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REVIEW

The effects of hyperprolactinemia and its control on metabolic diseases

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ABSTRACT

Introduction: Hyperprolactinaemia has been implicated in the pathogenesis of obesity and glucose intolerance and is reportedly associated with impaired metabolic profile and metabolic syndrome in approximately one third of patients.

Area covered: Suppression of dopaminergic tone has been proposed as a potential mechanism responsible for weight gain and metabolic abnormalities in such patients. Dopamine receptor type 2 (D_2R) is abundantly expressed on human pancreatic β-cell and adipocytes, suggesting a regulatory role for peripheral dopamine in insulin and adipose functions. Medical treatment with the dopamine-agonists bromocriptine and cabergoline has been shown to significantly improve gluco-insulinemic and lipid profile, also reducing the prevalence of metabolic syndrome. In patients with concomitant hypogonadism, simultaneous correction of both PRL excess and testosterone deficiency is mandatory to improve insulin resistance and metabolic abnormalities.

Expert commentary: Hyperprolactinemia promotes metabolic alterations. Control of PRL excess by dopamine agonists is mandatory to induce weight loss and to improve metabolic profile, and replacement treatment for concomitant hypogonadism effectively ameliorates insulin resistance and metabolic syndrome.

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Hyperprolactinemia; pituitary tumor; dopamine agonists; bromocriptine; cabergoline; body weight; obesity; glucose metabolism; insulin metabolism; lipid metabolism; metabolic syndrome

1. Introduction

Prolactin (PRL) is known to exert a wide variety of effects on metabolism besides the actions on lactation, gonadal function, and reproduction [1–4]. Over the last years, increasing evidence has associated hyperprolactinemia, induced by either treatment with antipsychotic drugs [5] or PRL-secreting pituitary tumors [6–8], with hyperphagia, increased food intake, and weight gain, leading to obesity, as PRL is known to influence the orexigenic–anorexigenic systems that regulate appetite [9–11]. Consequently, in patients with hyperprolactinemia, metabolic alterations frequently occur. PRL excess has been associated with disorders of lipid metabolism, although with discordant results. Indeed, PRL excess has been clearly demonstrated to inhibit the release of adipokines [11–15] and to promote central leptin resistance [16,17]. Moreover, PRL excess has been reported either to promote [6,18] or to inhibit [9] lipogenesis as well as either to suppress lipid storage [9] or to promote visceral fat storage [19]. Hyperprolactinemia is also associated with disorders of gluco-insulinemic metabolism [4,20–25]. Particularly, PRL excess has been shown to reduce glucose tolerance and to induce hyperinsulinemia [26–28], also increasing homeostatic model assessment (HOMA) index [29–31] and reducing insulin sensitivity index (ISI) [32] in both obese and lean patients.

Dopamine-agonists, mainly bromocriptine and cabergoline, represent the treatment of choice for patients with hyperprolactinemia [33,34] (Box 1). Both drugs have been shown to significantly improve glucose profile in diabetic patients, regardless from the presence of concomitant hyperprolactinemia [35–44]. Particularly, bromocriptine-Quick Release, a fast-absorbing form of bromocriptine, has been shown to decrease plasma glucose levels in nondiabetic obese hyperinsulinemic women on a weight-maintaining diet [41], and to induce weight loss and improvement of glucose tolerance in both diabetic and nondiabetic subjects [37,42]. Therefore, bromocriptine-Quick Release has been officially approved in the US market as adjunctive treatment for type 2 diabetes mellitus [42]. The addition of cabergoline 0.5 mg/week to preexisting glucose-lowering drugs has been recently shown to significantly reduce glycated hemoglobin (HbA_{1c}) levels after 3 months, with 65% of patients achieving a HbA_{1c} <7% as compared to 45% of controls [44].

