Review

The Metabolic Consequences of Hyperprolactinemia

Roman Smolarczyk , Christian Unogu , Anna Duszewska , Anna Szeliga , Monika Grymowicz , Anna Kostrzak , Ewa Rudnicka , Marzena Maciejewska-Jeske , Katarzyna Smolarczyk , Gregory Bala , Blazej Meczekalski *

Posted Date: 5 May 2026

doi: 10.20944/preprints202605.0234.v1

Keywords: hyperprolactinemia; prolactin; insulin resistance; dyslipidemia; obesity; metabolic syndrome; cardiovascular risk; bone mineral density; dopamine agonists; endocrine disorders

 doi:10.20944/preprints202605.0234.v1

Review

The Metabolic Consequences of Hyperprolactinemia

Roman Smolarczyk [1], Christian Unogu [2], Anna Duszewska [3], Anna Szeliga [2], Monika Grymowicz [1], Anna Kostrzak [2], Ewa Rudnicka [1], Marzena Maciejewska-Jeske [2], Katarzyna Smolarczyk [4], Gregory Bala [5] and Blazej Meczekalski [2,*]

[1] Department of Gynaecological Endocrinology, Medical University of Warsaw, Warsaw, Poland
[2] Department of Gynaecological Endocrinology, Poznan University of Medical Sciences, Poznan, Poland
[3] Department of Morphological Sciences, Faculty of Veterinary Medicine, Warsaw University of Life Sciences, Poland
[4] Department of Dermatology Medical, Warsaw Medical University, 00-927 Warsaw, Poland
[5] UCD School of Medicine, University College Dublin, Dublin, Ireland
* Correspondence: blazejmeczekalski@yahoo.com

Abstract

Hyperprolactinemia, defined as persistently elevated serum prolactin levels, is a common endocrine disorder with systemic metabolic consequences that extend beyond its classical roles in lactation and reproductive function. This review summarizes current evidence regarding the interplay between prolactin excess and metabolic regulation. Chronic hyperprolactinemia is associated with increased appetite, weight gain, and elevated BMI, likely mediated through altered dopaminergic tone, leptin resistance, and direct effects on adipose tissue. Dyslipidemia is frequently observed, characterized by elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, alongside reduced high-density lipoprotein cholesterol (HDL-C). Additionally, prolactin excess contributes to impaired glucose homeostasis, manifesting as increased fasting glucose levels, elevated HbA1c, and insulin resistance. Emerging data also suggest associations with endothelial dysfunction, cardiovascular risk, neuropsychiatric disturbances, and reduced bone mineral density. These findings support the conceptualization of hyperprolactinemia as a multisystem disorder requiring comprehensive clinical evaluation and management. Further studies are needed to elucidate the underlying mechanisms and optimize therapeutic strategies.

Keywords: hyperprolactinemia; prolactin; insulin resistance; dyslipidemia; obesity; metabolic syndrome; cardiovascular risk; bone mineral density; dopamine agonists; endocrine disorders

Prolactin as a Classical Hormone Synthesized and Secreted by Lactotroph Cells of the Anterior Pituitary Gland

Prolactin (PRL), also known as lactotropin or mammotropin, is a polypeptide hormone synthesized and secreted by lactotroph cells of the anterior pituitary gland [1]. The secretion of prolactin is primarily regulated by dopamine. Prolactin is composed of 199 amino acids and possesses a chemical structure similar to that of growth hormone and placental lactogen.

Prolactin was first discovered in animals, including sheep, cattle, and birds, and was subsequently confirmed in humans in 1970 by Henry Friesen [2].

Approximately 85% of circulating prolactin exists in the monomeric form, with a molecular weight of 23 kDa. This form is recognized as biologically active [3]. Different forms of prolactin circulate in the blood serum, including a dimeric form (molecular weight 48–56 kDa) and a macroprolactin form (molecular weight 150–170 kDa). Macroprolactin is biologically inactive and is composed of prolactin bound to antiprolactin autoantibodies [4].

In women, prolactin is essential for milk production and lactation, stimulating the proliferation of breast alveolar elements during pregnancy and the postpartum period [5]. During pregnancy,

 doi:10.20944/preprints202605.0234.v1

rising estrogen levels stimulate the proliferation of lactotroph cells in the pituitary gland, leading to increased prolactin secretion.

Prolactin also exerts significant effects on metabolic homeostasis, neurodevelopment, neuroprotection, and immunoregulation. Recent studies have focused on the effects of prolactin on food intake and body weight [6]. Most recently, prolactin is recognized as having a novel impact on BMI, total cholesterol, LDL cholesterol, and triglycerides.

Hyperprolactinemia: Clinical Conditions and Etiologies

Hyperprolactinemia is one of the most frequently diagnosed clinical disorders in routine endocrine practice and affects approximately 5–10% of women with secondary amenorrhea.

The normal reference range for serum prolactin is approximately 5–20 ng/mL. Excess prolactin secretion may occur in various physiological and pathological conditions and can also be drug-induced. Physiological hyperprolactinemia occurs following coitus, exercise, chronic stress, and during sleep, as well as naturally during pregnancy and breastfeeding [7].

The most common cause of non-tumoral hyperprolactinemia is medication. Among the drugs that can induce elevated serum prolactin concentrations are oral contraceptives, antipsychotics (including phenothiazines, risperidone, haloperidol, olanzapine, amisulpride, clozapine, and quetiapine), antiemetics (such as metoclopramide, domperidone, and prochlorperazine), antidepressants (including tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs], monoamine oxidase inhibitors, and serotonin-norepinephrine reuptake inhibitors [SNRIs] such as venlafaxine), antihypertensives (e.g., verapamil), antihistamines (H2 receptor blockers), and opiates [8].

Prolactinoma is a pituitary adenoma that secretes prolactin. Prolactinomas account for approximately 40% of all pituitary adenomas and occur more commonly in women. Based on size, they are classified as either microprolactinomas (diameter <10 mm) or macroprolactinomas (diameter ≥10 mm). Most adenomas (approximately 90%) are microadenomas and remain asymptomatic. The classical clinical presentation of a pituitary tumor includes menstrual irregularity, galactorrhea, infertility, headache, and visual field changes [9].

Certain systemic disorders can also lead to elevated serum prolactin concentrations. These include polycystic ovarian syndrome (PCOS), chronic kidney disease, hepatic cirrhosis, and chest wall irritation (resulting from trauma, herpes zoster, or surgery).

Effects of Prolactin Excess on Food Intake and Body Weight

Prolactin exerts numerous metabolic effects through the regulation of energy balance and cellular metabolism in both the central nervous system and peripheral organs. These pleiotropic actions of prolactin likely play a crucial role in adapting the maternal body to the biological demands of pregnancy and lactation [10].

Chronic hyperprolactinemia has been linked to increased food intake and weight gain [11]. Patients with pathological hyperprolactinemia due to prolactinoma or chronic blockade of dopamine receptors in the course of psychiatric treatment are observed to have a higher BMI and increased prevalence of obesity [12,13]. The proposed pathophysiology of obesity in patients with prolactinomas includes decreased dopaminergic tone, hypogonadism, hypothalamic compression, development of leptin resistance, and direct effects on adipose tissue [14].

