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The interplay between prolactin and cardiovascular disease

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Hyperprolactinemia can be caused by several conditions and its effects on the hypothalamic-pituitary-gonadal axis are understood in more detail. Nevertheless, in recent decades, other metabolic effects have been studied and data pointed to a potential increased cardiovascular disease (CVD) risk. A recent study showed a decrease in total and LDL-cholesterol only in men with prolactinoma treated with dopamine agonists (DA) supporting the previous results of a population study with increased CVD risk in men harboring prolactinoma. However, other population studies did not find a correlation between prolactin (PRL) levels and CVD risk or mortality. There is also data pointing to an increase in high-density lipoprotein levels, and decreases in triglycerides, carotid-intima-media thickness, C-reactive protein, and homocysteine levels in patients with prolactinoma on DA treatment. PRL was also implicated in endothelial dysfunction in pre and postmenopausal women. Withdrawal of DA resulted in negative changes in vascular parameters and an increase in plasma fibrinogen. It has been shown that PRL levels were positively correlated with blood pressure and inversely correlated with dilatation of the brachial artery and insulin sensitivity, increased homocysteine levels, and elevated D-dimer levels. Regarding possible mechanisms for the association between hyperprolactinemia and CVD risk, they include a possible direct effect of PRL, hypogonadism, and even effects of DA treatment, independently of changes in PRL levels. In conclusion, hyperprolactinemia seems to be associated with impaired endothelial function and DA treatment could improve CVD risk. More studies evaluating CVD risk in hyperprolactinemic patients are important to define a potential indication of treatment beyond hypogonadism.

KEYWORDS

metabolic syndrome, hyperglycemia, systemic arterial hypertension, prolactinoma, cardiovascular risk, dyslipidemia, dopaminergic agonist, prolactin

Introduction

Prolactin (PRL), as a classic hormone, is synthesized and secreted mainly by lactotroph cells from the anterior pituitary gland, which are tonically inhibited by hypothalamic dopamine (1). PRL is also secreted by extra-pituitary sources such as adipose tissue (2), with autocrine and paracrine actions, playing a dual role as a hormone and cytokine (2, 3). PRL can be classified according to its molecular weight into monomeric, dimeric, and macroprolactin, being monomeric the predominant isoform. Nevertheless, if the main isoform in circulation is macroprolactin, a condition known as macroprolactinemia can occur, without the clinical picture normally observed in hyperprolactinemia, as macroprolactin presents a low biological activity (4). Additionally, PRL can be cleaved by proteases into vasoinhibin, with anti-angiogenic properties, being 16 kDa fragment related to peripartum cardiomyopathy (5).

The diagnosis of hyperprolactinemia is defined when a single measurement of serum PRL is above the upper limit of normal, if there was no excessive venipuncture stress (6) and there are several causes of hyperprolactinemia as physiological (pregnancy and lactation), pharmacological (especially antipsychotic drugs), primary hypothyroidism, renal failure, hepatic insufficiency, pituitary stalk disconnection and pituitary tumors with autonomous prolactin secretion as somatotrophinomas and prolactinomas (7). Pathological hyperprolactinemia can cause hypogonadotrophic hypogonadism, infertility, and galactorrhea (7), and the gold-standard treatment for prolactinoma is the use of dopaminergic agonists (DA) (7). Microprolactinomas in asymptomatic individuals, without bothersome galactorrhea, bone loss, and no fertility desire, could be followed without specific treatment (8). However, data associating hyperprolactinemia with other comorbidities such as obesity, metabolic syndrome, diabetes, and cardiovascular risk raise the question if serum PRL levels should be always normalized (9).

Cardiovascular disease (CVD) is the leading cause of death worldwide, and its global prevalence has increased every year (10, 11). There are traditional and established risk factors for CVD such as systemic arterial hypertension, dyslipidemia (12), atherosclerosis, insulin resistance (13), hyperglycemia (14), and obesity (15). Interestingly enough, there are literature data associating PRL with insulin resistance (16), hyperglycemia (17), and weight gain (18, 19), contributing indirectly to CVD risk. Also, there are case-controls, cohorts and populational studies evaluating PRL with CVD and the results are controversial.

This review focuses on the role of PRL and hyperprolactinemia on important CVD risk factors such as systemic arterial hypertension, dyslipidemia, atherosclerosis, endothelial dysfunction, glucose metabolism, and body weight. We also reviewed cohorts, case-control, and populational studies with normoprolactinemic individuals, and hyperprolactinemic patients, using or not DA, regarding CVD outcomes.

Systemic arterial hypertension

PRL has biological effects on water and salt balance in different species (2, 20), including humans (21–23). In humans, two studies have shown that increased levels of PRL were associated with elevated arterial pressure in women with hypertension (24) and normotensive pregnant women (25). Recently, a cohort study has demonstrated that a higher daytime plasma PRL level, even within the normal range, was associated with an increased risk of incident hypertension among postmenopausal women from the Nurses' Health Study (26). The levels of PRL in the urine were significantly higher in patients with preeclampsia than in subjects with normal pregnancy and antiangiogenic PRL fragments (14–16 kDa) in urine was detected only in patients with severe preeclampsia (27, 28). Cord blood PRL was high in newborns of hypertensive women (29).

Although in animal models, there were controversial results, in transgenic mice with inducible hepatic production of PRL and its cleavage product, an increase in PRL increased blood pressure by modulating the activity of endothelial nitric oxide synthase (30). Beyond PRL, dopamine also has a role in hypertension. Dysregulation of dopamine-dependent mechanisms has been pointed to as a determinant of hypertension, in studies in dopamine receptor knockout mice (31).

In a cross-sectional study, PRL levels within the normal range were associated with blood pressure values and arterial stiffness (32) but in another study, there were no differences in central, peripheral blood pressure, and arterial stiffness between patients with idiopathic hyperprolactinemia and controls (33).

Dyslipidemia

Most studies have shown that patients harboring prolactinoma have modestly increased total cholesterol and LDL cholesterol levels (17, 34–39) with decreasing levels after dopamine agonist (DA) treatment and normalization of serum PRL levels (17, 38–47), which can occur independently of PRL levels (48). In some studies, cholesterol and LDL levels were decreased only in men (49). DA dose and length of treatment were variable, from 10 weeks (49) to 60 months (45, 48), differences that may interfere with the results found. Higher plasma triglycerides levels (17, 34, 50) and low HDL cholesterol (39, 50, 51) levels were also described in some cohorts of patients with prolactinoma, with decreasing levels of triglycerides after DA treatment in some studies (17, 46, 48).

The mechanisms associating PRL with dyslipidemia are not completely understood and there are some hypotheses: 1) PRL decreases lipoprotein lipase activity in human adipose tissue and plasma lipoprotein lipase activity is decreased in patients with prolactinomas (34, 52); 2) hyperprolactinemia causes hypogonadism, which is a risk factor for hypercholesterolemia;

3) hyperprolactinemia can be related to weight gain and obesity, causing adverse lipid profile (17, 36) and 4) in macroprolactinomas with impairment of GH secretion, it could result in abnormal lipid levels (34) (Figure 1). Treatment with DA (bromocriptine or cabergoline) decreased LDL cholesterol and triglycerides levels in some studies and these effects could be related to the normalization of steroid sexual levels, and normalization of serum PRL levels, or, even, a direct effect of DA (53). In a study comparing metabolic outcomes in patients with prolactinoma treated by neurosurgery or DA, there was an improvement in lipid metabolism after a rapid decrease in PRL levels with surgery, while a high dose of CAB seemed to exert a beneficial impact on both insulin secretion and peripheral sensitivity (54). Auriemma et al (47) treated hypogonadic men with prolactinoma with CAB and testosterone replacement and showed that proper testosterone replacement induced a significant improvement in the metabolic profile, even though the amelioration in the lipid profile might reflect the direct action of CAB. Atorvastatin could reduce lipid levels in both hyperprolactinemic and normoprolactinemic women, with or without using DA (55).

