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ORIGINAL ARTICLE

Higher doses of cabergoline further improve metabolic parameters in patients with prolactinoma regardless of the degree of reduction in prolactin levels

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Summary

Objective Currently available studies that fully analyse the metabolic parameters in patients with prolactinoma are scarce and discordant. The aim of this study was to evaluate the metabolic effects of cabergoline (CAB) treatment in patients with newly diagnosed prolactinoma in relation to disease control and CAB dosage.

Design This is a retrospective clinical-based therapy analysis.

Patients Forty-three patients with prolactinoma (eight men, 35 women), aged 33.65 ± 11.23 years, were evaluated metabolically at baseline and after 12 months of CAB treatment.

Measurements Body mass index (BMI), systolic and diastolic blood pressure, waist circumference (WC), lipid profile, haemoglobinA1c (HbA1c), glucose and insulin levels (and their areas under the curve, AUC) after an oral glucose tolerance test, homoeostasis model assessment of insulin resistance (Homa-IR) index, insulin sensitivity index (ISI) Matsuda, oral disposition index (DIo) and visceral adiposity index (VAI) were measured at baseline and after 12 months of treatment.

Results Twelve months of CAB reduced WC ($P < 0.001$), total ($P = 0.001$) and low-density lipoprotein \terol ($P < 0.001$), triglycerides ($P = 0.024$), fasting insulin ($P < 0.001$), $AUC_{INSULIN}$ ($P < 0.001$), HbA1c ($P = 0.022$), Homa-IR ($P < 0.001$) and VAI ($P < 0.001$), with a concomitant increase in high-density lipoprotein cholesterol ($P < 0.001$) and in ISI Matsuda ($P < 0.001$), regardless of the degree of reduction in prolactin levels. The patients receiving higher doses (>0.50 mg/week) of CAB showed lower BMI ($P = 0.009$), fasting insulin ($P = 0.001$), Homa-IR ($P < 0.001$) and VAI ($P = 0.018$) and higher ISI Matsuda ($P = 0.002$) and DIo ($P = 0.011$), compared with those on lower doses.

Conclusions A significant metabolic improvement was observed in patients with prolactinoma after 12 months of CAB treatment, especially when higher doses were used, highlighting the importance of considering the metabolic profile in these patients and the role of active treatment with high CAB doses.

Introduction

Prolactinoma is the most frequent secreting pituitary tumour and mainly affects the female gender.[1] Besides the well-known consequences on the reproductive axis both in men and women, hyperprolactinaemia can be associated with alterations in body composition and obesity,[2] although the evidence is discordant. Reduced bone density [3,4] and total body fat [5,6] have been positively associated with high prolactin (PRL) levels in patients with prolactinoma. Schmid *et al.*[7] demonstrated significantly higher body mass index (BMI) in patients with macroprolactinoma than both patients with inactive adenomas and the general population. Conversely, Naliato *et al.* showed similar body fat in women with prolactinoma and controls.[5]

Dopamine agonists (DA) are recognized as the recommended therapy to lower PRL levels and decrease tumour size for patients with prolactinoma, and the use of cabergoline (CAB) is suggested in preference to other DA because of its higher efficacy.[8] Several studies have analysed the effects of DA treatment on body fat and metabolism, but most of them used mainly bromocriptine.[9] In this setting, reduced body fat content and a lower risk of metabolic syndrome have been associated with the normalization of PRL during DA treatment.[5] Decreased BMI and waist circumference (WC) have been reported during DA therapy in some studies,[10] but not in others.[11] However, currently available studies that fully analyse the metabolic parameters in patients with prolactinoma at diagnosis and during treatment with CAB are scarce, and discordant data have been reported. Based on the data that link the body composition parameters with PRL levels and DA administration, the aim of the current study was to fully evaluate the effects of 12 months of CAB treatment on the metabolic syndrome (MS), insulin

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sensitivity and visceral adiposity index (VAI),[12] a surrogate parameter indicating adipose tissue dysfunction associated with cardiometabolic risk, in a group of patients with newly diagnosed prolactinoma in relation to disease control and CAB dosage.

Patients and methods

We conducted a retrospective chart review of patients affected by hyperprolactinaemia seen at the Unit of Endocrinology of the University of Palermo from 1 January 2011 to 30 October 2012. We analysed data from a total of 89 patients. The flow chart of patient distribution and inclusion in the study according to the criteria adopted is shown in Fig. 1.