Reduction in hypothalamic dopaminergic neurotransmission observed in hyperprolactinemia is associated with increased appetite and altered regulation of energy expenditure. Normalization of prolactin levels through treatment with dopamine agonists has been associated with weight loss in some studies [15]. Hypothalamic compression is proposed as a mechanism for weight gain; however, this hypothesis has yet to receive adequately confirmation. Some authors speculate that hypogonadism, which affects adipose tissue distribution, may also contribute to adverse metabolic

 doi:10.20944/preprints202605.0234.v1

and weight profiles. Nevertheless, animal experiments provide evidence that prolactin stimulates appetite independently of sex steroids [16].

It is well established that the anorexigenic pro-opiomelanocortin (POMC) neurons and the orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons of the arcuate nucleus within the hypothalamus play a crucial role in the regulation of appetite. However, studies suggest that it is unlikely that prolactin increases appetite through direct influence on these neurons [17]. Leptin, another well-known hormone regulating food intake, acts in the hypothalamus by stimulating POMC neurons and suppressing NPY/AgRP neurons, thereby decreasing appetite [18]. It has been suggested that elevated levels of prolactin induce leptin insensitivity [19].

Prolactin influences adipose tissue development. PRL not only impacts adipogenesis and adipocyte function but is also synthesized within adipose tissue itself, potentially acting as both an endocrine and paracrine agent [20]. Studies in rodent models have demonstrated that females may be more susceptible to the influence of hyperprolactinemia on energy balance and that prolactin can exert both positive and negative effects on adipose tissue accumulation [21–24].

This is consistent with the proposed dual role of prolactin in both fat mass accretion during pregnancy and fat mass mobilization during lactation. Prolactin may either increase or decrease adipogenesis and affects both white and brown adipose tissue depots. White adipose tissue (WAT) functions as an energy reservoir and as an endocrine organ capable of secreting metabolic adipokines. Brown adipose tissue (BAT) actively participates in thermogenesis and provides protection against hypothermia and obesity. Results from rodent models are mixed: chronically high prolactin levels have been shown to stimulate adipose accretion in some studies, while others demonstrated a small reduction in retroperitoneal fat mass [24,25]. Moreover, low serum PRL level were also associated with visceral adipocyte hypertrophy [26]. The exact mechanisms by which PRL regulates fat tissue depots requires further study.

Hyperprolactinemia and the Lipid Profile

Disruption of lipid metabolism is a common finding in hyperprolactinemia [27,28]. Patients with elevated prolactin levels exhibit increased concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides [29]. Decreased levels of high-density lipoprotein (HDL) cholesterol have also been reported in these patients [30]. In particular, increased total cholesterol, LDL-cholesterol, and triglycerides, alongside decreased HDL-cholesterol, have been observed more frequently in patients with prolactinomas than in healthy control subjects [31]. In a study by Posawetz et al. (2021), patients with prolactinomas demonstrated significantly higher body mass index (BMI) and LDL-cholesterol levels, as well as significantly lower HDL-cholesterol levels [32]. Subsequent studies have reported similar results [33,34]. Excess prolactin affects lipid intake, synthesis, and utilization [11]. Patients with elevated prolactin levels experience hyperphagia and increased appetite, leading to elevated calorie intake [35]. Moreover, high prolactin levels facilitate the release of free fatty acids from adipose tissue, thereby promoting LDL secretion [36]. Hyperprolactinemia also enhances hepatic fatty acid synthesis. In a calorimetry-based study of patients with elevated prolactin levels, decreased insulin sensitivity impaired the peripheral degradation and metabolism of fatty acids [37]. Additionally, significant decreases in apolipoprotein A-I and apolipoprotein A-II have been observed in hyperprolactinemic women compared with healthy controls. Impairment of apolipoprotein biosynthesis induced by prolactin excess has been proposed as a potential mechanism for the lower apolipoprotein levels observed in these patients [38].

A direct effect of prolactin on lipid metabolism has been suspected, as increased prolactin receptor expression has been observed during adipocyte differentiation, suggesting its involvement in the regulation of mature adipocytes [39]. It has also been suggested that dopaminergic tone may influence adipose tissue regulation due to the expression of dopamine D2 receptors (D2DR) on human adipocytes [40]. In patients with prolactin excess treated with bromocriptine or cabergoline, improvements in lipid profiles were observed regardless of changes in body weight and BMI [41].

 doi:10.20944/preprints202605.0234.v1

Dopamine agonists could influence lipid metabolism through D2DR activation, independent of food intake and body weight [42].

Additionally, hyperprolactinemia-induced hypogonadism may also contribute to adverse body composition and dyslipidemia, particularly in men, as androgen deficiency itself increases body fat and facilitates lean mass reduction [43]. In women, hypoestrogenism caused by hypogonadism during hyperprolactinemia also leads to decreased HDL cholesterol and increased total and LDL cholesterol [44].

Recent results from several studies suggest that prolactin deficiency may also be associated with dyslipidemia and metabolic complications [45]. In young women with previously elevated prolactin levels treated with cabergoline, low prolactin levels have been associated with higher triglyceride and lower HDL levels compared to healthy controls. The lipid profiles of similar young women but who achieved normal prolactin levels after administered cabergoline did not differ significantly from healthy controls [46]. Serum prolactin concentrations below the normal range have also been associated with adipocyte hypertrophy in visceral adipose tissue, impaired insulin sensitivity, and elevated body mass index (BMI), blood pressure, and waist circumference [47,48].

Chronic Prolactin Excess and the Glucose-Insulin Profile: Implications for HbA1c, Fasting Glucose, HOMA-IR, and Insulin Secretion

Chronic hyperprolactinemia, a condition characterized by persistently elevated serum prolactin, has been shown to impact various metabolic processes, including glucose and insulin regulation. Prolactin, a hormone traditionally associated with lactation, is also involved in the regulation of multiple body systems. Evidence from recent studies suggests that prolonged prolactin excess may lead to dysregulation of glucose metabolism, resulting in impaired insulin sensitivity and glucose intolerance.

Prolactin and Insulin Sensitivity

One of the most significant metabolic disturbances associated with chronic prolactin excess is alteration of the glucose-insulin profile. Studies have demonstrated increases in HbA1c, fasting glucose, and insulin resistance in individuals with prolonged hyperprolactinemia. Elevated prolactin levels have been linked to the development of insulin resistance, which is often quantified using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Hyperprolactinemia-induced insulin resistance is thought to occur through multiple mechanisms, including increased adiposity and direct effects of prolactin on insulin signaling pathways.

A recent study demonstrated that patients with chronic prolactin excess had significantly higher HbA1c levels compared to healthy controls, suggesting chronic glycemic dysregulation. The increase in HbA1c levels is indicative of prolonged hyperglycemia, a key factor in the development of type 2 diabetes. Additionally, fasting glucose levels in these patients were also elevated, further indicating that hyperprolactinemia impairs glucose homeostasis [49].

Insulin Secretion and Resistance

The secretory response of insulin is an important aspect of metabolic dysfunction observed in chronic hyperprolactinemia. Insulin secretion may be altered in individuals with high prolactin levels, resulting in inappropriate compensatory insulin release to overcome insulin resistance. Despite elevated insulin levels, insulin sensitivity remains compromised, as evidenced by higher HOMA-IR scores in affected individuals [50]. Elevated prolactin may interfere with pancreatic β-cell function, affecting insulin secretion and exacerbating insulin resistance.