Several studies have demonstrated that bromocriptine administration induces the significant reduction in body weight and percent body fat [45–52], together with a notable improvement in glucose homeostasis and insulin resistance in patients with prolactinomas [7,8,45,46]. In obese men with prolactinomas, 6-month treatment with either bromocriptine or cabergoline has been demonstrated to induce a significant decrease in body weight [49]. Following treatment with cabergoline, patients with hyperprolactinemia have been reported to have significantly lower body fat percentage as compared to newly diagnosed treatment-naïve patients [47,48], suggesting that adequate control of PRL excess induced by cabergoline might reduce the risk of obesity and metabolic complications. In fact, a significant improvement in insulin

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Box 1. Drug summary box

Drug name	Bromocriptine
Phase	Not applicable
Indication	Treatment of hyperprolactinemia
Pharmacology description/ mechanism of action	Ergot derivative D_2 receptor agonist
Route of administration	Oral
Chemical structure	Ergotaman-3′,6′,18-trione,2-bromo-12′-hydroxy-2′-(1-methylethyl)-5′-(2-methylpropyl)-(5′α)-monomethanesulfonate (salt)
Drug name	Cabergoline
Phase	Not applicable
Indication	Treatment of hyperprolactinemia
Pharmacology description/ mechanism of action	Ergot derivative D_2 receptor agonist
Route of administration	Oral
Chemical structure	[(6-Allylergolin-8β-yl)-carbonyl]-1-[3 (dimethylamino)propyl]-3-ethylurea

resistance and in glucose and lipid profile has been described in patients receiving long-term treatment with dopamine-agonists, mainly cabergoline [49–52]. Such metabolic amelioration has been shown to be independent on the degree of reduction in PRL levels, and to be ascribable to cabergoline dosage [51,52]. Noteworthy, in men with hyperprolactinemia, the recovery of gonadal function and testosterone deficiency, even beginning soon after starting of treatment with dopamine-agonists, is fully achieved in approximately half of the patients, and a permanent hypogonadism may persist in 50% of cases [53–55]. In these patients with concomitant androgen deficiency, proper testosterone addition to cabergoline treatment has been found to significantly improve metabolic profile [56], mainly insulin resistance and metabolic syndrome.

This review focuses on the effects of PRL excess and its control by medical treatment with dopamine-agonists on the modulation of food intake, body weight, and gluco-insulinemic and lipid profile.

2. Effects on food intake and body weight

Chronic hyperprolactinemia is associated with increased food intake and weight gain, therefore promoting obesity [5–10]. PRL-induced increase in appetite has been mainly linked to the functional blockade of dopaminergic tone. In fact, dopaminergic tone plays a key role in increasing energy expenditure and reducing food intake [5–8,57], and its suppression has been considered a potential mechanism contributing to hyperphagia and weight gain in patients with hyperprolactinemia, together with the increased hypothalamic levels of the appetite-stimulating hormones neuropeptide Y and corticotrophin-releasing hormone [9–11]. These findings led to the hypothesis that dopaminergic tone plays a pivotal role in regulating body weight. The decrease in body mass index (BMI) and body fat content following PRL normalization after treatment with cabergoline has been ascribed to dopamine receptor type 2 (D_2R) activation [48]. Indeed, the reduction in body weight and BMI after PRL normalization during treatment with dopamine-agonists has been documented in some studies [6,30]. More recently, in patients with prolactinomas body weight, BMI and waist circumference have been found to significantly reduce after long-term treatment with cabergoline [51,52,56], suggesting a clinically relevant improvement of visceral obesity. In male patients with PRL excess-induced hypogonadism, the impact of low testosterone levels on weight gain cannot be excluded. Indeed, men with testosterone and dihydrotestosterone levels in the lower quartiles have been found to have more than twofold higher risk of exhibiting obesity and metabolic syndrome [58]. Noteworthy, changes in body weight have been shown to influence testosterone levels, at least in aging men [59], and losing 5% of weight has been found to significantly increase testosterone levels, which further increased with additional weight loss. In male patients with hyperprolactinemia-induced hypogonadism, body weight, BMI, and waist circumference have been found to be significantly greater as compared to non-hypogonadal patients after treatment with cabergoline and testosterone replacement [56], supporting the hypothesis that visceral obesity might be mainly influenced by androgen deficiency, and that weight loss might reflect a direct beneficial effect of both cabergoline treatment and adequate androgen replacement [56].