Patients with hyperprolactinaemia secondary to drugs (including neuroleptics, antidepressants, opiates and gastrointestinal prokinetics) or mixed-secreting tumours, those already receiving dopamine agonists at the baseline visit and those with a follow-up of less than 12 months were excluded from this analysis. In addition, we excluded patients with multiple pituitary hormone deficiencies and/or the presence of other concomitant causes of overt hypogonadism to avoid the potential impact of hormonal deficit or gonadal replacement therapy on metabolic parameters. No women receiving oestrogens and/or progesterone as contraceptives or postmenopausal hormone replacement therapy were included. All patients with already known glucose abnormalities were treated with diet alone. Patients already receiving hypoglycaemic agents were excluded from this study. For the purpose of this study, we enrolled 43 consecutive patients (8 men, 19%; 35 women, 81%) aged 33.65 ± 11.23 years (range: 16–63), with newly diagnosed prolactinoma. The diagnosis was based on signs and symptoms of hyperprolactinaemia, high-serum PRL levels and magnetic resonance imaging (MRI) demonstrating a pituitary tumour.[8] This study was conducted in compliance with the 'Ethical principles for medical research involving human subjects' of the Helsinki Declaration. At the time of hospitalization, all patients signed a consent form for the scientific use of their data and the identity of the participants remained anonymous during the analysis.

Study design

All patients, at baseline and after 12 months of CAB treatment, underwent a complete clinical and metabolic evaluation. Prolactin levels were considered as the mean value of measurements in at least three blood samples collected at 20-min intervals for 1 h, obtained through venous cannulation, without repeated venepuncture stress. Women who presented with menstrual cycles, even if irregular, were studied in the early follicular phase (1–7 days from bleeding). In all patients, MRI revealed the presence of a pituitary tumour. Tumour volume was calculated in line with the Di Chiro and Nelson formula (volume = height × length × width × π/6) and was expressed as mm^3. BMI and systolic (SBP) and diastolic (DBP) blood pressure were measured in all patients. WC was measured at the midpoint between the lower rib and the iliac crest. After an overnight fast, total, high-density lipoprotein (HDL) and
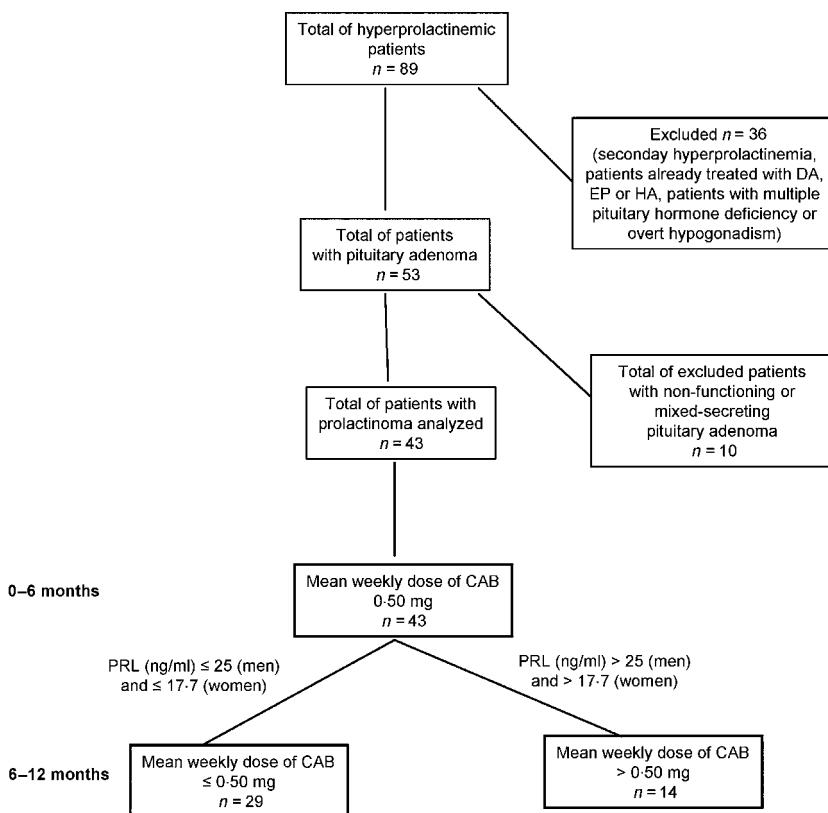