Interestingly, several studies have suggested that treatment of hyperprolactinemia, often with dopamine agonists such as bromocriptine, may improve the glucose-insulin profile. Normalization of prolactin levels has been shown to reduce HbA1c, fasting glucose, and insulin resistance markers, suggesting that prolactin plays a direct role in glucose metabolism [51].

 doi:10.20944/preprints202605.0234.v1

Table 1. Summary of Key Metabolic Parameters in Chronic Hyperprolactinemia.

Parameter	Control Group (n=50)	HPRL Group (n=50)	P-value
HbA1c (%)	5.4 ± 0.3	6.2 ± 0.4	<0.05
Fasting Glucose (mg/dL)	90 ± 10	115 ± 12	<0.01
HOMA-IR	1.0 ± 0.2	2.5 ± 0.3	<0.01
Secretory Insulin (μU/mL)	10 ± 3	16 ± 4	<0.05

(Adapted from Jahan et al., 2020).

Mechanisms Behind Prolactin-Induced Metabolic Changes

The exact molecular mechanisms linking chronic prolactin excess to metabolic disturbances remain incompletely understood; however, several hypotheses have been proposed. Prolactin may interfere with insulin signalling pathways, leading to reduced glucose uptake in tissues such as skeletal muscle and adipose tissue. In addition, prolactin has been shown to influence adipogenesis and lipid metabolism, which may indirectly exacerbate insulin resistance [52].

Furthermore, chronic elevation of prolactin has been associated with increased cortisol levels, which are known to impair glucose metabolism. This effect may further compound the impact of hyperprolactinemia on glucose homeostasis and insulin regulation.

Chronic hyperprolactinemia is increasingly recognized as a contributor to metabolic disturbances, particularly in the regulation of glucose and insulin. Observed increases in HbA1c, fasting glucose, and markers of insulin resistance in affected patients underscore the importance of addressing prolactin excess as part of a comprehensive metabolic management strategy. Future research should focus on elucidating the precise mechanisms by which prolactin excess leads to metabolic dysfunction, as well as evaluating the therapeutic potential of normalizing prolactin levels in these patients.

Skin

Prolactin (PRL) exerts effects on the skin and its appendages. PRL receptors are widely expressed in the skin, including in the hair follicle, sebaceous gland, eccrine sweat gland, epidermis, adipose tissue, and lymphocytes [53]. Associations between elevated PRL levels and the exacerbation of certain skin diseases have been described in the literature, including its potential role in acne and hair loss [54,55].

Hair

Several studies have sought to evaluate the prevalence of hyperprolactinemia in both women and men with hair loss [54,56,57]. Potential hormonal contributors to androgenetic hair loss have been investigated by Schmidt et al., who demonstrated that PRL levels increased following thyrotropin-releasing hormone (TRH) stimulation. It has also been suggested that complex interactions between thyroid hormones and androgens in hyperthyroid patients contribute to the development of androgenetic hair loss [57]. Evidence from in vitr

models indicates that only supraphysiological concentrations of prolactin exert an inhibitory effect on human hair follicles [54] and this postulation is not confirmed beyond in vitro models. As there is no definitive evidence to suggest an influence on the extent or duration of androgenetic alopecia, it is suggested that elevated prolactin levels not be considered a causative factor in hair loss.

Acne Vulgaris

Patients with acne frequently seek to identify an underlying cause and often request hormonal evaluation. However, it remains unclear whether routine measurement of prolactin levels is justified in this context. Szybiak et al. reported that patients with acne had significantly higher serum PRL levels compared with control subjects [55]. Similar findings have been described in other studies

 doi:10.20944/preprints202605.0234.v1

[58,59]. Despite these observations, routine measurement of prolactin levels in patients with acne is not generally recommended and should be reserved for cases in which clinical features suggest an underlying endocrine disorder.

Psoriasis

The role of PRL in the pathogenesis of psoriasis, its serum levels in affected patients, and its correlation with disease activity have been investigated in multiple studies. Girolomoni et al. demonstrated, in an in vitro study, that PRL may contribute to the pathogenesis of psoriasis by stimulating keratinocyte proliferation, enhancing T-lymphocyte interferon-gamma production, and promoting angiogenesis [60].

Serum prolactin levels in patients with psoriasis have also been examined. In one study, 55 male patients from India aged 22–66 years with chronic plaque psoriasis of at least six months' duration were enrolled. PRL levels in patients with psoriasis vulgaris were significantly higher compared with those in patients with atopic dermatitis and in healthy controls [61]. A smaller study involving 20 patients confirmed these findings and additionally demonstrated a reduction in prolactin levels following treatment of psoriatic lesions [62]. These findings have been confirmed in a number of other studies as well [63,64].

Hyperprolactinemia and Cardiovascular Disease (CVD) Risk

Cardiovascular diseases (CVDs) are among the leading causes of morbidity and mortality worldwide. Multiple etiological factors contribute to CVDs, including endocrine disturbances such as elevated prolactin (PRL) levels, although the evidence regarding the direct impact of PRL on CVD risk remains inconsistent [65–69]. Hyperprolactinemia may occur under physiological, pathological, or idiopathic conditions, and its levels may vary according to factors such as sex, age, pregnancy, lactation, and the menstrual cycle [69,70].

PRL exists in several isoforms, including full-length PRL (23 kDa), big PRL (a dimer of the monomeric form), big-big PRL (complexes of monomeric PRL and IgG autoantibodies), and vasoinhibins (5.6, 14, 16, 18, and 22 kDa). PRL receptors (PRLRs), particularly those binding the 23 kDa isoform, play a key role in mediating its biological activity, as they do not bind vasoinhibins or other isoforms and therefore activate distinct intracellular pathways. Although vasoinhibins exert biological effects via receptors on target cells, these receptors have not yet been fully characterized. Both PRL and vasoinhibins act on endothelial cells, immune cells, fibroblasts, pericytes, and vascular smooth muscle cells in paracrine and autocrine manners. They may either stimulate or inhibit vascular processes such as proliferation, dilation, permeability, and regression. Specifically, 23 kDa PRL promotes angiogenesis, whereas vasoinhibins exhibit antiangiogenic effects and inhibit vascular remodeling, vasodilation, vasoconstriction, and capillary dissociation [71].

The 23 kDa PRL isoform does not appear to exert deleterious effects on cardiac function. In contrast, the 16 kDa isoform has been shown to impair cardiac microcirculation, reduce cardiac function, and promote ventricular dilatation and cardiomyocyte damage [71,72].

Even modest increases in PRL levels have been associated with elevated serum endocan concentrations, a glycoprotein released by vascular endothelium and considered a marker of endothelial dysfunction in conditions such as coronary artery disease, acute myocardial infarction, and hypertension [73]. Under physiological conditions, hyperprolactinemia has been associated with incident hypertension, a potential predictor of aortic stiffness and endothelial dysfunction [69]. Moreover, chronic exposure to pathologically elevated prolactin levels has been linked to hypertension, endothelial dysfunction, obesity, increased visceral adiposity, insulin resistance, dyslipidemia, and atherosclerosis, thereby increasing overall cardiovascular risk [66,69]. Interestingly, in idiopathic hyperprolactinemia, no significant increase in central or peripheral blood pressure or vascular stiffness has been observed [66,74].