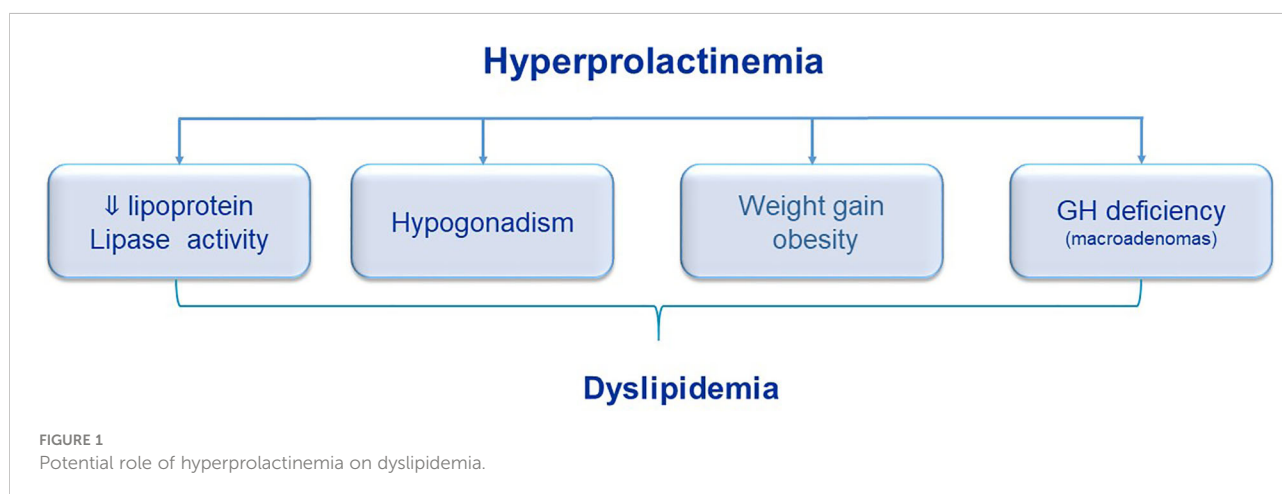
As mentioned above, macroprolactinemia is usually a benign condition. However, compared with healthy controls, it was shown that women with isolated macroprolactinemia had increased levels of triglycerides and high sensitivity C-reactive protein (hsCRP), as well as lower levels of HDL cholesterol (56). Thereafter, the authors compared two groups of women with hypercholesterolemia treated with atorvastatin, one with macroprolactinemia and the other with normal PRL levels. The effect of atorvastatin in reducing cholesterol and LDL was more pronounced in the normoprolactinemic group (57). Comparing men with macroprolactinemia to subjects with monomeric hyperprolactinemia and normoprolactinemic men, the cardiometabolic risk was higher in macroprolactinemia compared to controls but to a lesser extent than in monomeric hyperprolactinemia (58).

Atherosclerosis and endothelial dysfunction

In vitro studies have shown that PRL can modulate inflammatory responses, stimulate vascular smooth muscle cell proliferation, and play a role in the adhesion of circulating mononuclear cells to endothelium, pointing to a role of PRL in endothelial dysfunction (59). Reuwer et al. demonstrated that the PRL receptor was present in macrophages of the atherosclerotic plaque, proposing that prolactin receptor signaling contributes to the local inflammatory response within the atherosclerotic plaque and thus to atherogenesis (60).

PRL stimulates angiogenesis either directly, by promoting endothelial cell proliferation, or indirectly, by upregulating pro-angiogenic factors such as vascular endothelial growth factor (61). In addition, in experiments with animals, PRL might alter endothelial function through its vasoconstrictive features, reducing NO production directly (62), or indirectly, *via* its cleaved fragment 16KDa, contributing to an increase in blood pressure (30) and *via* its role in the trophic response of vascular smooth muscle (63).

An endothelial dysfunction is an event that precedes the formation of atherosclerosis and influences the progression of this disease and its adverse events. Endothelial function can be evaluated, *in vivo*, by measuring flow-mediated dilatation (FMD) on a brachial artery and/or measuring carotid-intima media thickness (CMT). FMD was lower in patients in prolactinoma in some studies (50, 64, 65). In patients with prolactinomas, carotid-intima media thickness is increased when compared to healthy volunteers (50, 59, 66), with a decrease obtained after six months of DA treatment, independently of PRL levels (43). In one study including patients with prolactinoma treated with CAB who presented remission, at the moment of cessation of CAB therapy, the FMD percentage in patients with prolactinoma was worse than that in healthy controls and after the withdrawal of CAB treatment,



fibrinogen, mean platelet volume, CIMIT, and HDL cholesterol were worse in the relapse patients than those in the remission patients. All these data pointed to a direct benefit of DA treatment in CVD risk (65).

Low-grade inflammation was also observed in hyperprolactinemic patients. High sensitivity C-reactive protein (hsCRP) was found in patients with prolactinoma (59, 64, 67) with decreasing levels after DA treatment (43, 64, 67). No differences in lipid profile and inflammatory markers were found in premenopausal women with hyperprolactinemia and hypercholesterolemia on atorvastatin, treated with BRC or

metformin (68). After CAB treatment, inflammatory markers were reduced in two series of patients with prolactinoma (43, 67).

It is suggested that epicardial adipose tissue plays a role in adiposity-related inflammation and atherosclerosis through paracrine secretion of pro- and anti-inflammatory cytokines (69). A recent study showed a greater thickness of epicardial adipose tissue in patients with prolactinoma, despite having normal systolic and diastolic cardiac functions (66).

Case-controls and retrospective/prospective studies evaluating dyslipidemia, atherosclerosis, and CVD risk factors in hyperprolactinemic patients are summarized in Table 1

TABLE 1 Studies with patients with hyperprolactinemia/prolactinoma without using DA.

Authors, year	Study design	Population studied	Results
Pelkonen et al, 1982 (34)	Case-control	Prolactinomas (N=44) vs healthy controls (N=8)	Cholesterol and TG higher in patients vs controls
Heshmati et al, 1987 (51)	Case-control	Women with prolactinomas (N=15) vs healthy matched-controls (N=15)	Cholesterol, LDL, and TG were similar in both groups, while HDL was lower in the hyperprolactinemic group.
Oppenheim et al, 1989 (36)	Case-control	Men with prolactinoma and hypogonadism (N=18), men with secondary hypogonadism and normal PRL (N=15) vs healthy men in control (N=33)	Cholesterol, LDL, and TG are higher in patients with hypogonadism, with or without hyperprolactinemia
Erem et al, 2010 (35)	Case-control	Prolactinoma (N=22) vs healthy controls (N=20)	Increased levels of total cholesterol, LDL-cholesterol, apolipoprotein B, platelet count, fibrinogen, AT-III, PAI-1, and PAI-1/t-PA ratio in patients vs controls
Jiang et al, 2014 (50)	Case-control	Patients with prolactinoma without previous treatment (N=31) vs healthy patients (N=60)	Higher levels of triglycerides, ApoB/ApoA-1, CRP, and fibrinogen and lower HDL and ApoA-1 in patients vs controls Higher levels of PRL determined lower FMD of the brachial artery and higher carotid intimal mean thickness independent of traditional risk factors
Arslan et al, 2014 (59)	Case-control	Prolactinomas (N=35) vs healthy controls (N=36)	hs-CRP level and carotid intimal mean thickness were significantly higher in patients vs controls
Peric et al, 2016 (37)	Case-control	Patients with prolactinomas (N=29) vs clinically non-functioning pituitary adenomas (N=57)	Prolactinomas were associated with higher LDL cholesterol, DHEA-S, and lower GH levels
Soto-Pedre et al, 2017 (70)	Retrospective cohort	1204 individuals, followed for 10 years, divided into 4 groups: 1) Pituitary disorders (N=331): MIC (N=196), MAC (N=54), and without MRI reports (N=81) 2) Drug-induced hyperprolactinemia (N=598) 3) Hyperprolactinemia due to hypothyroidism (N=79) 4) Idiopathic hyperprolactinemia (N=196)	No increase in outcomes (death, diabetes, bone fractures, non-fatal cardiovascular disease, cancer, autoimmune disease, and infectious disease) was observed in patients with MIC. MAC carriers, drug-induced and idiopathic hyperprolactinemia groups with an increased risk of death. The increased risk was not related to PRL levels.
Toulis et al, 2018 (71)	Retrospective Cohort	Patients with prolactinoma (1822 women and 411 men)	Increased incidence of cardiovascular outcomes only in men
Koca et al., 2021 (33)	Case-control	Idiopathic hyperprolactinemia (N=54) vs healthy controls (N=55)	There were no differences in central, peripheral pressure, and arterial stiffness between groups or with PRL levels