3. Effects on lipid profile

Previous evidence has associated hyperprolactinemia with the impairment in lipid profile (Table 1). Particularly, decreased HDL cholesterol and increased total or LDL cholesterol and triglycerides have been reported in patients with prolactinomas as compared to healthy control subjects [45,60–65] (Table 1). Similarly, total body fat percentage has been demonstrated to be increased in newly diagnosed treatment-naïve hyperprolactinemic patients as compared to controls [48,61] (Table 1). A direct correlation between lipid metabolism and PRL levels has been proposed [46,60] (Table 1). In fact, PRL can directly act on

Table 1. Effects of hyperprolactinemia on lipid profile.

Reference	Model	Effects on lipids
[45]	Human	↑ LDL and TG in hyperprolactinemic patients compared to controls
[48]	Human	↑ Body fat percentage in hyperprolactinemic patients compared to controls
[60]	Human	↑ TC, TG, LDL and ↓ HDL in hyperprolactinemic patients compared to controls
[63]	Human	↓ HDL in hyperprolactinemic patients compared to controls
[64]	Human	↓ Apolipoprotein A-I and A-II in hyperprolactinemic patients compared to controls
[65]	Human	↑ TC, LDL, and apolipoprotein B in hyperprolactinemic patients compared to controls
[66]	Murine	↑ PRL-receptor expression upon adipocyte differentiation
[67]	Sheep	↑ PRL-receptor expression during rapid deposition of perinatal adipose tissue
[68]	Rat	↑ PRL-induced leptin synthesis and secretion
[69]	Human + LS14 cell line	↑ PRL release by human visceral and subcutaneous adipose explants, mature adipocytes, differentiated primary subcutaneous presdipocytes, and LS14 cells.

TC: total cholesterol; LDL: LDL-cholesterol; HDL: HDL-cholesterol; TG: triglycerides; PRL: prolactin.

adipose tissue because PRL receptors increase during adipocyte differentiation and may be involved on lipid metabolism of mature adipocytes [66–69] (Table 1). Also, D_2R is expressed on human adipocytes, suggesting that peripheral dopamine may play a regulatory role in adipose functions [70], and dopamine-agonists have been shown to inhibit *in vitro* adipocyte PRL expression and release. In patients receiving long-term treatment with cabergoline, a significant decrease in visceral adiposity index, a surrogate parameter of adipose tissue dysfunction associated with cardiometabolic risk in healthy subjects [71] and in patients with endocrine diseases [72,73], has been observed [51,52], mainly in patients receiving cabergoline doses higher than 0.5 mg/week [51,52]. These findings support the hypothesis of a beneficial action of dopaminergic activation on adipose dysfunction in patients with hyperprolactinemia. Studies evaluating the effects of dopamine-agonists on lipid metabolism are not fully consistent; however, several investigations have demonstrated that in patients with hyperprolactinemia, either bromocriptine or cabergoline improves lipid profile independently on changes in body weight and BMI [43,45,48,51,52,56,74], supporting the hypothesis of a direct beneficial effect of dopamine-agonist treatment on lipids. Indeed, previous studies have demonstrated that D_2R activation induced by dopamine-agonists improves several features of metabolic syndrome and obesity including hyperlipidemia, even apart from its impact on food intake and body weight [35,37,39,75]. In male hyperprolactinemic patients with concomitant hypogonadism, treatment with cabergoline has been found to induce *per se* the significant improvement in total and LDL-cholesterol and in triglycerides, without a further amelioration of lipid fractions following 12 months of testosterone replacement [56]. Altogether, these findings straighten the hypothesis that in patients treated with dopamine-agonists, the improvement seen in lipid profile may reflect the direct effect of dopaminergic agents on lipids rather than the sole association between PRL normalization and BMI [52,56]. Conversely, in a few studies [30,76], dopamine and/or dopaminergic drugs failed to induce a significant change in lipid profile in either healthy or diabetic subjects. This difference could be explained considering the heterogeneity of administered treatments, the small size of patient populations, and the short-term treatment with dopamine-agonists.