Fig. 1 Flow chart of patient distribution and inclusion in the study according to criteria adopted and dosage of cabergoline used. Dopamine agonists: dopamine agonists; EP: oestro/progesterone; HA: hypoglycaemic agents; CAB: cabergoline; PRL: prolactin.

low-density lipoprotein (LDL) cholesterol, triglycerides and haemoglobinA1c (HbA1c) were measured. In addition, an oral glucose tolerance test (OGTT) was performed by measuring plasma blood glucose and insulin levels every 30 min for 2 h after a 75-g oral glucose load. The areas under the curve of glucose (AUC_{GLU}) and insulin (AUC_{INS}) during the 2-h OGTT were also calculated. The diagnosis of diabetes or glucose tolerance abnormalities was made according to the American Association of Clinical Endocrinologists medical guidelines.[13] Basal insulin resistance (IR) was assessed using homoeostasis model assessment of the insulin resistance (Homa-IR) index.[14] Stimulated insulin sensitivity was measured using the insulin sensitivity index (ISI), a composite index derived from the OGTT and validated by Matsuda *et al.*[15] Total insulin secretion was assessed by AUC_{INS}, while *β*-cell function relative to insulin sensitivity was assessed by oral disposition index (DIo).[16]

VAI was calculated as described,[12] using the following formula differentiated according to sex, when TG is triglyceride level expressed in mM and HDL is HDL cholesterol level expressed in mM:

$$Men: VAI = [WC/39\cdot68 + (1\cdot88 \times BMI)] \times (TG/1\cdot03) \times (1\cdot31/HDL)$$

$$Women: VAI = [WC/36\cdot58 + (1\cdot89 \times BMI)] \times (TG/0\cdot81) \times (1\cdot52/HDL)$$

After the diagnosis was made, all patients received CAB at the initial weekly dose of 0·50 mg for the first 6 months. After this period, the CAB dose was adjusted to maintain serum PRL levels within the normal range for sex or was increased to the maximal tolerable dose for patients who did not achieve normal PRL levels or did not show significant tumour shrinkage. We considered disease control to be attained when PRL levels decreased to normal values for healthy subjects, according to gender (Fig. 1). The mean weekly dose used during the study period was 0·58 ± 0·30 mg (range: 0·25–1·80).

Hormone and biochemical assays

Glucose and lipid (HDL, LDL and total cholesterol, triglycerides) levels were measured in our centralized laboratory by standard methods. Serum insulin was measured by ELISA (DRG Instruments GmbH, Germany). The sensitivity of the methods was 1 mIU/l. The normal insulin range (mIU/l) was 5–19. The conversion factor from conventional to SI units was 6·945. During the entire study period, serum PRL was measured by chemiluminescent assay (Immulite 2000; Diagnostic Products, Los Angeles, CA) with a sensitivity of 3·2 mU/l. The intra- and interassay coefficients of variation were 2·3 and 5·9%, respectively. Normal ranges were 38–500 and 40–354 mU/l for women and men, respectively.

Statistical analysis

The Statistical Packages for Social Sciences SPSS version 17 were used for data analysis. All quantitative variables showed normal distribution (normality of distribution was assessed by the Kolmogorov–Smirnov test). Baseline and after-treatment variables were presented as mean ± Standard Deviation (SD) for continuous variables; rates and proportions were calculated for categorical data. Differences between groups in univariate analysis were detected by the unpaired Student's *t*-test for continuous variables and by the chi-square test and Fisher's exact test (when appropriate) for categorical variables. The differences between paired continuous variables (before and after 12 months of therapy) were analysed by the paired Student's *t*-test for continuous variables and by the McNemar test for categorical variables. A *P* value of <0·05 was considered statistically significant.

Results

Baseline

The hormonal and metabolic parameters of patients at diagnosis are shown in Table 1. The mean PRL levels at diagnosis were 3715 ± 5718 mU/l with a mean tumour volume of

Table 1. Hormonal and metabolic parameters before and after 12 months of treatment with cabergoline