MIC, microprolactinoma; MAC, macroprolactinoma; CAB, cabergoline; BRC, bromocriptine; DA, dopamine agonist; CRP, C reactive protein; PRL, prolactin; OR, odds ratio; CKI, chronic kidney insufficiency; T2DM, type 2 diabetes mellitus; FMD, flow mediated dilation; TG, triglycerides; AT-III, Antithrombin-III; PAI-1, plasminogen activator inhibitor 1; MRI, magnetic resonance imaging.

(Table 1). Table 2 summarizes clinical trials, retrospective and prospective cohorts evaluating the effect of DA treatment in dyslipidemia, atherosclerosis, and CVD risk factors (Table 2).

Insulin resistance and hyperglycemia

PRL plays a role in glucose metabolism during pregnancy. Results from animal studies showed that PRL stimulates the

growth of pancreatic islets, and insulin secretion during the perinatal period in the fetus (72, 73). In the mothers, the expression of the PRL receptor in the pancreatic islets increases during pregnancy (74), and the threshold for glucose-stimulated insulin secretion is reduced (73). However, two studies have shown PRL that levels during pregnancy were associated with gestational diabetes mellitus risk (75) and reduced tolerance glucose during pregnancy (76). Polymorphisms in the PRL receptor were associated with

TABLE 2 Studies with patients with hyperprolactinemia/prolactinoma on DA treatment.

Authors, year	Study design	Population studied	Results
Fahy et al, 1999 (40)	Case-control	Women with hyperprolactinemia on BRC (N=15) vs healthy control (N=15)	No differences in the lipoprotein profile between cases and controls. On BRC, total cholesterol and LDL-cholesterol reduced
Yavuz et al, 2003 (64)	Case-control	Premenopausal women with prolactinomas on BRC (N=16) vs healthy controls (N=20)	Higher levels of Homocysteine, CRP, and acid uric and lower FMD of a brachial artery in cases, with improvement in BRC
Serri et al, 2006 (67)	Clinic Trial	Patients with hyperprolactinemia on CAB for 12 weeks (N=15)	After CAB, inflammatory markers reduced
Berinder et al, 2011 (38)	Clinic Trial	Prolactinomas (8 women, 1 postmenopausal) on BRC or CAB (N=14)	LDL reduced after 2 months on DA
dos Santos Silva et al, 2011 (46)	Prospective cohort	Patients with prolactinoma on DA (N=22)	Improvement of LDL-cholesterol and TG levels after 6 months on DA
Ciresi et al, 2013 (48)	Retrospective Cohort	Patients with prolactinoma on CAB (N=43)	On CAB, after 12 months, total and LDL- cholesterol, and TG were reduced and HDL-cholesterol levels increased, regardless of PRL levels
Inancil et al, 2013 (43)	Retrospective study	Women with prolactinoma on CAB (N=21)	Improvement in inflammatory markers and a decrease in carotid intimal mean thickness on CAB, after 6 months, regardless of PRL, LDL- cholesterol levels and BMI
Auriemma et al, 2013 (45)	Prospective study	Patients with prolactinomas on CAB (N=61)	Lipid profile improved after 12 and 60 months on DA
Krysiak et al, 2015 (39)	Clinical Trial	20 women with hyperprolactinemia: Group 1 = BRC-resistant on CAB for 6 months (N=8) Group 2 = hyperprolactinemia prolactinoma-non-related on BRC for 6 months (N=12)	Only CAB reduced triglycerides, CRP, homocysteine, fibrinogen, and increased cholesterol HDL. CAB was superior to BRC in the effect on free fatty acids, CRP, homocysteine, and fibrinogen.
Krysiak et al, 2015 (68)	Clinical Trial	Premenopausal women with hyperprolactinemia and isolated hypercholesterolemia (N=31) on atorvastatin 20mg for 12 weeks: Group 1 = on BRC (N=14) Group 2 =on metformin (N=17)	No differences in lipid profile and inflammatory markers were found after intervention in both groups
Pala et al, 2015 (17)	Case-control	Prolactinomas (N=19) evaluated metabolically at baseline, 3 and 6 months after on CAB vs healthy controls (N=20)	Increased levels of LDL-cholesterol and TG at baseline in patients vs controls. After 6 months on CAB, total cholesterol, LDL-cholesterol, and TG reduced
Medic-Stojanoska et al, 2015 (42)	Case-control	Premenopausal women with prolactinoma on DA (N=22) vs healthy controls (N=16)	Total cholesterol and LDL levels reduced on DA
Auriemma et al, 2015 (47)	Prospective study	Men with prolactinomas (N=32): with (N=22) or without (N=10) hypogonadism on CAB	Lipid parameters improved after 12 months on CAB with further ameliorating after 24 months
(Continued)			

TABLE 2 Continued

Authors, year	Study design	Population studied	Results
Dogan et al, 2016 (65)	Case-control	Premenopausal women, non-obese with MIC on CAB, evaluated at baseline, 3 months, and 12 months after CAB is withdrawn vs healthy controls (N=30)	FMD of the brachial artery was worse at baseline in patients vs controls. Fibrinogen, mean platelet volume, mean carotid thickness, and HDL were worse in patients with relapses than in those with remission, after CAB is withdrawn. Only mean platelet volume was associated with recurrence of hyperprolactinemia.
Schwetz et al, 2017 (41)	Clinical Trial	Patients with prolactinoma (N=53), 22 MIC, and 31 MAC, on CAB for 9 months until PRL normalization	Decrease in LDL levels after PRL normalization with DA
Krysiak et al, 2019 (55)	Clinical Trial	59 overweight premenopausal women with hypercholesterolemia divided into 3 groups, on atorvastatin for 12 weeks: Group A = hyperprolactinemia (N=19) Group B = normoprolactinemia on BRC (N=20) Group C = normoprolactinemia without DA (N=20)	Atorvastatin reduced lipid levels in all groups. Higher levels of acid uric, CRP, homocysteine, and fibrinogen in Group A
Khalil et al, 2021 (44)	Prospective observational	Patients with prolactinoma on BRC (N=32)	LD-cholesterol reduced on BRC
Yazici et al, 2021 (66)	Case-control	Patients with prolactinoma with and without CAB (N=67) vs healthy controls (N=57)	The greater thickness of epicardial adipose tissue and carotid intimal media in patients vs controls
Posawetz et al, 2021 (49)	Case-control	Patients with prolactinoma (MIC and MAC) with CAB in a 10-week follow-up (N=21) vs healthy controls (N=30)	Reduction of total and LDL cholesterol with CAB in men with MAC
Pirchio et al, 2021 (54)	Clinical Trial	Patients with prolactinoma resistant to CAB on conventional doses (N=34): Group 1 (N=17): pituitary surgery. Group 2 (N=17): on CAB (>2mg/week)	The rapid decrease in PRL levels induced by pituitary surgery might improve lipid metabolism. No impact in medical therapy with high dose CAB.
MIC, microprolactinoma; MAC, macroprolactinoma; CAB, cabergoline; BRC, bromocriptine; DA, dopamine agonist; CRP, C reactive protein; PRL, prolactin; OR, odds ratio; CKI, chronic kidney insufficiency; T2DM, type 2 diabetes mellitus; FMD, flow mediated dilation; TG, triglycerides; AT-III, Antithrombin-III; PAI-1, plasminogen activator inhibitor 1; MRI, magnetic resonance imaging.			