4. Effects on gluco-insulinemic profile

The link between PRL levels and gluco-insulinemic metabolism has been studied in several investigations [20–25,77–91] (Table 2). Pregnancy represents a unique model to study mechanisms regulating the effects of prolonged hyperprolactinemia on glucose and insulin metabolism. In rodents, PRL has been shown to induce the characteristic pregnancy-associated changes in pancreatic β-cell mass and function [20–25] (Table 2). During pregnancy, the rise in PRL levels parallels the increase in β-cell mass and glucose-induced insulin hypersecretion [20] (Table 2). PRL receptors have been found expressed on insulin-secreting cell lines [21] and β-cells [22], and this expression has been reported to increase during pregnancy [23]. *In vitro* exposure of isolated pancreatic islet to PRL results in increased insulin secretion and β-cell proliferation [21,24] (Table 2), and overexpression of PRL in β-cells leads to inappropriately elevated serum insulin concentrations, increased islet insulin content, and sustained β-cell replication [25] (Table 2). In rats and humans, PRL increases β-cell proliferation, insulin gene transcription, and glucose-dependent insulin secretion [78–81] (Table 2).

Table 2. Effects of hyperprolactinemia on insulin profile.

Reference	Model	Effects on insulin
[20]	Rodent	↑ β-Cell mass and insulin secretion during pregnancy
[21]	Rodent	↑ Glucose-induced insulin secretion during pregnancy
[23]	Rodent	↑ PRL-receptor expression on β-cell during pregnancy
[24]	Rodent	↑ Islet cell proliferation and insulin secretion during pregnancy
[25]	Rodent	↑ Insulin secretion and β-cell replication during pregnancy
[78]	Rodent	↑ Insulin secretion during pregnancy
[79]	Rodent	↑ Insulin secretion and β-cell replication during pregnancy
	Human	↑ Insulin secretion during pregnancy
[80]	Rodent	↑ Number of glucose-transporters (GLUT-2) and ↑ glucose-dependent and glucose-independent insulin secretion
[81]	Rodent	↑ Glucose-dependent and glucose-independent insulin secretion

In diabetic non-hyperprolactinemic patients, both bromocriptine and cabergoline have been demonstrated to significantly improve glucose profile [37–44]. The fast-absorbing form of bromocriptine, namely bromocriptine-Quick Release, has been shown to decrease plasma glucose levels and to improve glucose tolerance in both diabetic and nondiabetic subjects [37,41,42]. Similarly, according to a recent double-blind placebo-controlled study [44] in diabetic non-hyperprolactinemic patients with HbA_{1C} ranging 7–10%, the addition of cabergoline 0.5 mg/week to treatment by ≥2 oral glucose-lowering drugs has been shown to significantly reduce HbA_{1c} levels after 3 months as compared to placebo [44]. A HbA_{1c} level <7% was achieved in 65% of patients as compared to 45% of controls [44].

Men and women with chronic hyperprolactinemia have been demonstrated to display postprandial hyperinsulinemia and exaggerated insulin secretory response to glucose [82–84]. Noteworthy, pancreatic β-cells express also dopamine receptors, and treatment with the selective D_2R agonist quinpirole has been found to cause the inhibition of glucose-stimulated insulin secretion [85]. In rodents, a single injection with the dopamine precursor L-dopa resulted in inhibited insulin secretory response [86,87], whereas treatment with L-dopa in humans with Parkinson's disease has been reported to reduce insulin secretion upon a glucose load [88]. Fasting glucose and insulin and HOMA-IR have been found to significantly improve also in patients with Cushing's disease following 24 months of treatment with cabergoline after unsuccessful surgery [89]. Moreover, in healthy nonobese subjects, activation of D_2R has also been shown to affect circulating growth hormone (GH) and IGF-levels [90]. As IGF-I bioactivity has been found inversely associated to insulin sensitivity [91], the decrease in GH levels and/or in IGF-I bioactivity could represent another potential mechanism involved in insulin sensitivity amelioration.