	Patients with prolactinoma (No. 43)		
	Basal Mean ± SD	12 months Mean ± SD	*P*
Tumour volume (mm³)	10·56 ± 5·19	8·16 ± 3·58	<0·001
Prolactin (mU/l)	3715 ± 5718	529 ± 712	0·001
	No. (%)	*No. (%)*	
Normal glucose tolerance (NGT)	27 (62·8)	39 (90·7)	0·004
Impaired fasting glucose (IFG)	5 (11·6)	1 (2·3)	0·218
Impaired glucose tolerance (IGT)	10 (23·3)	3 (7)	0·039
Diabetes mellitus (DM)	1 (2·3)	–	1
Metabolic syndrome	13 (30·2)	6 (14)	0·016
	Mean ± SD	Mean ± SD	
BMI (kg/m²)	25·57 ± 5·18	25·41 ± 4·97	0·177
WC (cm)	88·81 ± 10·48	87·13 ± 10·15	<0·001
Total cholesterol (mM)	4·70 ± 0·98	4·30 ± 0·73	0·001
HDL cholesterol (mM)	1·19 ± 0·21	1·28 ± 0·21	<0·001
LDL cholesterol (mM)	2·85 ± 0·93	2·42 ± 0·68	<0·001
Triglycerides (mM)	1·43 ± 0·65	1·30 ± 0·50	0·024
Fasting glucose (mM)	5·18 ± 0·81	5·33 ± 0·99	0·337
Fasting Insulin (pM)	117·98 ± 46·89	86·42 ± 25·90	<0·001
HbA1c (%)	5·36 ± 0·62	5·18 ± 0·43	0·022
Homa-IR	3·87 ± 1·53	2·93 ± 0·96	<0·001
Matsuda Index	3·20 ± 1·28	4·75 ± 1·44	<0·001
$AUC_{2hGlucose}$ (mM;120 min)	860 ± 167	840 ± 161	0·357
$AUC_{2hInsulin}$ (pM;120 min)	58963 ± 21286	37739 ± 11249	<0·001
DIo	1·72 ± 1·53	2 ± 2·21	0·404
Visceral adiposity index (VAI)	2·36 ± 1·32	1·94 ± 1·01	<0·001

$10.56 \pm 5.19 \text{ mm}^3$. The mean BMI and WC values were 25.57 ± 5.18 and 88.81 ± 10.48, respectively. Using the National Cholesterol Education Program (NCEP-Adult Treatment Panel III, ATP III) criteria,[17] MS was found in 13 patients (30.2%). Twenty-seven of 43 patients (62.8%) were classified as having normal glucose tolerance (NGT), 5 (11.6%) impaired fasting glucose (IFG), 10 (23.3%) impaired glucose tolerance (IGT) and only 1 patient had newly diagnosed overt diabetes mellitus (DM), according to the American Association of Clinical Endocrinologists medical guidelines.[13] No correlation between PRL levels and BMI, CV, VAI and other metabolic parameters at diagnosis was found (data not shown).

At 12 months of treatment

The hormonal and metabolic parameters of patients after CAB treatment are shown in Table 1. As expected, at 12 months of treatment, a significant decrease in PRL levels (529.2 ± 712 *vs* $3715 \pm 5718 \text{ mU/l}$; $P = 0.001$) and tumour volume (8.16 ± 3.58 *vs* $10.56 \pm 5.19 \text{ mm3}$; $P < 0.001$) was found. As a whole, 24 of 43 patients (55.8%) were classified as controlled and 19 of 43 (44.2%) as uncontrolled.

We found a significant increase in the prevalence of NGT (90.7 *vs* 62.8%; $P = 0.004$) with a concomitant decrease in cases of IGT (7 *vs* 23.3%; $P = 0.039$) and a trend to reduction in the cases of IFG, although not statistically significant (2.3 *vs* 11.6%; $P = 0.218$). The single case of DM diagnosed at baseline was not confirmed after 12 months of treatment. MS was detected in 6 (14%) patients *versus* 13 patients (30.2%) before treatment ($P = 0.016$). A significant decrease in WC (87.13 ± 10.15 *vs* $88.81 \pm 10.48 \text{ cm}$; $P < 0.001$), without a significant decrease in BMI (25.41 ± 4.97 *vs* $25.57 \pm 5.18 \text{ kg/m}^2$; $P = 0.177$), was also found.

As regards the lipid profile, we found a significant decrease in total cholesterol (4.30 ± 0.73 *vs* $4.70 \pm 0.98 \text{ mM}$; $P = 0.001$), LDL cholesterol (2.42 ± 0.68 *vs* $2.85 \pm 0.93 \text{ mM}$; $P < 0.001$) and triglycerides (1.30 ± 0.50 *vs* $1.43 \pm 0.65 \text{ mM}$; $P = 0.024$), with a concomitant significant increase in HDL cholesterol (1.28 ± 0.21 *vs* $1.19 \pm 0.21 \text{ mM}$; $P < 0.001$).