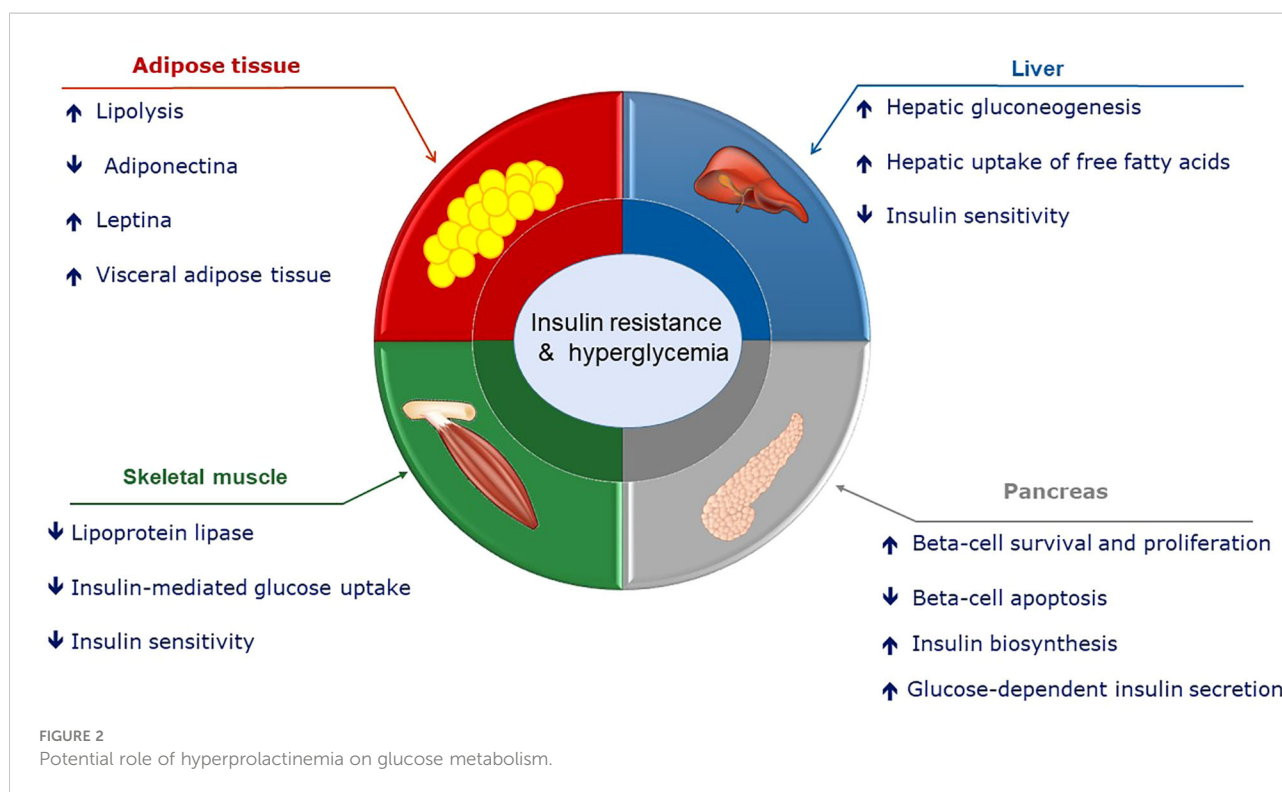
gestational diabetes (77). However, other studies have demonstrated an opposite result: an inverse association between PRL and risk for gestational diabetes mellitus (78, 79). Interestingly enough, lactation has been reported to significantly reduce the risk of metabolic syndrome, and type 2 diabetes (80). In a prospective cohort of women who presented gestational diabetes, decreasing prolactin quartiles in postpartum, associated with higher lactation intensity and duration, were also associated with increased future T2D risk and in women who maintained normoglycemia during the 10-year follow-up, higher prolactin at baseline was associated with higher insulin sensitivity (81).

In non-pregnant status, PRL also seems to play a role in insulin secretion, β -cell proliferation, and glucose metabolism (82–84). Data regarding PRL and glucose metabolism are controversial. In the normoprolactinemic population in general, higher PRL levels within the normal range were associated with improved insulin sensitivity and glucose metabolism, and lower prevalence of diabetes and metabolic syndrome (85–88). Nevertheless, some studies showed that PRL levels were inversely associated with T2D risk (89, 90), particularly in women (91, 92), while others show a positive or

no association in clinical cohorts including men and women (93, 94). A recent meta-analysis (95) reported that a higher PRL level within the normal range was associated with reduced risk of prevalence but not incidence T2D.

Regarding hyperprolactinemia in non-pregnant status, a study in 1977 showed a decrease in glucose tolerance and hyperinsulinemia, so the authors suggested a diabetogenic effect of PRL in hyperprolactinemic patients (96) (Figure 2). Using the hyperinsulinemic-euglycemic clamp technique, it has been shown that hyperprolactinemic patients were more insulin resistant than control subjects, and these findings were not associated with obesity or anthropometric parameters such as fat content, waist circumference, and body mass index (BMI) (97).

DA treatment seems to improve glucose metabolism alterations found in hyperprolactinemia. Hyperprolactinemia induced by hCG in female mice leads to metabolic disturbances such as hyperinsulinemia, hypertriglyceridemia, dyslipidemia, and glucose intolerance, and those disturbances were prevented by treatment with CAB (98). Dos Santos Silva et al. evaluated 22 patients with prolactinoma and after six months of treatment with DA and normal PRL levels, there



was a significant decrease in homeostasis model assessment of insulin resistance (HOMA(IR)) index, normalization of glycemia, although no significant difference in BMI was observed (46). In another study including 43 patients with prolactinoma treated with CAB for 12 months, fasting insulin, HbA1c, and HOMA-IR were reduced, independently of PRL levels, while lower BMI was observed only in patients receiving higher doses (>0.50 mg/week) of CAB (48). Metabolic syndrome prevalence was higher in 61 patients with prolactinoma at baseline, especially with higher levels of serum PRL. Fasting insulin and HOMA(IR) significantly decreased after 1 year of CAB and further improved after 60 months (45).

