |
| HOMA-IR | 1.6 (0.6–3.3) | 2.5 (0.8–3.5) | NS |

Data are shown as median and range
 NS non-significant (at diagnosis vs. 6 months)

changes in glucose, HbA1c, insulin or C-peptide levels after DA agonist treatment in the whole patient group. However, the patient with DM type 2 displayed a dramatic improvement with a decrease in HbA1c from 8.2 to 5.6% during BRC treatment and diet information.

Hyperprolactinemia has also been associated with elevated hsCRP, with reduction after treatment with DA agonists [7, 9]. In contrast, we found no change in hsCRP

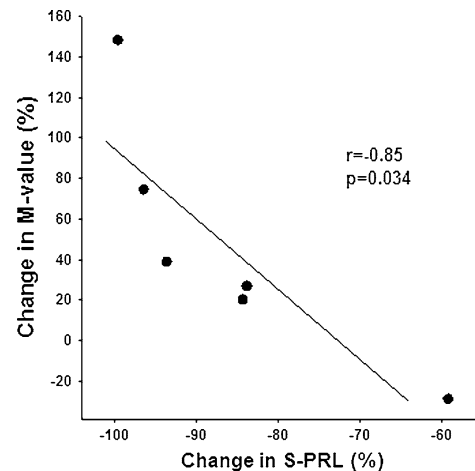


Fig. 4 The correlation between per cent change in M-value and in S-PRL after 6 months of DA agonist treatment when compared with diagnosis in the six prolactinoma patients who performed the clamp

levels between the hyperprolactinemic and normalized state. Furthermore, there was no change in the pro-inflammatory cytokine TNF- α levels after DA agonist treatment, supporting the view that hyperprolactinemia, at least in this study, does not induce low-grade inflammation.

In agreement with others, we found that weight gain and obesity in our hyperprolactinemic patients were predominantly seen in men [16, 17]; after treatment, only the men demonstrated a reduction of weight, waist circumference and body fat%. In the current study, a control group was not established since our aim was to evaluate metabolic variables in patients before and after treatment, and thus we used the patients as their own controls. To compare with a

healthy control group would probably not have helped us in defining the effects of PRL vs. other factors on metabolism.

In conclusion, total and LDL cholesterol decreased significantly after treatment with DA agonists in patients with hyperprolactinemia and improvement in insulin sensitivity correlated to the decrease in PRL levels. Our results may indicate a direct relation between LDL cholesterol and PRL, however the reasons for the metabolic changes seen in prolactinoma patients after treatment are complex and probably due to several factors. Our findings in a limited group of patients have to be confirmed in larger prospective studies, but underscore the importance of normalizing PRL levels in hyperprolactinemia patients as well as to evaluate and follow-up the metabolic status. Furthermore, it might be important to consider the metabolic profile, when not treating patients with asymptomatic hyperprolactinemia or in connection with discontinuation of DA agonist treatment, for example in postmenopausal women.

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Conflict of interest The authors have nothing to declare.

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