PRL is also thought to modulate inflammatory processes by stimulating vascular smooth muscle cells and promoting adhesion of circulating mononuclear cells to the endothelium [66]. While this

 doi:10.20944/preprints202605.0234.v1

may contribute to the progression of atherosclerotic disease, it does not appear to directly increase the incidence of ischemic events [67].

Elevated levels of the 16 kDa PRL isoform have been implicated in myocardial damage. Epicardial adipose tissue may further contribute to inflammation and atherosclerosis through the secretion of paracrine pro- and anti-inflammatory cytokines [66]. These mechanisms may play a role in the pathogenesis of peripartum cardiomyopathy (PPCM), which is characterized primarily by left ventricular dysfunction and reduced left ventricular ejection fraction [67,71,75,76].

Hyperprolactinemia may also influence cardiovascular disease risk indirectly through its interactions with metabolic disorders such as diabetes mellitus, thereby contributing to increased cardiovascular mortality [67,77]. Additional indirect associations have been observed between prolactin, blood pressure regulation, and renal function. Prolactin levels are also strongly associated with N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker of cardiac function [78,79].

Hyperprolactinemia is commonly observed in patients with pituitary adenomas (prolactinomas), and in such cases may contribute to premature atherosclerotic disease in both women and men [80]. Furthermore, elevated prolactin levels in these patients have been associated with increased carotid intima–media thickness, a recognized marker of subclinical atherosclerosis and early vascular damage [67].

Prolactin and Psycho-Neuro-Cognitive Health

Hyperprolactinemia and the Brain

Prolactin receptors are widely expressed in the brain, particularly in the hypothalamus. Prolactin exerts well-characterized actions within the nervous system, including regulation of its own secretion, stimulation of neurogenesis, modulation of pain and stress responses, and neuroprotection against excitotoxicity [81].

It should be emphasized that prolactin excess, as observed in hyperprolactinemia, exerts effects on the brain that differ in important respects from those seen at physiological prolactin levels [82]. These effects are complex and multifactorial and may be classified as both direct and indirect. In addition, hyperprolactinemia may influence anatomical, biochemical, and neurohormonal aspects of brain function [83].

Hyperprolactinemia has been associated with depression and anxiety. The underlying mechanisms are thought to involve disruption of neurotransmitter systems, particularly those mediated by serotonin and dopamine. Prolactin inhibits dopamine release and alters dopamine receptor sensitivity, which may contribute to the development of neuropsychiatric disorders, including depression, psychosis, and other mood disturbances. Furthermore, elevated prolactin levels have been shown to affect the serotonergic system, potentially exacerbating symptoms of depression and anxiety [84]. Several studies have demonstrated that hyperprolactinemia is associated with grey matter loss in the left hypothalamus and prefrontal cortex [85]. These brain regions play critical roles in memory processing and emotional regulation.

Hyperprolactinemia has a significant impact on cognitive function and is reported to reduce global cerebral blood flow, particularly affecting the temporal and frontal gyri [86]. In 1992, Grattan-Smith et al. conducted one of the first studies in this area, demonstrating that neuropsychological changes are common in patients with hyperprolactinemia, particularly those with pituitary adenomas, and therefore warrant clinical attention [87].

The impact of hyperprolactinemia on cognition includes reduced attentional processing, impaired working memory, and decreased overall cognitive performance. Some studies have suggested that the severity of these impairments correlates with the degree of prolactin elevation [88]. Xu et al. evaluated 295 patients with severe mental disorders (SMD) and 195 healthy controls, demonstrating a significant association between elevated prolactin levels and cognitive impairment in female patients with SMD. These findings underscore the importance of monitoring prolactin levels to prevent cognitive decline in this population [89].

 doi:10.20944/preprints202605.0234.v1

Another important effect of hyperprolactinemia is its impact on the hypothalamic–pituitary–adrenal (HPA) axis. Hyperprolactinemia leads to activation of this axis, resulting in increased serum levels of dehydroepiandrosterone sulfate (DHEA-S) and cortisol [90]. Consequently, affected patients may experience symptoms such as anxiety, hostility, and depression.

Further studies are required to better characterize the broad spectrum of effects of hyperprolactinemia on brain function.

Hyperprolactinemia and Bone Mineral Density

Hyperprolactinemia is increasingly recognized as an important secondary cause of impaired skeletal health, with detrimental effects on bone mineral density (BMD), bone microarchitecture, and fracture risk. The mechanisms underlying bone loss in this context are multifactorial. Traditionally, reduced BMD in hyperprolactinemic patients has been attributed primarily to hypogonadotropic hypogonadism, with estrogen deficiency leading to increased bone resorption and reduced bone formation. However, more recent evidence suggests that prolactin excess may also directly contribute to skeletal fragility through its effects on osteoblast and osteoclast function, as well as through disturbances in calcium homeostasis, although the relative contribution of direct versus indirect mechanisms remains incompletely defined [90,91].

The identification of prolactin receptor (PRLR) expression on osteoblasts in both trabecular and cortical bone has led to the hypothesis that prolactin may exert direct skeletal effects. Notably, prolactin appears to have bimodal actions on bone metabolism, influencing both osteoblastogenesis and bone formation, which may help explain the adverse skeletal outcomes observed in both hypo- and hyperprolactinemic states [91]. Experimental studies have shown that PRLR knockout mice exhibit delayed bone formation, supporting a physiological role for prolactin in bone remodelling.

In addition to its inhibitory effects on osteoblast function, prolactin promotes osteoclastogenesis through several mechanisms. It enhances the expression of receptor activator of nuclear factor κB ligand (RANKL), including at the mRNA level, thereby stimulating osteoclast differentiation and activity. Furthermore, prolactin upregulates other osteoclastogenic mediators, such as monocyte chemoattractant protein-1, cyclooxygenase-2, and ephrin-B1, suggesting a role in modulating osteoblast–osteoclast crosstalk. Importantly, the effects of prolactin on bone cells appear to be concentration-dependent. High prolactin levels (approximately 100 ng/mL) reduce osteoblast number while increasing early differentiation markers, whereas lower concentrations (10–100 ng/mL) may reduce osteoclast activity by promoting apoptosis. These findings indicate a complex, dose-dependent regulation of bone metabolism [91].

Contemporary evidence suggests that trabecular bone is particularly vulnerable to the effects of prolactin excess. A 2024 systematic review and meta-analysis demonstrated that patients with prolactinomas had significantly lower lumbar spine Z-scores compared with controls, whereas findings at the femoral neck were less consistent. This supports the concept that prolactin excess preferentially affects trabecular rather than cortical bone. Importantly, the same analysis reported a significantly increased fracture risk in patients with prolactinomas, with an odds ratio of 3.21 compared with controls [92].

High-resolution peripheral quantitative computed tomography (HR-pQCT) studies have demonstrated significant microarchitectural impairment in patients withprolactinomas. Trabecular thickness was reduced at both the radius [MD −0.01; 95% CI: −0.02 to −0.00; P = 0.0006] and tibia [MD −0.01; 95% CI: −0.02 to −0.00; P = 0.03], while cortical thickness at the radius was also significantly decreased [MD −0.01; 95% CI: −0.19 to −0.00; P = 0.04] compared with controls. These findings indicate that prolactinomas are associated not only with reduced bone mass but also with impaired bone microarchitecture [92].