The observed dose-dependent effect of PRL on glucose metabolism may provide a possible answer to understanding the conflicting data regarding PRL effects on glycemia. Increased insulin sensitivity in liver tissue as well as β -cell growth, leads to greater insulin production in the presence of slightly increased prolactin levels (99, 100). Moreover, it is also possible that mildly higher PRL levels may affect glucose metabolism in an indirect pathway *via* increasing dopamine secretion (100) (101). Low PRL levels were associated with higher risk of MS, polycystic ovary syndrome, postpartum diabetes and diabetes mellitus type 2 in population studies. In a recent study, prolactin receptor knock out mice fed with a high fat diet presented obesity, exacerbated glucose intolerance, insulin resistance, and enlarged adipocytes, compared to the wild type (87). However, more data supporting a causal role of low PRL levels to those findings are needed (102). PRL levels ~ 40 mcg/L were associated

with lower prevalence of metabolic disease while PRL levels higher than 100 mcg/L were associated with deleterious metabolic alterations (91, 103). Therefore, some authors hypothesized that upregulation of PRL levels is a mechanism to maintain metabolic homeostasis and proposed that either very low levels of PRL (< 7 ng/mL) or higher levels of PRL (> 100 ng/mL) were associated with insulin resistance and metabolic syndrome. They suggest defining PRL levels in the range between 25 to 100 mcg/L with no other causal explanations as “HomeoFIT-PRL”, which could represent a physiological response to an increase in metabolic demand (102).

There is evidence that the phases and amplitudes of the plasma rhythms of prolactin and corticosterone are different between insulin-sensitive and insulin-resistant rats. Daily injections of corticosterone and prolactin to simulate the endogenous rhythms of these hormones observed in metabolically healthy animals improve insulin sensitivity and reduce body fat stores of insulin resistance, obese animals (104). Thus, the circadian rhythm of plasma prolactin plays an important role in determining the metabolic effects of this hormone on different tissues.

It is also important to stress that DA treatment may have a central effect on improving glucose metabolism, probably by regulating central nervous system dopaminergic activity. Thus, dysfunctions in prolactin release (either by hyperprolactinemia or low prolactin secretion) can dysregulate the circadian rhythm of central dopaminergic activity, especially at the level of the hypothalamic suprachiasmatic nucleus that works as our

biological clock, leading to alterations in the systemic metabolism (105). This dopaminergic-clock regulatory neurocircuit modulates the activity of the sympathetic nervous system, affecting multiple metabolic processes like hepatic glucose production, adipose tissue lipolysis, and peripheral insulin sensitivity (106). It is also possible that a decreased central dopaminergic tone may alter the activity of the hypothalamic-pituitary-adrenal axis, which plays a fundamental role in controlling glucose homeostasis, body adiposity, and other metabolic aspects (107). A bromocriptine quick-release formulation was designed as a glucose-lowering drug and approved for clinical use by the FDA in 2009 (commercialized as CYCLOSET®). Recent evidence indicates that circadian-timed bromocriptine quick-release treatment reduces the sympathetic tone and improves systemic low-grade inflammation in type 2 diabetes subjects (108). Thus, these findings help to explain how circadian-timed DA administration is able to improve the metabolic status of patients and reduce the risk of cardiovascular diseases, independently of their effects on prolactin secretion. However, additional studies are necessary to investigate the potential metabolic effects of circadian-timed administration of DA in hyperprolactinemic subjects.

Finally, human and animal studies indicate that reduction in striatal dopamine causes a decreased peripheral insulin sensitivity in healthy subjects (109, 110). On the other hand, deep brain stimulation that results in dopamine release in the striatal area increases peripheral insulin sensitivity in diabetic and nondiabetic patients. Furthermore, optogenetic activation of dopamine D1 receptor-expressing neurons in the ventral striatum increases glucose tolerance and insulin sensitivity in mice (109). Thus, the central dopamine system regulates systemic glucose homeostasis, so this mechanism should be taken into account for the metabolic effects induced by DA treatment.

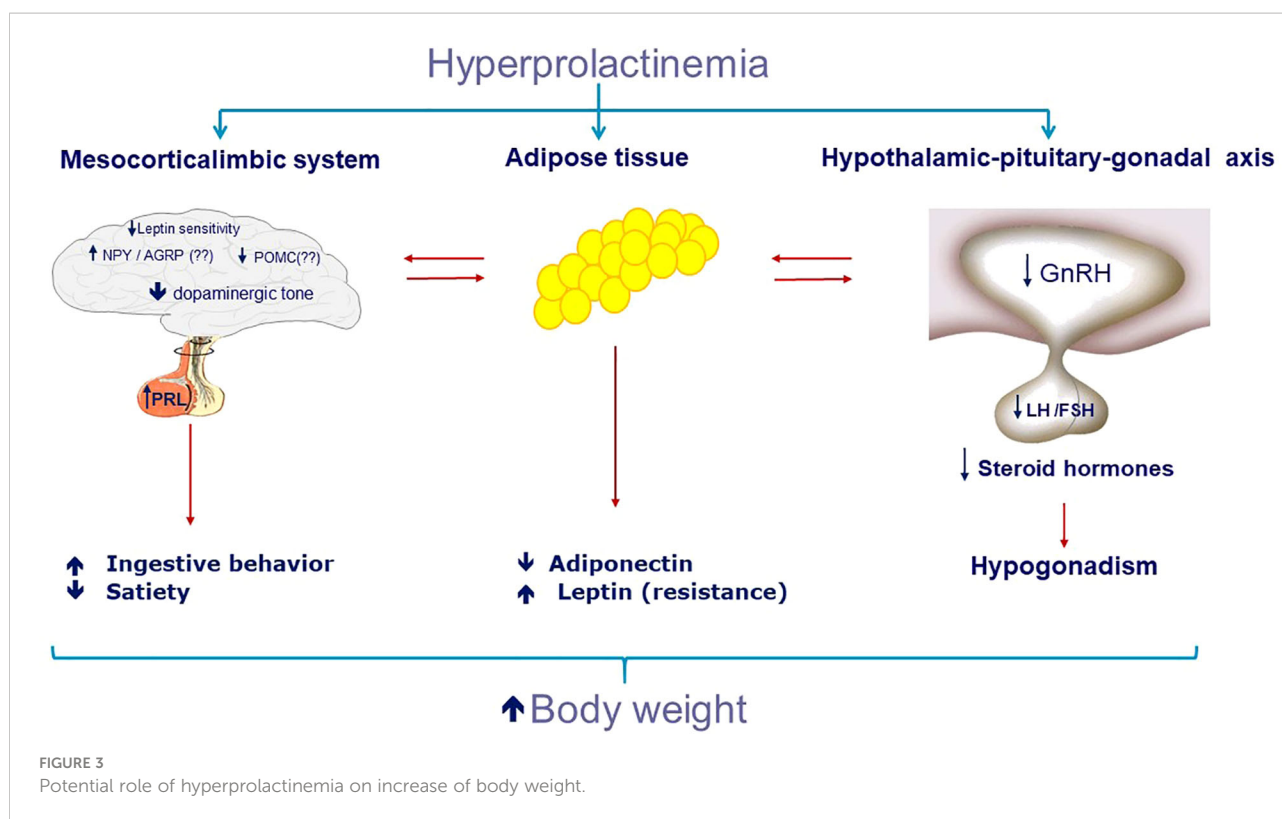
Weight gain and obesity

Body weight is regulated by a complex system that coordinates food intake and energy expenditure. The neuroendocrine system involved in the control of energy balance and body composition comprises the action of several organs including the gastrointestinal tract (pancreas, small intestine, liver), brain, adrenals, and adipose tissue. PRL mRNA is expressed in all of these organs and PRL integrates endogenous or environmental signals to ensure metabolic homeostasis (111–113).

Several animal and human studies (especially in men) describe a higher body weight in patients with hyperprolactinemia (67, 113–115). In some series, the prevalence of obesity and overweight reaches values of 45 and 37%, respectively (46). The exact mechanism has not yet been fully elucidated and may include decreased dopaminergic tonus (101, 116), hypogonadism, low adiponectin (111, 117, 118), and leptin resistance (119) (Figure 3).