As regards glucose metabolism, a significant reduction in fasting insulin (86.42 ± 25.90 *vs* $117.98 \pm 46.89 \text{ pM}$; $P < 0.001$), AUC_{INS} (37739 ± 11249 *vs* 58963 ± 21286; $P < 0.001$), HbA1c (5.18 ± 0.43 *vs* $5.36 \pm 0.62\%$; $P = 0.022$) and Homa-IR (2.93 ± 0.96 *vs* 3.87 ± 1.53; $P < 0.001$) with a significant increase in ISI Matsuda (4.75 ± 1.44 *vs* 3.20 ± 1.28; $P < 0.001$) was detected (Fig. 2a). VAI was significantly decreased (1.94 ± 1.01 *vs* 2.36 ± 1.32, $P < 0.001$) after 12 months of treatment (Fig. 2d). No significant difference was found in fasting glucose ($P = 0.337$), AUC_{GLU} ($P = 0.357$) and DIo ($P = 0.404$) (Fig. 2g). No correlation between PRL and BMI, CV, VAI and other metabolic parameters was found at 12 months of treatment (data not shown).

When we analysed the hormonal and metabolic parameters in patients grouped according to achievement of disease control, the two groups only differed in PRL levels ($P < 0.001$) and tumour volume ($P = 0.016$) (Table 2, Fig. 2b,e,h).

Grouping the patients according to median weekly dose of CAB used during the 12-month-follow-up [0.50 (0.37–0.75) mg], those treated with a low dose (LD: $\leq$ 50th centile; i.e. $\leq$ 0.50 mg) were 29 (67.4%) and those with a high dose (HD: >50th centile; i.e. >0.50 mg) were 14 (32.6%). No difference was found in tumour volume ($P = 0.625$) or PRL levels ($P = 0.430$) between the two groups. MS was found in 1 patient (7.2%) receiving HD of CAB and in 5 patients (17.2%) on LD ($P = 0.645$). NGT, IFG and IGT were found in 26 (89.6%) and 13 (92.8%), 0 and 1 (7.2%), 3 (10.4%) and 0 patients receiving HD and LD, respectively, without significant differences between the two patient groups. The data of patients grouped according to CAB dose are shown in Table 3. The patients receiving HD showed lower BMI (23.12 ± 2.71 *vs* $26.51 \pm 5.45 \text{ Kg/m}^2$; $P = 0.009$), fasting insulin (69.20 ± 17.67 *vs* 94.73 ± 25.33; $P = 0.001$), Homa-IR (2.21 ± 0.64 *vs* 3.28 ± 0.90; $P < 0.001$) and VAI (1.31 ± 0.44 *vs* 2.07 ± 1.11; $P = 0.018$) (Fig. 2f) compared with those receiving LD, with concomitant higher ISI Matsuda (5.70 ± 1.28 *vs* 4.29 ± 1.29; $P = 0.002$) (Fig. 2c) and DIo (3.20 ± 3.52 *vs*. 1.41 ± 0.74; $P = 0.011$).(Fig. 2i). No difference in the other metabolic parameters was found between the two groups of patients.

Discussion

The role of PRL as a metabolic hormone and the metabolic effect of DA treatment in patients with prolactinoma are not fully understood. Our data demonstrate that 12 months of CAB treatment improves most of the metabolic parameters and the degree of glucose tolerance, mainly when higher doses of CAB are used.

In this study, a control group was not recruited as our aim was to evaluate the metabolic parameters during DA treatment, and for this purpose, we used patients as their own controls.