A significant improvement in glucose metabolism and insulin resistance after 6 months of treatment with either bromocriptine or cabergoline has been described in patients with

prolactinomas [48,49,51,52,56]. Particularly, after long-term treatment with cabergoline, fasting insulin and HOMA-IR have been reported to significantly reduce, mainly in patients receiving cabergoline doses higher than 0.5 mg/week [51,52], regardless of changes in body weight and BMI [52]. HOMA-β and ISI were also significantly improved after treatment with cabergoline compared to baseline [52], confirming the hypothesis of a beneficial direct effect of cabergoline on insulin secretion and sensitivity, even though some effect could be explained by weight loss and lifestyle changes during therapy with cabergoline, at least partly [92,93]. Noteworthy, cabergoline dose has been demonstrated to be the best predictor of percent decrease in fasting insulin [52], supporting the hypothesis of a direct beneficial effect of cabergoline itself on pancreatic β-cell and insulin secretion. The improvement of insulin sensitivity has been found associated with the significant reduction in glucose levels both in lean and obese patients independently on PRL levels [52]. In hyperprolactinemic male patients with concomitant hypogonadism, fasting insulin, HOMA-IR, HOMA-β, and ISI have been found to significantly improve after long-term treatment with cabergoline, and further ameliorated by complete testosterone normalization following androgen replacement [56]. Interestingly, cabergoline dose has been shown to significantly correlate with fasting insulin and HOMA-β [56], confirming the hypothesis of a direct dopaminergic role on the regulation of insulin secretion [52]. Testosterone levels have been found to significantly correlate with ISI [56], suggesting a potential direct beneficial action of androgen therapy on the regulation of peripheral insulin sensitivity.

5. Effects on metabolic syndrome

Few studies have investigated changes in metabolic syndrome prevalence in patients with hyperprolacinemia receiving treatment with dopamine-agonists [49,51,52,56] (Table 3). Overall, metabolic syndrome has been reported in approximately one-third of patients with hyperprolactinemia, ranging 23–50% in the different series (Table 3). Therapy with dopamine-agonists, mainly cabergoline, has been found to reduce metabolic syndrome prevalence up to 5% [52] in patients treated for 6–60 months (Table 3). This notable reduction in the prevalence of metabolic syndrome is the obvious consequence of the significant decrease in body weight and the significant improvement in lipid and glucoinsulinemic profile seen following treatment with dopamine-agonists, likely due to the direct role of PRL excess and its control on the modulation of food intake and adipocyte and pancreatic β-cell function.

Altogether, these findings have demonstrated the beneficial impact of bromocriptine and cabergoline on metabolic alterations in patients with hyperprolactinemia, raising the question of whether dopamine-agonists might be proposed as valid alternative or adjunctive treatment in obese hyperlipidaemic diabetic and nondiabetic patients failing to achieve adequate metabolic control with standard therapies.

6. Effects on autoimmunity

Since the early 1990s, several lines of evidence have demonstrated that PRL plays a role as an immunomodulator. Immune system cells produce PRL and express PRL receptors [94], suggesting that PRL acts on immune system likely via endocrine and paracrine/autocrine pathways [94]. PRL stimulates proliferation of B and T lymphocytes, and PRL excess may result in occurrence or worsening of preexisting systemic and nonsystemic autoimmune diseases. Particularly, a pathogenic role for PRL has been supported in patients with systemic lupus erythematosus [95–100], rheumatoid arthritis [101], systemic sclerosis [101], autoimmune thyroid diseases [102–104], and type 1 diabetes mellitus [105]. Also, duration of hyperprolactinemia has been found to significantly correlate to disease duration or severity in patients with multiple sclerosis [106] and pemphigus [107]. Treating PRL excess by the dopamine-agonist bromocriptine has been shown to significantly improve the course and to induce the disappearance of clinical manifestations in mouse models of systemic lupus erythematosus [108] and antiphospholipid syndrome [109]. In patients with active systemic lupus erythematosus, treatment with bromocriptine for 6–9 months has resulted in the significant decrease in disease activity [110]. Similarly, treatment with bromocriptine has been reported to prevent relapses of systemic lupus erythematosus during the postpartum period [111,112]. Prevalence of postpartum relapse has been found to be lower in patients receiving bromocriptine as compared to controls [112].

Altogether, these findings support a correlation between hyperprolactinemia and autoimmunity, and suggest that PRL-mediated effects on immune system might represent a potential therapeutic target for the treatment of autoimmune diseases.

7. Expert commentary

PRL excess is associated with metabolic syndrome in approximately one-third of patients, and suppression of dopaminergic tone likely represents a potential mechanism responsible for weight gain and metabolic abnormalities in patients with prolactinomas. Long-term treatment with dopamine-agonists, mainly cabergoline, significantly reduces body weight and

Table 3. Effects of treatment with dopamine-agonists on metabolic syndrome prevalence.