Central dopamine is a neurotransmitter, essential to the regulation of food intake, and serves to drive behaviors necessary for food consumption (120). In particular, the mesolimbic dopamine pathway in the midbrain serves to drive behaviors necessary for food consumption by integrating homeostatic signals and modulating the rewarding and motivational value of food (121, 122). Dopaminergic neurons project from the ventral tegmental area (VTA) to the nucleus accumbens and participate in the regulation of the brain reward pathway (123, 124). Several studies point to the role of dopamine in the development and maintenance of diet-induced obesity (125). Also observed in obesity, chronic low-grade inflammation can disturb dopamine tone, which can result in the inability to put in the effort required to achieve the desired goal (123). The two dopamine receptors classes D1 receptor (D1R and D5R) and D2 receptor (D2R, D3R and D4R) are present in the cerebral cortex, the limbic system and the striatum (126). The D1R can influence appetite motivation, stimulating the individual to eat more food. The D2R is also expressed in the pituitary and in the hypothalamus, and is associated with satiety (124, 126, 127). Molecular imaging studies showed structural dopamine alterations in human obesity, especially lower dopamine D2/D3 receptor expression in striatal regions in extreme obesity (128, 129). In contrast to Wang and colleagues (130), most studies show no linear correlation between BMI and D2/D3 receptor binding potential (131). For mild to severe obesity, the evidence points towards higher striatal D2/D3 receptor binding potential, although the picture is less clear (132). Animal studies have found that insulin interacts with dopamine in the VTA and striatum (133) and the administration of insulin directly into the VTA suppresses ingestive behavior (133). Dopaminergic tone suppression has been considered as the mechanism contributing to increased food intake and weight gain in hyperprolactinemia obesity (18, 101, 134–136), together with increased hypothalamic levels of the appetite-stimulating hormones neuropeptide Y and corticotrophin-releasing hormone (136–138). Treatment with DA in hyperprolactinemic patients can lead to weight reduction possibly by increasing dopaminergic tone, beyond normalization of PRL levels and reverting hypogonadism (138).

Regarding sex differences, men with hyperprolactinemia presented higher risk of cardiovascular disease (71) and higher mortality rates (139). Only men with prolactinoma presented significantly higher fat mass and higher levels of cholesterol and LDL-cholesterol, compared to controls (49). On the other hand, in patients harboring prolactinoma, weight and body mass index reduction were more pronounced in men than women, after six months of bromocriptine treatment (101). Usually, men with prolactinoma are later diagnosed compared to women, being exposed to hyperprolactinemia and hypogonadism for a longer period. Additionally, men presented macroprolactinomas in a higher frequency, what could be related to a longer time to recover gonadal axis after treatment is initiated. These aspects could differently impact cardiovascular risks in both sexes.



Adipocytes and preadipocytes possess both androgen (140) and estrogen (141) receptors and an increase in body fat has been demonstrated in hypogonadal women. Then, hyperprolactinemia-induced hypogonadism may explain the changes in the amount of body fat. However, although patients with hypogonadism have higher median levels of PRL, it was not possible to demonstrate weight differences according to gonadal function. PRL has been associated with changes in adiposity and appears to participate in multiple aspects of adipose tissue biology, including adipogenesis, lipolysis, and the release of adipokines such as adiponectin or leptin (121). During adipogenesis, there is an increase in the expression of PRL receptors, which promote adipogenesis through an increase in essential transcription factors such as the peroxisome proliferator-activated receptor- γ (142). In the study by Auffret et al., the absence of PRL signaling could have induced the formation of brown adipocytes, favoring the hypothesis that PRL may be involved in the differentiation of beige adipose tissue from white adipose tissue (143). On the other hand, some authors showed that, in mice, pathological hyperprolactinemia has a strong impact on brown adipose tissue, lowering thermogenic markers and evoking tissue whitening (111) (Figure 4).

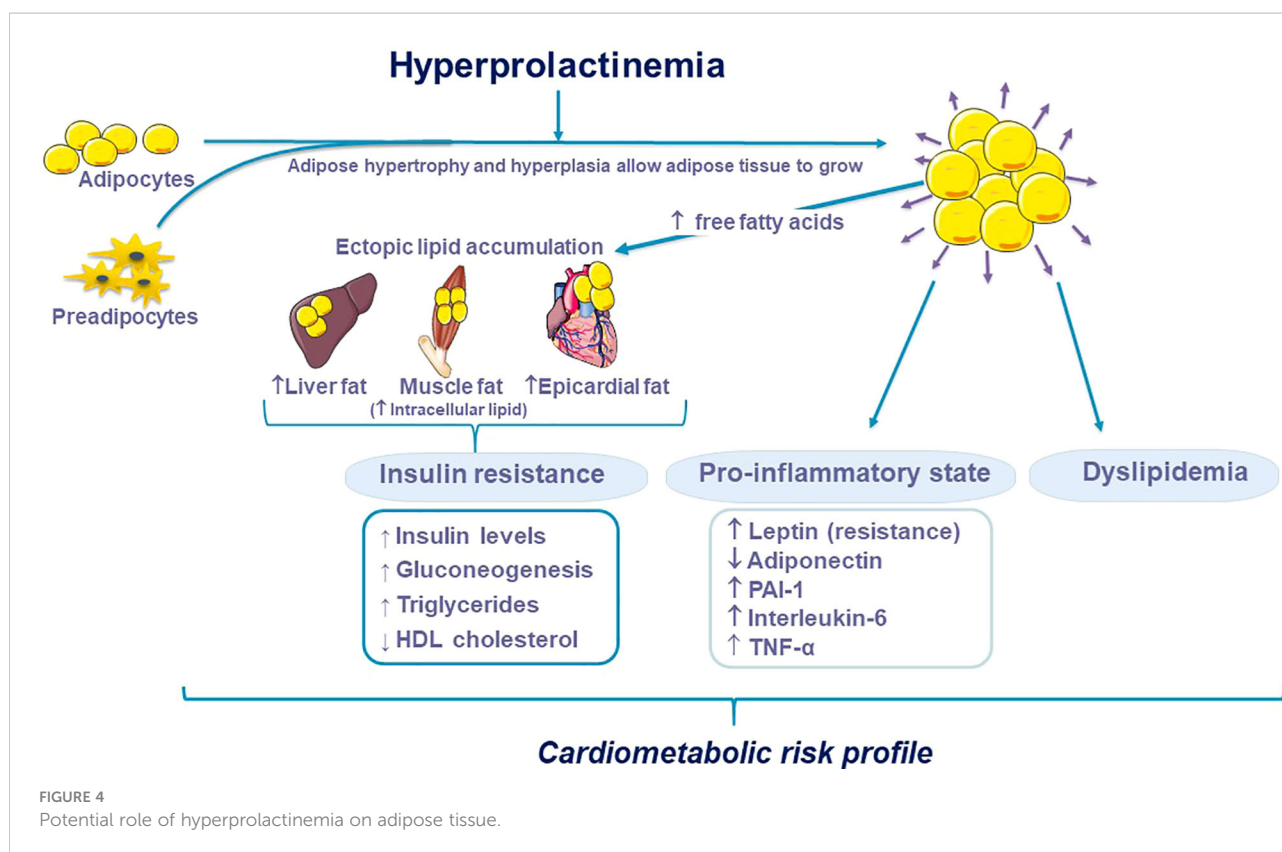
Although PRL decreases serum levels of adiponectin, by influencing its expression and secretion *in vitro*, in patients with prolactinomas there was no association between PRL and adiponectin levels (38). Regarding leptin, its synthesis and secretion are increased either through a direct action of PRL or indirectly through the increase of pro-inflammatory cytokines

(121, 144). In a cohort of patients with prolactinoma, treatment with DA led to a reduction in BMI, and leptin levels were associated with BMI but not with serum PRL (101).