Weight gain and impaired lipid profile have frequently been associated with hyperprolactinaemia, and a link between elevated PRL levels and glucose abnormalities or hyperinsulinaemia has been well documented.[18–21] The mechanisms of these associations are still poorly understood. The involvement of PRL in pancreatic β-cell and insulin production and secretion has been proposed,[22,23] and a role of PRL in reducing lipoprotein lipase activity in adipose tissue with consequent increase in triglycerides has been demonstrated.[24] An involvement of adipokines in prolactinoma has also been suggested. It is well known that leptin plays a major role in food intake and body energy balance,[25] and Balci *et al.* recently demonstrated strong immunoreactivity for leptin protein in prolactinomas, assuming a cosecretion of PRL and leptin.[26] These observations could partially explain some metabolic features observed in patients with prolactinoma, such as the presence of insulin resistance, although to date discordant data are available. Indeed, no correlation between PRL and leptin levels nor a decrease in leptin during DA treatment has been observed.[11] Hypogonadism, which is frequently associated with hyperprolactinaemia, has been considered an additional possible mechanism involved in weight gain in these patients.[27] For this reason, to avoid any
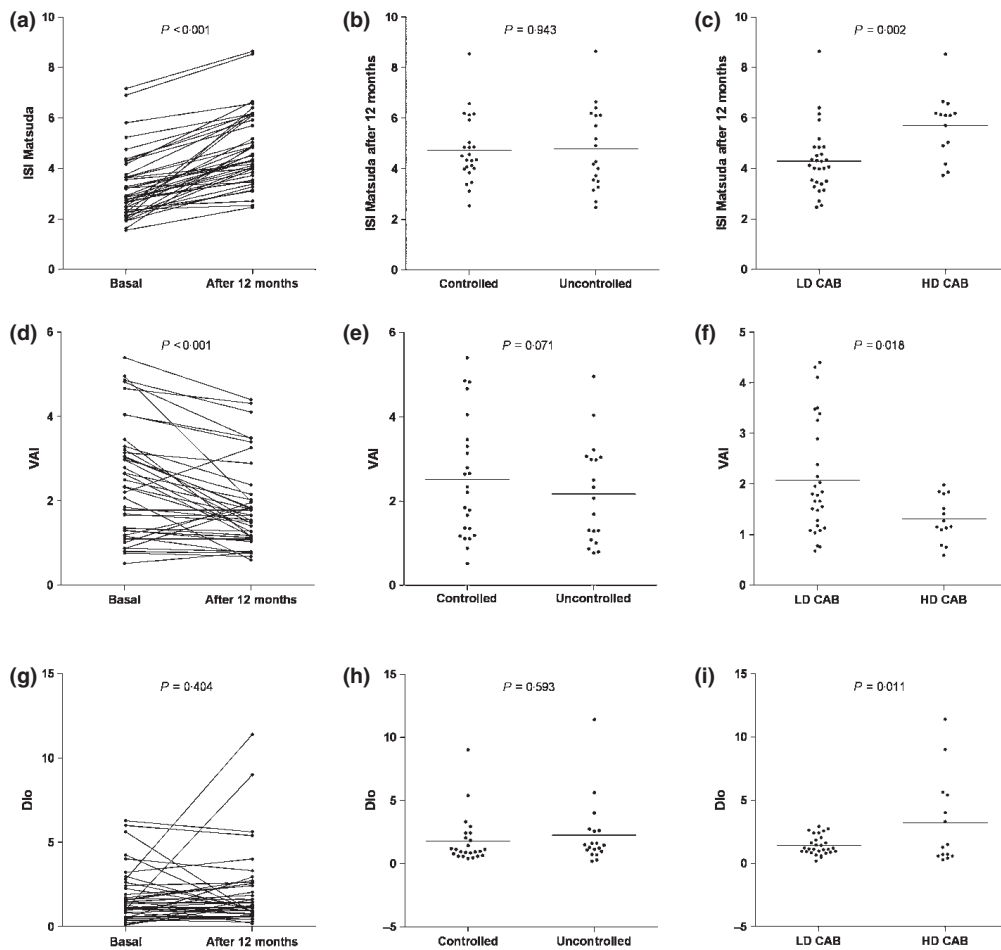
Fig. 2 Representation of insulin sensitivity index Matsuda, visceral adiposity index and oral disposition index (DIo) in patients with prolactinoma before and after cabergoline treatment (left), grouped according to control of the disease (in the middle) and according to cabergoline dosage used (right). CAB: cabergoline; LD: low dose; HD: high dose.

interference, we decided to exclude from this analysis patients with overt hypogonadism associated with prolactinoma. Recently, waist/hip ratio, lipid profile, Homa-IR and adiponectin levels were found significantly altered in 20 patients with prolactinoma with uncontrolled PRL levels compared with healthy subjects,[28] and Tuzcu *et al.*[29] demonstrated a state of insulin resistance in 16 patients with hyperprolactinaemia using a euglycaemic hyperinsulinaemic clamp. However, the reduced degree of insulin sensitivity described in patients with elevated PRL seems not to have any association with BMI or waist circumference.[30] Our results are in line with these findings. Indeed, in our patients, no association between PRL levels and metabolic parameters was found either at baseline or after 12 months of treatment with CAB, and no difference in metabolic profile was found between patients with uncontrolled and controlled PRL levels during treatment. In this light, PRL seems not to be directly involved in the metabolic features of patients with prolactinoma. The absence of significant differences in metabolic parameters between patients with persistent high PRL levels and patients with controlled disease strengthens this hypothesis.