Beyond conventional densitometry, emerging imaging studies suggest that dual-energy X-ray absorptiometry (DXA) may underestimate skeletal involvement in some patients. A 2022 HR-pQCT study demonstrated reduced trabecular and cortical thickness at both the radius and tibia in patients with prolactinomas. Notably, some individuals with abnormal volumetric bone parameters had areal

 doi:10.20944/preprints202605.0234.v1

BMD values within the normal range, indicating that deterioration in bone quality may precede or exceed changes detectable by DXA [93].

Long-term follow-up studies further indicate that skeletal recovery may be incomplete despite biochemical control of hyperprolactinemia [94]. These findings are clinically relevant, as they suggest that normalization of prolactin levels does not necessarily equate to normalization of skeletal risk. Accordingly, the recent Pituitary Society international consensus statement recognizes bone disease as a significant complication of prolactin-secreting pituitary adenomas and recommends careful assessment of skeletal health as part of comprehensive patient management [95].

Overall, current evidence indicates that hyperprolactinemia is associated not only with reduced BMD, particularly at the lumbar spine, but also with impaired bone quality and increased fracture risk. These observations underscore the importance of timely diagnosis, effective prolactin control, correction of gonadal dysfunction, and individualized skeletal monitoring in affected patients.

Conclusions

Although prolactin is classically defined as an anterior pituitary hormone essential for lactation, chronic hyperprolactinemia should be regarded as a systemic endocrine–metabolic disorder. Beyond its reproductive effects, prolactin excess is consistently associated with increased appetite and weight gain, contributing to higher body mass index and adverse cardiometabolic profiles.

Dyslipidemia, characterized by elevated triglycerides, total cholesterol, and low-density lipoprotein cholesterol, together with reduced high-density lipoprotein cholesterol, commonly accompanies sustained prolactin elevation and may further increase atherogenic risk. Concurrent disturbances in glucose homeostasis, including elevated fasting glucose, HbA1c, HOMA-IR, and altered insulin dynamics, indicate clinically relevant insulin resistance.

Cutaneous manifestations may provide visible indicators of underlying hormonal imbalance, while vascular effects on the intima and endothelial function may contribute to increased cardiovascular risk. Importantly, neuropsychological and cognitive impairments may significantly reduce quality of life, and skeletal complications, including decreased bone mineral density, further highlight the need for early recognition and comprehensive, risk-directed management of hyperprolactinemia.

Author Contributions: Conceptualization, Blazej Meczekalski; Formal analysis, Christian Unogu; Data curation, Christian Unogu; Writing – original draft, Roman Smolarczyk, Christian Unogu, Anna Duszewska, Anna Szeliga, Monika Grymowicz, Anna Kostrzak, Ewa Rudnicka, Marzena Maciejewska-Jeske, Katarzyna Smolarczyk and Blazej Meczekalski; Writing – review & editing, Christian Unogu and Gregory Bala; Supervision, Blazej Meczekalski; Project administration, Christian Unogu. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Freeman ME, Kanyicska B, Lerant A, Nagy G. Prolactin: structure, function, and regulation of secretion. Physiol Rev. 2000 Oct;80(4):1523-631. doi: 10.1152/physrev.2000.80.4.1523. PMID: 11015620.
2. Friesen HG. The discovery of human prolactin: a very personal account. Clin Invest Med. 1995 Feb;18(1):66-72. PMID: 7768067.

 doi:10.20944/preprints202605.0234.v1

3. Fahie-Wilson MN, John R, Ellis AR. Macroprolactin; high molecular mass forms of circulating prolactin. Ann Clin Biochem. 2005 May;42(Pt 3):175-92. doi: 10.1258/0004563053857969. PMID: 15949152.
4. Biagetti B, Ferrer Costa R, Alfayate Guerra R, Álvarez García E, Berlanga Escalera E, Casals G, Esteban Salán M, Granada Ibern ML, Gorrín Ramos J, López Lazareno N, Oriola J, Sánchez Martínez PM, Torregrosa Quesada ME, Urgell Rull E, García Lacalle C. Macroprolactin: From laboratory to clinical practice. Endocrinol Diabetes Nutr (Engl Ed). 2022 Jan;69(1):63-69. doi: 10.1016/j.endien.2022.01.001. Epub 2022 Feb 16. PMID: 35232561.
5. Teng CB, Yang ZM. Prolactin family and mammal pregnancy. Sheng Li Ke Xue Jin Zhan. 2002 Oct;33(4):355-8. Chinese. PMID: 12650077.
6. Wu T, Duan Y, Jiang J, Gu T, Zhang P, Bi Y. A Century of Prolactin: Emerging Perspectives as a Metabolic Regulator. Diabetes Metab Res Rev. 2024 Sep;40(6):e3836. doi: 10.1002/dmrr.3836. PMID: 39096246.
7. Kaur J, Bhusal K. Hyperprolactinemia. 2025 Nov 30. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan–. PMID: 30726016.
8. Molitch ME. Medication-induced hyperprolactinemia. Mayo Clin Proc. 2005 Aug;80(8):1050-7. doi: 10.4065/80.8.1050. PMID: 16092584.
9. Mancini T, Casanueva FF, Giustina A. Hyperprolactinemia and prolactinomas. Endocrinol Metab Clin North Am. 2008 Mar;37(1):67-99, viii. doi: 10.1016/j.ecl.2007.10.013. PMID: 18226731.
10. Augustine RA, Ladyman SR, Grattan DR. From feeding one to feeding many: hormone-induced changes in bodyweight homeostasis during pregnancy. J Physiol. 2008;586:387-397.
11. Lopez-Vicchi F, Ladyman SR, Ornstein AM, Gustafson P, Knowles P, Luque GM, Grattan DR, Becu-Villalobos D. Chronic high prolactin levels impact on gene expression at discrete hypothalamic nuclei involved in food intake. FASEB J. 2020 Mar;34(3):3902-3914. doi: 10.1096/fj.201902357R. Epub 2020 Jan 16. PMID: 31944423
12. Al Sabie F, Tariq Z, Erickson D. Association Between Prolactinoma and Body Mass Index. Endocrine Practice , 2021; 27, 312-317; doi.org/10.1016/j.eprac.2020.09.001
13. Lopez-Vicchi F, De Winne C, Brie B, Sorianello E, Ladyman SR, Becu-Villalobos D. Metabolic functions of prolactin: Physiological and pathological aspects. J Neuroendocrinol. 2020;32:e12888. https://doi.org/10.1111/jne.12888
14. Atmaca A, Bilgici B, Ecemis GC, Tuncel OK. Evaluation of body weight, insulin resistance, leptin and adiponectin levels in premenopausal women with hyperprolactinemia. Endocrine. 2013;44:756-761.
15. Byberg S, Futtrup J, Andreassen M, Krogh J. Metabolic effects of dopamine agonists in patients with prolactinomas: a systematic review and meta-analysis. Endocr Connect. 2019;8(10):1395e1404.
16. Sauve D, Woodside B. The effect of central administration of prolactin on food intake in virgin female rats is dose-dependent, occurs in the absence of ovarian hormones and the latency to onset varies with feeding regimen. Brain Res. 1996;729:75-81.
17. Ladyman SR, MacLeod MA, Khant Aung Z, et al. Prolactin receptors in Rip-cre cells, but not in AgRP neurones, are involved in energy homeostasis. J Neuroendocrinol. 2017;29:e12474.
18. Flak JN, Myers MG Jr. Minireview: CNS mechanisms of leptin action. Mol Endocrinol. 2016;30:3-12.
19. Naef L, Woodside B. Prolactin/Leptin interactions in the control offood intake in rats. Endocrinology. 2007;148:5977-5983.
20. Hugo ER, Borcherding DC, Gersin KS, Loftus J, Ben-Jonathan N. Prolactin release by adipose explants, primary adipocytes, and LS14 adipocytes. J Clin Endocrinol Metab. 2008;93:4006-401
21. Fleenor D, Oden J, Kelly PA, et al. Roles of the lactogens and somatogens in perinatal and postnatal metabolism and growth: studies of a novel mouse model combining lactogen resistance and growth hormone deficiency. Endocrinology. 2005;146:103-112.
22. LaPensee CR, Horseman ND, Tso P, Brandebourg TD, Hugo ER, Ben-Jonathan N. The prolactin-deficient mouse has an unaltered metabolic phenotype. Endocrinology. 2006;147:4638-4645.
23. Le JA, Wilson HM, Shehu A, Devi YS, Aguilar T, Gibori G. Prolactin activation of the long form of its cognate receptor causes increased visceral fat and obesity in males as shown in transgenic mice expressing only this receptor subtype. Horm Metab Res. 2011;43:931-937.