Human adipose tissue is a site of prolactin synthesis and secretion (145, 146). Adipose tissue is surrounded by connective tissue with proteoglycans rich in heparin sulfate, to which prolactin binds, causing most of the locally produced prolactin to be retained (147). It can be speculated that, when produced in large amounts, some of the PRL reaches the peripheral circulation, while when produced in smaller amounts it is retained by the producing cells, transforming prolactin into a true paracrine or autocrine agent. Corroborating this hypothesis, a study showed an increase in basal and pulsatile prolactin secretion in premenopausal women with visceral obesity, compared to lean women (146).

In obese humans, PRL levels were increased in metabolically healthy obesity. The authors suggested that increased circulating PRL might be a compensatory response for favoring energy metabolism during obesity (148).

Hyperprolactinemia is commonly associated with weight gain and obesity in humans (18, 101), although some findings are contradictory (67, 149). Animal studies indicate that PRL acts on the brain by stimulating food consumption, increasing body fat deposits, and promoting resistance to leptin and insulin (150–154). Hyperprolactinemia induces functional blockade of dopaminergic tone, which can be considered among the factors involved in the pathogenesis of hyperphagia and weight gain



observed in patients with hyperprolactinemia, thus contributing to obesity.

The waist circumference and BMI of patients with prolactinomas were found to be significantly higher than in the controls (155). While body fat percentage was similar in nonobese women with prolactinoma compared to controls (19), newly-diagnosed men with prolactinomas had higher body fat content (156). Greenman et al. showed that in patients with prolactinoma treated with DA there was weight reduction in 70% of patients and 90% of men with normal PRL levels (18). Similar results were found in two other studies (101, 157), one of them with more pronounced results in men (101). Despite the high prevalence of obesity and overweight in a cohort of patients with prolactinoma, six months of DA treatment and normal PRL levels did not lead to a significant difference in BMI (46). In other studies, with longer treatment duration, the visceral adiposity index significantly decreased after CAB treatment: 12 months, regardless of the degree of reduction in PRL levels (48), 60-months CAB treatment compared to baseline (45). In a recent systematic review and meta-analysis evaluating metabolic effects of DA in patients with prolactinomas, the pooled standardized mean difference of the primary outcome revealed a reduction in BMI and weight and a subgroup analysis suggested that the reduction of weight was primarily driven by studies with high prolactin levels at baseline (158).

Then, *in vivo* and *in vitro* work has demonstrated that prolactin may increase or decrease adipogenesis. PRL in physiological concentrations plays a role in adipogenesis, adipocyte differentiation, and protection from metabolic syndrome, while in physiological hyperprolactinemia during pregnancy and lactation it presents lipogenic activity. In pathological hyperprolactinemia, PRL predisposes to obesity, induces visceral fat depot hypertrophy, and decreases lipogenesis (112).

Peripartum cardiomyopathy

Another interesting cardiovascular effect described in association with hyperprolactinemia is peripartum cardiomyopathy (PPCM) (159). This is a rare disease associated with late pregnancy or the peripartum period, marked by severe systolic dysfunction leading to reduced ejection fraction and symptoms of heart failure (159, 160). It has been shown that in these patients, for reasons still unknown, cleavage of PRL from its 23 kDa form to a 16 kDa form by cathepsin-D occurs (160). This 16 kDa PRL induces endothelial cell apoptosis, vasoconstriction, reduced metabolism, and cardiomyocyte function, leading to PPCM (161). In 2010, a pilot study using standard treatment associated with bromocriptine in women with PPCM showed an

improvement in ejection fraction at 6 months when compared to the standard therapy group (162). A recent multi-centre randomized study showed that in severe PPCM, patients observed a high left ventricular recovery rate at 6 months with no mortality, even with short-term treatment with bromocriptine (2.5 mg daily for one week) (163) and in 2018 ESC (European Society of Cardiology) Guidelines for the management of cardiovascular diseases during pregnancy states that bromocriptine may be considered in women with newly diagnosed PPCM (164).

Populational studies

In an observational study including 457 normoprolactinemic non-dialyzed CKD patients and 173 hemodialysis patients, PRL levels were directly associated with endothelial dysfunction/stiffness and with increased risk of cardiovascular events and mortality (165). Then, a positive association between serum PRL concentrations and all-cause mortality and cardiovascular mortality was first reported in 2014, with a significant trend across PRL tertials, in a population-based Study of Health in Pomerania, including 3929 individuals (1946 men and 1983 women) aged 20–81 (mean 50.3 years) (166). Dourado et al. reviewed the main common aspects of CKD, prolactinemia, and cardiovascular risk (167). In a study conducted in Denmark, from a cohort of 3633 patients with a median follow-up time of 5.3 years, mean age of 39.7 years, and 78% of females, 10.3% presented hyperprolactinemia, without a history of pituitary disease. In males, hyperprolactinemia was associated with a high age-adjusted incidence ratio for cardiovascular mortality, even after adjusting for confounders such as chronic renal failure, diabetes, and antipsychotic medication (139). Finally, a population-based, retrospective, open-cohort study in the UK included 2233 patients with prolactinoma and 10355 age, sex, BMI, and smoking status-matched controls (1:5 ratio) demonstrated that the incidence of CVD was higher in the prolactinoma group, only amongst males, even after covariate adjustment (71). In a retrospective study including 1204 individuals, followed for 10 years, divided into 4 groups: pituitary disorders (N=331), drug-induced hyperprolactinemia (N=598), hyperprolactinemia due to hypothyroidism (N=79), and idiopathic hyperprolactinemia (N=196), there was an increased risk of death in patients harboring macroadenomas, drug-induced and idiopathic hyperprolactinemia groups, although not related to PRL levels.

However, in other studies, PRL levels were inversely correlated to the risk of diabetes and dyslipidemia. In a large population-based study including 2,377 participants (1,034 men and 1,343 postmenopausal women) without hyperprolactinemia, aged 40 years and older, in Shanghai, China (85), low PRL levels were

associated with risk of diabetes. In another study including 8615 women from the NHS and NHSII, with documented normal serum PRL levels, divided into quartiles, followed up to 10 years, there were 99 incident type 2 diabetes cases reported and diabetes incidence was correlated with the lowest quartile (91), irrespective to menopausal status. In an Indian case-control study, PRL in T2DM patients (n=112) was significantly lower compared to healthy controls (n=112) and PRL levels were inversely correlated with total cholesterol, LDL-cholesterol, and triglycerides (70).

Moreover, PRL levels were not associated with CVD in the other two populational studies. No association was found between normal PRL levels and cardiovascular risk factors in a study including 3232 individuals, mean age 40.4 years, 52.1% women, from the Framingham Heart Study participants who attended 2 examinations an average of 6.1 years apart (94). In a case-control study from a prospective EPIC-Norfolk cohort, men and women, aged 45 to 79 years, who developed fatal or nonfatal coronary arterial disease (882) were compared to controls (1490) regarding serum PRL levels and there was no association between the highest prolactin tertile and CVD (168).

Studies in normoprolactinemic individuals evaluating dyslipidemia, CVD, and CVD mortality populational studies evaluating PRL, CVD risk factors, and CVD mortality are summarized in tables (Table 3) (Table 4).

A meta-analysis and a systematic review evaluating the effect of reducing PRL with DA on established cardiovascular risk factors in 387 patients with prolactinomas suggested, beyond the reduction in weight and BMI, a small decrease in waist circumference, a small-to-moderate decrease in triglycerides, fasting glucose levels, HOMA-IR, HbA1c and hs-CRP, and a moderate decrease in LDL, total cholesterol and insulin, however, data were considered of low-quality evidence (158). Noteworthy, clinical studies have shown that circadian-timed quick-release bromocriptine treatment reduces significantly the risk of major adverse cardiovascular events in type 2 diabetes mellitus, non-hyperprolactinemic patients (109, 169). Among other effects (e.g., improving insulin sensitivity), a potential sympatholytic mechanism has been proposed (170).