Dopamine has been shown to play a role in increased energy expenditure and downregulated food intake.[31] The reduction in dopaminergic tone associated with hyperprolactinaemia has been considered as an additional possible mechanism involved in weight gain in patients with prolactinoma, and the lower body fat content in patients that normalizes the PRL levels is likely due to dopamine receptor type 2 (DR2) activation as a result of DA treatment.[5] In this connection, it has been suggested that the DR2 gene may play a role in the regulation of weight.[32] A role of DA in glucose and lipid metabolism has been well documented both in diabetic and obese subjects,[33,34] but most of the available data are under bromocriptine treatment.[35,36] For these reasons, we aimed to evaluate the CAB effect on metabolic parameters. Most of the available studies have focused on metabolic parameters such as weight or BMI, highlighting the prevalence of obesity in patients with prolactinoma,[7] and the reduction in weight after the normalization of PRL levels during DA treatment [2,37] although with discordant results.[29,38] In our cohort of patients with hyperprolactinaemia, while WC significantly decreased after treatment, BMI did not change significantly, suggesting the presence of other factors influencing the improvement in metabolic parameters.

Table 2. Hormonal and metabolic parameters of patients grouped according to control of disease after 12 months of treatment with cabergoline

	Controlled patients (No. 24) Mean ± SD	Uncontrolled patients (No. 19) Mean ± SD	P
Tumor volume (mm^3)	6·95 ± 2·39	9·75 ± 4·29	0·016
Prolactin (mU/l)	143 ± 110	996 ± 781	<0·001
	No. (%)	No. (%)	
Normal glucose tolerance (NGT)	21 (87·5)	18 (94·7)	0·618
Impaired fasting glucose (IFG)	1 (4·1)	–	1
Impaired glucose tolerance (IGT)	2 (8·3)	1 (5·2)	1
Diabetes mellitus (DM)	–	–	–
Metabolic syndrome	4 (16·6)	2 (10·5)	0·678
	Mean ± SD	Mean ± SD	
BMI (kg/m^2)	25·06 ± 5·42	25·86 ± 4·43	0·596
WC (cm)	87·25 ± 9·25	87 ± 11·45	0·939
Total cholesterol (mM)	4·22 ± 0·74	4·40 ± 0·72	0·450
HDL cholesterol (mM)	1·26 ± 0·21	1·30 ± 0·21	0·510
LDL cholesterol (mM)	2·34 ± 0·73	2·51 ± 0·63	0·412
Triglycerides (mM)	1·34 ± 0·55	1·25 ± 0·43	0·537
Fasting glucose (mM)	5·30 ± 0·57	5·36 ± 1·36	0·869
Fasting Insulin (pM)	85·94 ± 23·24	87·03 ± 29·58	0·896
HbA1c (%)	5·15 ± 0·43	5·22 ± 0·43	0·597
Homa-IR	2·93 ± 0·93	2·92 ± 1·02	0·982
Matsuda Index	4·73 ± 1·31	4·77 ± 1·62	0·936
AUC$_{2hGlucose}$ (mM;120 min)	821 ± 120	862 ± 204	0·444
AUC$_{2hInsulin}$ (pM;120 min)	36561 ± 7811	39227 ± 14599	0·447
Oral Disposition Index (DIo)	1·79 ± 1·92	2·25 ± 2·57	0·521
Visceral adiposity index (VAI)	2·05 ± 1·17	1·53 ± 0·66	0·096

Table 3. Hormonal and metabolic parameters of patients grouped according to cabergoline dosage after 12 months of treatment