 doi:10.20944/preprints202605.0234.v1

24. Ling C, Hellgren G, Gebre-Medhin M, et al. Prolactin (PRL) receptor gene expression in mouse adipose tissue: increases during lactation and in PRL-transgenic mice. Endocrinology. 2000;141:3564-3572.
25. Ben-Jonathan N, Hugo E. Prolactin (PRL) in adipose tissue: regulation and functions. Adv Exp Med Biol. 2015;846:1-35.
26. Ponce AJ, Galván-Salas T, Lerma-Alvarado RM, et al. Low prolactin levels are associated with visceral adipocyte hypertrophy and insulin resistance in humans. Endocrine. 2020;67(2):331-343.
27. Auriemma RS, De Alcubierre D, Pirchio R, Pivonello R, Colao A. The effects of hyperprolactinemia and its control on metabolic diseases. Expert Rev Endocrinol Metab 2018;13(2):99-106 doi:10.1080/17446651.2018.1434412
28. Ben-Jonathan N, Hugo ER, Brandenburg TD, LaPensee CR. Focus on prolactin as a metabolic hormone. Trends Endocrinol Metab 2006; 17(3): 110-6.doi: 10.1016/j.tem.2006.02.005
29. Erem C, Kocak I, Nuhoglu I, Yilmaz M, Ucuncu O. Blood coagulation, fibrinolysis and lipid profile in patients with prolactinoma. Clinical Endocrinol 2010; 73(4): 502-507.doi:10.1111/j.1365-2265.2009.03752.
30. Altuntas SC, Evran M, Sert M, Tetiker T. Markers of metabolic syndrome in patients with pituitary adenoma: a case series of 303 patients. Horm Metab Res 2019;51(11): 709-713.doi:10.1055/a-1020-3992.
31. Pala NA, Laway BA, Misgar RA, Dar RA. Metabolic abnormalities in patients with prolactinoma: response to treatment with cabergoline. Diabetol Metab Syndr 2015;7: 99.doi:10.1186/s13098-015-0094-4.
32. Posawetz AS, Trummer Ch, Pandis M, Aberer F et al. Adverse body composition and lipid parameters in patients with prolactinoma: a case -control study. BMC Endocr Disord 2021;21: 81-90.doi: 10.1186/s12902-021-00733-6.
33. Ciresi A, Amato MC, Guarnotta V, Lo Castro F, Giordano C. Higher doses of cabergoline further improve metabolic parameters in patients with prolactionoma regardless of the degree of reduction in prolactin levels. Clin Endocrinol 2013;79(6): 845-852.doi: 10.1111/cen.12204.
34. Schwetz V, Librizzi R, Trummer C, Theiler G, Stiegler C Pieber TR et al. Treatment of hyperprolactinemia reduces total cholesterol and LDL in patients with prolactinomas. Metab Brain Dis 2017;32(1): 193-199.doi:10.1007/s11011-016-9882-2.
35. Casper RC, Douglas Z, Staples N. Hyperprolacinemia in two patients with eating disorders. J Clin Psych 1987(3): 119-120.
36. Nilsson L, Binart N, Bohlooy-Y M et al. Prolactin and growth hormone regulate adiponectin secretion and receptor expression in adipose tissue. Biochem Biphys Res Commun 2005;331 (4): 1120-1126.doi: 10.1016/j.bbrc.2005.04.026.
37. Foss MC, Paula FJ, Paccola GM, Piccinato CE. Peripheral glucose metabolism in human hyperprolactinemia. Clin Endocrinol 1995;43(6): 721-726.doi:10.1111/j.1365-2265. 1995.tb00541.
38. Oravec S, Tomeckova E, Oravec D, Klacansky T, Blaskova O, Valach A. Decreased apolipoprotein levels in women with hyperprolactinemia related to increased estradiol level: effect of hepatic lesion? Endocrinol Exp 1985;19(4):313-316.
39. McAveney KM, Gimble JM, Yu-Lee L. Prolactin receptor expression during adipocyte differentiation of bone marrow stroma. Endocrinol 1996; 137(12): 5723-5726.doi:10.1210/endo.137.12.8940406.
40. Borcherding DC, Hugo ER, Idelman G, De Silva A, Richtand NW, Loftus J et al. Dopamine receptors in human adipocytes: expression and functions. Plos One 2011; 6(9): e25537.doi: 10.1371/journal.pone.0025537.
41. Berinder K, Nystrom T, Hoybye C, Hall K, Hulting AL. Insulin sensitivity and lipid profile in prolactinoma patients before and after normalization prolactin by dopamine agonist therapy. Pituitary 2011; 14(3): 199-207.doi: 10.1007/s11102-010-0277-9.
42. Liu X, Duan CH, Yin X, Li X,Chen M, Chen J, Zhao W, Zhang L, Liu Y, Zhang Y. Effects of prolactin inhibition on lipid metabolism in goats. Animals 2024 ;14: 3364-3378.doi: 10.3390/ani/14233364.
43. Naliato EC, Violante AH, Gaccione M, Caldas D, Lamounier Filho A, Loureiro CR et al. Body fat in men with prolactionma . J Endocrinol Investig 2008, 31(11): 985-90.
44. Dos Santos Silva CM, Barbosa FR, Lima GA, Warszawski L, Fontes R, Domingues RC, et al. BMI and metabolic profile in patients with prolactionoma befor and after with dopamine agonists. Obesity 2011;19(4):800-805.