Therefore, well-designed studies will be necessary to strengthen or not those findings as well as a better understanding of the mechanism of association between PRL, DA, and cardiovascular risk.

Conclusions

Hyperprolactinemia is classically associated with hypogonadism and reproductive symptoms. Beyond these

TABLE 3 Studies with normoprolactinemic individuals.

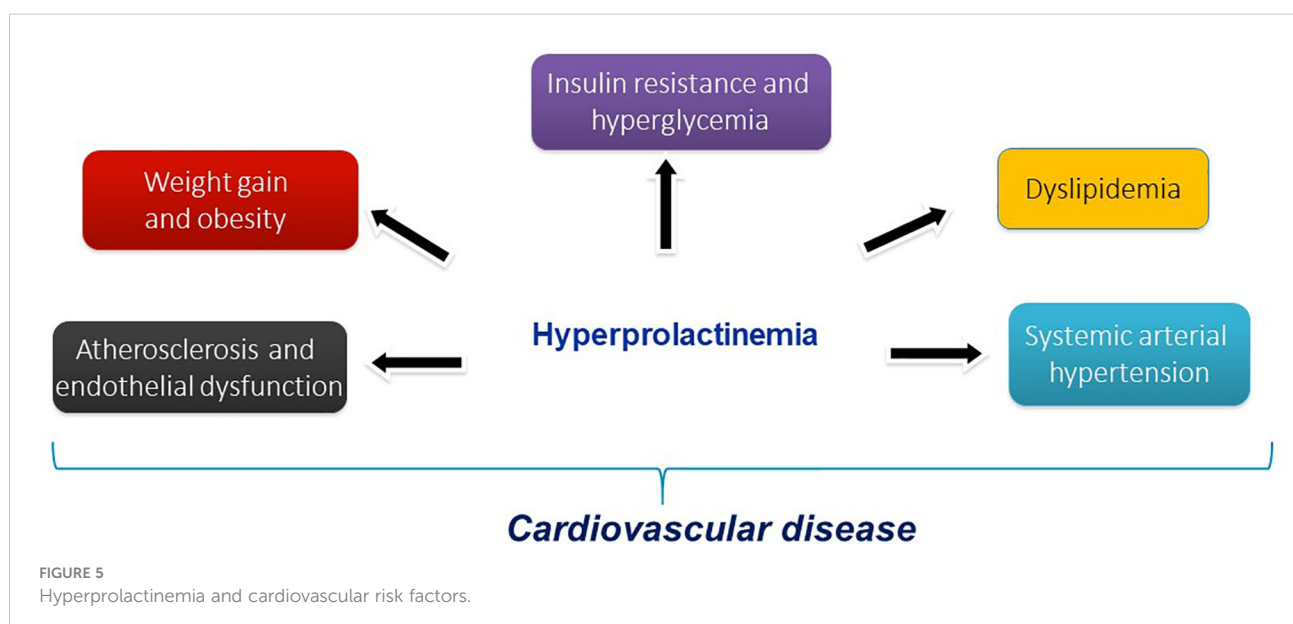
Authors, year	Study design	Population studied	Results
Georgiopoulos et al, 2009 (32)	Cross-sectional study	Postmenopausal women (N=76)	PRL levels associated with blood pressure and arterial stiffness
Reuwer et al, 2009 (168)	Prospective Cohort	Patients with fatal or nonfatal CVD (N=882) and healthy controls (N=1490)	No association between higher tertile levels of PRL and CVD
Carrero et al, 2012 (165)	Prospective cohort	Patients with CKI without dialysis (N=457) and 173 in dialysis (N=173).	PRL is associated with endothelial dysfunction/stiffness and with an increased risk of CVD and mortality in both groups
Jayashankar et al, 2022 (89)	Case-control	Patients with T2DM (N=112) vs Healthy control (N=112)	PRL in T2DM patients was significantly lower compared to healthy control. PRL levels were inversely correlated with total cholesterol, LDL-cholesterol, and TG, but not with HDL cholesterol.

MIC, microprolactinoma; MAC, macroprolactinoma; CAB, cabergoline; BRC, bromocriptine; DA, dopamine agonist; CRP, C reactive protein; PRL, prolactin; OR, odds ratio; CKI, chronic kidney insufficiency; T2DM, type 2 diabetes mellitus; FMD, flow mediated dilation; TG, triglycerides; AT-III, Antithrombin- III; PAI-1, plasminogen activator inhibitor 1; MRI, magnetic resonance imaging.

TABLE 4 Populational studies.

Authors, year	Study design	Population studied	Results
Haring et al, 2014 (166)	Population study	3929 individuals aged 20–81 yrs from the population-based Study of Health in Pomerania	Independent positive association of PRL levels with all-cause and cardiovascular mortality
Therkelsen et al, 2016 (94)	Population study (prospective)	3232 patients with normoprolactinemia were drawn from Framingham Heart Study, who attended 2 examinations 6 years apart	PRL was not associated with a CVD risk factor. In women, for each 5-mg/dL increment in PRL, increase OR for low HDL-cholesterol. In men, a 5-mg/dL increment in PRL was associated with increased OR of hypertension and diabetes
Krogh et al, 2017 (139)	Prospective Cohort	3633 individuals (mean age 39.7 years, 78% women)	373 patients developed hyperprolactinemia: there was an association between hyperprolactinemia and an increased risk of death from all causes and cardiovascular causes only in men

MIC, microprolactinoma; MAC, macroprolactinoma; CAB, cabergoline; BRC, bromocriptine; DA, dopamine agonist; CRP, C reactive protein; PRL, prolactin; OR, odds ratio; CKI, chronic kidney insufficiency; T2DM, type 2 diabetes mellitus; FMD, flow mediated dilation; TG, triglycerides; AT-III, Antithrombin- III; PAI-1, plasminogen activator inhibitor 1; MRI, magnetic resonance imaging.



effects, hyperprolactinemia presents recognized metabolic influences. However, the clinical impact of PRL role on metabolism and cardiovascular risk is not established.

Accordingly, no consistent data supports that DA treatment or normalization of PRL levels can prevent cardiovascular events (9). Studies suggested that DA treatment could improve CVD risk, either directly by normalizing serum PRL levels and reducing dopamine tone, or indirectly by restoring eugonadism. More studies evaluating CVD risk in hyperprolactinemic patients are important to define a potential indication of treatment beyond hypogonadism. Interestingly enough, low levels of PRL in population studies were associated with diabetes mellitus type 2 risk and metabolic syndrome (102). However, there are no data pointing to a negative influence of low serum PRL levels during DA treatment in glucose metabolism.

DA improves metabolic parameters such as glucose profile, and insulin resistance in patients with diabetes mellitus (171, 172) and patients with prolactinoma (38, 45). Cabergoline was able to improve metabolic parameters even without the correction of PRL excess (45, 48) or concomitant hypogonadism (47, 156). Similarly, both BRC and CAB have been demonstrated to significantly improve lipid profile independently of their impact on concomitant obesity (45, 47, 48, 156) and hypogonadism (47), leading to the hypothesis of a direct beneficial effect of DA on lipid profile (45, 47).

In conclusion, hyperprolactinemia seems to be associated with insulin resistance and hyperglycemia, dyslipidemia, weight gain and obesity, systemic arterial hypertension, atherosclerosis

and endothelial dysfunction increasing CVD (Figure 5). Additionally, hyperprolactinemia can be associated with metabolic abnormalities such as obesity, insulin resistance, and alterations in glucose metabolism that could accelerate atherosclerosis (173).

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Conflict of interest

The authors declare that this review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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