					Metabolic syndrome	
Reference	Author, year	Patients	Drug	Duration (months)	*Baseline (%)*	*After therapy (%)*
[49]	dos Santos Silva, 2010	22	3 BRC 19 CAB	6	23	14
[51]	Ciresi, 2013	43	CAB	12	30.2	14
[52]	Auriemma, 2013	61	CAB	60	28	5
[56]	Auriemma, 2015	32	CAB	24	50	12.5
Total	–	158	–	–	32	10

BRC: bromocriptine; CAB: cabergoline.

improves adipose tissue dysfunction, insulin resistance, and the entire metabolic profile. The effects seen in patients with prolactinomas confirm previous findings in obese non-hyperprolactinemic patients, with or without diabetes mellitus, who have shown a clinically relevant weight loss associated with the significant amelioration in lipid fractions, fasting glucose levels, and insulin metabolism after treatment with bromocriptine or cabergoline. These results can be explained taking into account that both PRL receptors and D_2R are abundantly expressed on human adipocytes and pancreatic β-cells, therefore supporting the hypothesis that dopaminergic system plays a key role in the modulation of lipid and gluco-insulinemic profile. Dopamine-agonists, mainly cabergoline, might act as direct modulator of insulin sensitivity, and in turn the decrease in PRL levels together with the improvement in insulin sensitivity and the other metabolic parameters might reflect the direct effect of cabergoline treatment in patients with prolactinomas. Even in the presence of concomitant hypogonadism in male patients, treatment with cabergoline *per se* improves lipid profile, insulin resistance, and insulin secretion, although adequate androgen replacement is necessary to improve visceral obesity and peripheral insulin sensitivity. Altogether, increasing evidence collected in hyperprolactinemic and non-hyperprolactinemic patients over the last years raises the question of whether dopamine-agonists may be used as valid alternative or adjunctive therapy in patients with metabolic abnormalities not achieving adequate metabolic control with standard treatments. In fact, bromocriptine has been already officially approved in US market for the treatment of type 2 diabetes mellitus, and promising results have been provided by the addition of low-dose cabergoline to standard glucose-lowering drugs in diabetic patients. Further studies are still needed to elucidate the burden and the differential role of PRL and dopamine-agonists on the modulation of metabolism in patients with hyperprolactinemia.

8. Five-year view

Prolactin is a metabolic hormone, besides the well-known actions on fertility and reproduction. Dopaminergic tone plays a key role in the regulation of the metabolic system by modulating PRL secretion. Treatment of PRL excess with the dopamine-agonists bromocriptine and cabergoline has demonstrated to produce beneficial effects on gluco-insulinemic and lipid metabolism in obese diabetic patients, regardless of concomitant hyperprolactinemia, also providing promising results about their potential use as alternative or adjunctive treatment for type 2 diabetes mellitus. Future studies will better elucidate the burden and the differential role of PRL and dopamine-agonists on the modulation of metabolism in patients with hyperprolactinemia.

Key issues

- PRL is a metabolic hormone.
- PRL excess induces hyperphagia and obesity, and promotes abnormalities in gluco-insulinemic and lipid profile, leading to metabolic syndrome in approximately one third of patients with hyperprolactinemia.
- Medical treatment of hyperprolactinemia with dopamine-agonists bromocriptine and cabergoline induces weight loss and improves lipid profile by reducing total and LDL-cholesterol and triglycerides, and increasing HDL-cholesterol.
- Fasting glucose and insulin levels reduce while on dopamine-agonists, together with a significant amelioration in insulin resistance and peripheral insulin sensitivity.
- Prevalence of metabolic syndrome significantly reduces after treatment with dopamine-agonists in patients with hyperprolactinemia.
- The metabolic improvement seen after treatment is independent on the degree of reduction in PRL levels, and should be ascribed to dopamine-agonists dosage, mainly in patients receiving cabergoline.
- In male patients with concomitant hypogonadism, proper androgen replacement is mandatory to effectively ameliorate insulin resistance and metabolic syndrome.

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Declaration of interest

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