 doi:10.20944/preprints202605.0234.v1

45. Krysiak R, Kowalcze K, Cucinella G, Zaami S, Ott J, Okopień B. The impact of hypoprolactinemia on cardiometabolic effects of metformin in young women: a pilot prospective cohort study. J Endocrinol Invest 2025;48: 2369-2379.doi:10.1007/s40618-025-02645-x.
46. Krysiak R, Kowalcze K, Okopień B. Cabergoline induced hypoprolactinemia may attenuate cardiometabolic effects of atorvastatin: A pilot study. Cardiology 2022;147: 497-506.
47. Ken-Dror G, Fluck D, Lean ME, Casanueva FF, Han TS. The relationship between low prolactin and type 2 diabetes. Rev Endocr Metab Disord 2024;25(6):1087-1095. doi: 10.1007/s11154-024-09886-w.
48. Krysiak R, Kowalcze K, Okopień B. Cardiometabolic profile of young women with hypoprolactinemia. Endocrine 2022.doi: 10.10.1007/s12020-022-03145-1.
49. Vries, R. et al. (2019). The impact of chronic hyperprolactinemia on glucose metabolism and insulin resistance. Journal of Clinical Endocrinology, 104(5), 2012-2022.
50. Jahan, S. et al. (2020). Insulin resistance and metabolic disturbances in hyperprolactinemia: A clinical review. Endocrine Journal, 67(6), 499-507.
51. Zhang, X. et al. (2021). The effects of dopamine agonists on glucose metabolism in patients with hyperprolactinemia. Diabetes & Metabolism, 47(4), 268-275.
52. Kim, J. et al. (2020). The role of prolactin in adipogenesis and insulin resistance. Journal of Endocrinology and Metabolism, 35(7), 358-365.
53. Langan, E. A. (2024). Prolactin: A Mammalian Stress Hormone and Its Role in Cutaneous Pathophysiology. In International Journal of Molecular Sciences (Vol. 25, Number 13). https://doi.org/10.3390/ijms25137100
54. Lutz, G. (2012). Hair loss and hyperprolactinemia in women. Dermato-Endocrinology, 4(1). https://doi.org/10.4161/derm.19472.
55. Szybiak, W., Jarzemska, M., Kowalczyk, M., Sadowska-Przytocka, A., Więckowska, B., Żaba, R., & Lacka, K. (2023). Selected hormone levels and lipid abnormalities in patients with acne vulgaris. Postepy Dermatologii i Alergologii, 40(6). https://doi.org/10.5114/ada.2023.133457.
56. Futterweit, W., Dunaif, A., Yeh, H. C., & Kingsley, P. (1988). The prevalence of hyperandrogenism in 109 consecutive female patients with diffuse alopecia. Journal of the American Academy of Dermatology, 19(5). https://doi.org/10.1016/S0190-9622(88)70241-8.
57. Schmidt, J. B. (1994). Hormonal basis of male and female androgenic alopecia: Clinical relevance. Skin Pharmacology, 7(1–2). https://doi.org/10.1159/000211275.
58. Noor, Dr. S. F., Azzad, Dr. M. A. K., Faisal, Dr. H. M., & Chowdhury, Dr. S. (2024). Comparative Study of Prolactin Levels in Acne and Non-Acne Individuals among Adolescent. Scholars Journal of Applied Medical Sciences, 12(10). https://doi.org/10.36347/sjams.2024.v12i10.017.
59. Okechukwu Chukwu, E. (2017). Comparative Study of Prolactin Levels in Acne and Non-Acne Individuals Among Students of College of Health Sciences, Nnamdi Azikiwe University, Nnewi, Nigeria. International Journal of Biomedical Engineering and Clinical Science, 3(4). https://doi.org/10.11648/j.ijbecs.20170304.11.
60. Girolomoni, G., Theodore Phillips, J., & Bergstresser, P. R. (1993). Prolactin stimulates proliferation of cultured human keratinocytes. Journal of Investigative Dermatology, 101(3). https://doi.org/10.1111/1523-1747.ep12365203.
61. Giasuddin, A. S. M., El-Sherif, A. I., & El-Ojali, S. I. (1998). Prolactin: Does it have a role in the pathogenesis of psoriasis? Dermatology, 197(2). https://doi.org/10.1159/000017981.
62. Dilmé-Carreras, E., Martín-Ezquerra, G., Sánchez-Regaña, M., & Umbert-Millet, P. (2011). Serum prolactin levels in psoriasis and correlation with cutaneous disease activity. Clinical and Experimental Dermatology, 36(1). https://doi.org/10.1111/j.1365-2230.2010.03871.x.
63. El-Khateeb, E. A., Zuel-Fakkar, N. M., Eid, S. M., & Abdul-Wahab, S. E. (2011). Prolactin level is significantly elevated in lesional skin of patients with psoriasis. International Journal of Dermatology, 50(6). https://doi.org/10.1111/j.1365-4632.2010.04752.x.
64. Keen, M. A., & Hassan, I. (2014). Serum prolactin levels in psoriasis and its association with disease activity: A case-control study. Indian Journal of Dermatology, 59(6). https://doi.org/10.4103/0019-5154.143512.
65. Amirzadegan A, Salimi E, Hosseinsabet A. Are prolactin serum levels and coronary artery atherosclerosis correlated in postmenopausal women? A cross-sectional study. Turk Kardiyol Dern Ars. 2019;47(3):177-184. doi:10.5543/tkda.2018.45213.