	Patients under high-dose cabergoline (No. 14) Mean ± SD	Patients under low-dose cabergoline (No. 29) Mean ± SD	P
Tumour volume (mm^3)	8·66 ± 4·77	7·92 ± 2·94	0·625
Prolactin (mU/l)	683 ± 965	449 ± 544	0·430
	No. (%)	No. (%)	
Normal glucose tolerance (NGT)	13 (92·8)	26 (89·6)	1
Impaired fasting glucose (IFG)	1 (7·2)	–	0·326
Impaired glucose tolerance (IGT)	–	3 (10·4)	0·539
Diabetes mellitus (DM)	–	–	–
Metabolic syndrome	1 (7·2)	5 (17·2)	0·645
	Mean ± SD	Mean ± SD	
BMI (kg/m^2)	23·12 ± 2·71	26·51 ± 5·45	0·009
WC (cm)	84·14 ± 7·10	88·58 ± 11·16	0·182
Total cholesterol (mM)	4·45 ± 0·62	4·23 ± 0·78	0·321
HDL cholesterol (mM)	1·33 ± 0·26	1·25 ± 0·18	0·324
LDL cholesterol (mM)	2·57 ± 0·58	2·34 ± 0·72	0·282
Triglycerides (mM)	1·18 ± 0·42	1·36 ± 0·53	0·243
Fasting glucose (mM)	4·99 ± 0·61	5·49 ± 1·10	0·067
Fasting insulin (pM)	69·20 ± 17·67	94·73 ± 25·33	0·001
HbA1c (%)	5·01 ± 0·38	5·26 ± 0·43	0·070
Homa-IR	2·21 ± 0·64	3·28 ± 0·90	<0·001
Matsuda Index	5·70 ± 1·28	4·29 ± 1·29	0·002
AUC$_{2hGlucose}$ (mM;120 min)	790 ± 105	864 ± 179	0·099
AUC$_{2hInsulin}$ (pM;120 min)	34354 ± 9431	39373 ± 11834	0·143
Oral Disposition Index (DIo)	3·20 ± 3·52	1·41 ± 0·74	0·011
Visceral adiposity index (VAI)	1·31 ± 0·44	2·07 ± 1·11	0·018

The available studies on the effect of DA on lipid metabolism are not fully consistent.[38,39] We found a significant improvement in lipid profile, as demonstrated by the increase in HDL cholesterol and the decrease in LDL cholesterol and triglycerides, in line with the data of Berinder *et al.*[10]

The mechanisms by which DA could improve glucose metabolism may include suppression of endogenous glucose production or increased splanchnic glucose uptake after glucose ingestion.[36] A tendency to an improvement in insulin sensitivity, assessed by both ISI Matsuda and clamp, was reported after DA treatment.[9,10] These findings are concordant with our results. Indeed, we observed a significant improvement in glucose tolerance and prevalence of MS, with a decrease in insulin levels, an improvement in insulin sensitivity indices and a concomitant reduction in HbA1c. The improvement of the sole case of DM after 12 months of treatment, without glucose lowering treatment, is in line with previous data.[10] Our data demonstrated that the relationship between the decrease in PRL levels and the improvement in insulin sensitivity and the other metabolic parameters seems to reflect the effect of CAB treatment, rather than the association between PRL and BMI. Because our patients did not show signifi-

cant changes in BMI, other mechanisms seem to be involved in the beneficial effects of DA treatment on metabolic profile. In this light, the role of VAI cannot be ruled out. VAI is a sex-specific mathematical index based on anthropometric and metabolic parameters and could be considered a surrogate marker of adipose tissue function and distribution. This index has been demonstrated to be independently correlated with insulin sensitivity and cardiometabolic risk in the general population,[12] in women with polycystic ovary syndrome[40] and in newly diagnosed patients with acromegaly, where VAI significantly correlates with adipocytokine levels.[41] After CAB treatment, our patients had significantly reduced VAI. Therefore, an improvement in adipose tissue function could be considered to have a major role in the change in metabolic profile after treatment. In this light, in line with previous studies, the improvement in insulin sensitivity after DA treatment could be considered to be linked to the decrease in PRL levels, to the improvement of body composition, as

demonstrated by the reduction in WC and VAI, to DA treatment or to a combination of these factors. In this connection, our data show that patients treated with HD of CAB had a more marked improvement in metabolic profile, highlighted by BMI, insulin, Homa-IR, ISI Matsuda and VAI values, than patients treated with LD. In addition, the first group of patients showed higher DIo, demonstrating a more efficient and adequate insulin secretion relative to insulin sensitivity.

In conclusion, a significant metabolic improvement is observed in patients with prolactinoma after 12 months of CAB treatment and the reason for this is probably multifactorial. Our data highlight the importance of considering the metabolic profile in these patients and the role of active treatment with high CAB doses which, besides normalizing hormonal levels, also improve metabolic parameters and insulin sensitivity indices.

Conflicting Interest

The authors state that there is no potential conflict of interest.

Financial Disclosure

The authors have nothing to declare.

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