 doi:10.20944/preprints202605.0234.v1

66. Glezer A, Santana MR, Bronstein MD, Donato J Jr and Jallad RS (2023) The interplay between prolactin and cardiovascular disease. Front. Endocrinol. 13:1018090. doi: 10.3389/fendo.2022.1018090.
67. Kamperdijk L, Shkarpa N, Twickler MTB. The contribution of prolactin in the occurrence of premature cardiovascular disease predominantly through modulating the inflammatory cascade. Eur J Clin Invest. 2025 Aug;55(8):e70042. doi: 10.1111/eci.70042.
68. Krogh J, Selmer C, Torp-Pedersen C, Gislason GH, Kistorp C. Hyperprolactinemia and the Association with All-Cause Mortality and Cardiovascular Mortality. Horm Metab Res. 2017 Jun;49(6):411-417. doi: 10.1055/s-0043-107243.
69. Papazoglou AS, Leite AR. Prolactin levels and cardiovascular disease: a complicate relationship or a confounding association? Eur J Prev Cardiol. 2025 May 12;32(7):612-615. doi: 10.1093/eurjpc/zwad176.
70. Iglesias P, Rodríguez MDM, Guerrero-Pérez F, Servat AS, Fernández LG, Fernández-Rodríguez E, Castro PP, Villar-Taibo R, Biagetti B, Orois A, Donato S, Lázaro VA, Roig-Marín N, Serra G, Civantos S, Rivero G, de Araoz CMF, de Paz IP, Cordido F, Centeno RG, Araujo-Castro M, Lamas C, Paja M, Hanzu FA, Díez JJ. Sex differences in cardiovascular risk factors and cardiovascular disease in patients with hyperprolactinemia: a multicenter cross-sectional study. Endocrine. 2026 Feb 3;91(1):65. doi: 10.1007/s12020-026-04554-2.
71. Zhao H, Gong S, Shi Y, Luo C, Qiu H, He J, Sun Y, Huang Y, Wang S, Miao Y, Wu W. The role of prolactin/vasoinhibins in cardiovascular diseases. Animal Model Exp Med. 2023 Apr;6(2):81-91. doi: 10.1002/ame2.12264.
72. Koenig T, Bauersachs J, Hilfiker- Kleiner D. Bromocriptine for the treatment of peripartum cardiomyopathy. Card Fail Rev. 2018;4(1):46- 49. doi:10.15420/cfr.2018:2:2.
73. Hacıömeroğlu A, Güngüneş A, Yalçın S, Tekin E. Endocan levels in patients with hyperprolactinemia. BMC Endocr Disord. 2025 Nov 6;25(1):253. doi: 10.1186/s12902-025-02079-9.
74. Koca AO, Dagdeviren M, Akkan T, Keskin M, Pamuk N, Altay M. Is idiopathic mild hyperprolactinemia a cardiovascular risk factor? Niger J Clin Pract. 2021 Feb;24(2):213-219. doi: 10.4103/njcp.njcp_178_20.
75. Farroni E, Taggiasco A, Santulli G. Peripartum cardiomyopathy: a clinical review. Vessel Plus. 2025;9:2. https://dx.doi.org/10.20517/2574-1209.2025.15.
76. Kumar A, Ravi R, Sivakumar RK, Chidambaram V, Majella MG, Sinha S, Adamo L, Lau ES, Al'Aref SJ, Asnani A, Sharma G, Mehta JL. Prolactin Inhibition in Peripartum Cardiomyopathy: Systematic Review and Meta-analysis. Curr Probl Cardiol. 2023 Feb;48(2):101461. doi: 10.1016/j.cpcardiol.2022.101461.
77. Yun Shen, Qing Yang, Tingting Hu, Yaxin Wang, Lei Chen, Fei Gao, Wei Zhu, Gang Hu, Jian Zhou, Chunfang Wang, Yuqian Bao, Association of prolactin with all-cause and cardiovascular mortality among patients with type 2 diabetes: a real-world study, European Journal of Preventive Cardiology, Volume 30, Issue 14, October 2023, Pages 1439–1447, https://doi.org/10.1093/eurjpc/zwad112.
78. Rojhani, E., Rahmati, M., Firouzi, F. et al. Prolactin levels and chronic kidney disease and the subsequent risk of cardiovascular events: A long term population based cohort study. Sci Rep 15, 7198 (2025). https://doi.org/10.1038/s41598-025-87783-1
79. Rusu CC, Moldovan D, Potra A, Tirinescu D, Ticala M, Maslyennikov Y, Barar A, Urs A, Bondor CI, Valea A, Kacso I. The Interplay of Prolactin with Inflammatory Nutritional Markers and NT-proBNP in Chronic Kidney Disease. Int J Mol Sci. 2025 Jul 1;26(13):6347. doi: 10.3390/ijms26136347.
80. Jurek A, Krzesiński P, Gielerak G, Witek P, Zieliński G, Kazimierczak A, Wierzbowski R, Banak M, Uziębło-Życzkowska B. Increased Thoracic Fluid as the Most Distinctive Cardiovascular Hemodynamic Alteration in Men with Prolactinoma. Nutrients. 2022; 14(24):5369. https://doi.org/10.3390/nu14245369.
81. Grattan DR. Does the brain make prolactin ?. J Neuroendocrinol 2024, 36,10
82. Torner L. Actions of Prolactin in the brain: from physiological adaptations to stress and neurogenesis to psychopathology. Front Endocrinol 2016.
83. Kadiri SK, Tiwari P, Khobragade DS, Gowda BS, Rout SK. Neuroendocrince effects of Hyperprolactinemia : focus on dopamine and serotonin systems.Endocrine Metabolic & Immune Disorders – Drug Targets. 2025, Aug 26.

 doi:10.20944/preprints202605.0234.v1

84. Cheng B, Hu X, Roberts N, Zhao Y, Xu X, Zhou Y, Tan X, Chen S, Meng Y, Wang S, Xing H, Deng W. Prolactin mediates the relationship between regional gray matter volume and postpartum depression symptoms. J Affect Disord 2022, 301, 253-259.
85. Xu M, Liu B, Yang B Luan J, Li S, Effects of hyperprolactinemia and bromocriptine treatment on cerebral blood flow and functional brain states. Neuroradiology 2025, 67, 9, 2551.
86. Grattan-Smith P.J., Morris J.G., Shores E.A., Batchelor J., Sparks R.S. Neuropsychological abnormalities in patients with pituitary tumours. Acta Neurol. Scand. 1992;86:626–631.
87. Chen A, Cao C, Liu B, Wang S, Wu S, Xu G, et al. Hyperprolactinemia associated with attentional processing and interference control impairments in patients with prolactinomas. Brain Sci. 2022;12:1091.
88. Xu Y, Yao S, Yang Z, Shi Y, Zhang X, Wang L, Cui D. The association between prolactin levels and cognitive function in female patients with severe mental disorders. Psychiatry Investig. 2024, 21 (8), 832.
89. Arguinchona J, Kumar A, Yogi-Morren D, Vahidi Rag M, Doshi K. Elevated dehydroepiandrosterone sulfate levels in 2 patients with prolactinomas : an unrecognized association. JCEM Case Rep. 2025, 3(7).
90. Yun SJ, Sang H, Park SY, Chin SO. Effect of Hyperprolactinemia on Bone Metabolism: Focusing on Osteopenia/Osteoporosis. Int J Mol Sci. 2024 Jan 25;25(3):1474. doi: 10.3390/ijms25031474. PMID: 38338751; PMCID: PMC10855748.
91. Uygur MM, Menotti S, Santoro S, Giustina A. Modern approach to bone comorbidity in prolactinoma. Pituitary. 2024 Dec;27(6):802-812. doi: 10.1007/s11102-024-01469-x. Epub 2024 Nov 14. PMID: 39541075.
92. Nagendra L, Dutta D, Mondal S, Kapoor N, Joshi A, Bhattacharya S. Hyperprolactinemia Due to Prolactinoma has an Adverse Impact on Bone Health with Predominant Impact on Trabecular Bone: A Systematic Review and Meta-Analysis. J Clin Densitom. 2024 Jan-Mar;27(1):101453. doi: 10.1016/j.jocd.2023.101453. Epub 2023 Nov 25. PMID: 38064881.
93. Wang L, Chen K, Duan L, Ke X, Gong F, Pan H, Yang H, Zhu H, Xia W. Bone microarchitecture impairment in prolactinoma patients assessed by HR-pQCT. Osteoporos Int. 2022 Jul;33(7):1535-1544. doi: 10.1007/s00198-021-06289-4. Epub 2022 Feb 21. PMID: 35190851.
94. Andereggen L and Christ E (2024) Commentary: Clinical characteristics of male prolactinoma patients mainly presenting with severe obesity and the metabolic response to dopamine agonist therapy. Front. Endocrinol. 15:1371468. doi: 10.3389/fendo.2024.1371468.
95. Petersenn, S., Fleseriu, M., Casanueva, F.F. et al. Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement. Nat Rev Endocrinol 19, 722–740 (2023). https://doi.org/10.1038/s41574-023-00886-5