The role of prolactin (PRL) favoring metabolic homeostasis is supported by multiple preclinical and clinical studies. PRL levels are key to explaining the direction of its actions. In contrast with the negative outcomes associated with very high (>100 μg/L) and very low (<7 μg/L) PRL levels, moderately high PRL levels, both within but also above the classically considered physiological range are beneficial for metabolism and have been defined as HomeoFIT-PRL. In animal models, HomeoFIT-PRL levels counteract insulin resistance, glucose intolerance, adipose tissue hypertrophy and fatty liver; and in humans associate with reduced prevalence of insulin resistance, fatty liver, glucose intolerance, metabolic syndrome, reduced adipocyte hypertrophy, and protection from type 2 diabetes development. The beneficial actions of PRL can be explained by its positive effects on main metabolic organs including the pancreas, liver, adipose tissue, and hypothalamus. Here, we briefly review work supporting PRL as a promoter of metabolic homeostasis in rodents and humans, the PRL levels associated with metabolic protection, and the proposed mechanisms involved. Finally, we discuss the possibility of using drugs elevating PRL for the treatment of metabolic diseases.

**KEYWORDS**
prolactin levels, homeoFIT-PRL, metabolically healthy and unhealthy obesity, metabolic homeostasis, insulin resistance, homeorhetic response

**Introduction**

Defining the role of prolactin (PRL) in metabolism has been challenging due to contrasting findings demonstrating positive and negative effects of PRL on metabolic homeostasis. This contradiction is disentangled after realizing that PRL levels and the physio-pathological context influence the direction of PRL action (1). Low and very high PRL levels are deleterious to the metabolism, whereas medium and moderately high levels are usually beneficial.

PRL action is necessary to maintain metabolic homeostasis, as the absence or reduction of PRL signaling due to the lack of PRL receptors (PRLR) or low PRL levels associate with exacerbated metabolic alterations, particularly in the context of a metabolic challenge or disease. In humans, low PRL levels associate with increased prevalence of metabolic diseases (1). In contrast, patients with overweight and obesity (OW/OB) having elevated PRL levels...
show better metabolic profiles than BMI-matched patients with lower PRL values (2–6), to imply that elevated PRL is a mechanism dealing with metabolic challenge.

The mechanisms by which PRL promotes metabolic homeostasis involves actions in different metabolic organs. A detailed description of the levels of PRL and their cellular and molecular mechanisms mediating metabolic benefits warrant further research. Also, a careful evaluation of drugs that elevate PRL levels is needed in the context of metabolic diseases.

**Prolactin promotes metabolic homeostasis in rodents**

Serum PRL decreases in rodents with obesity, diabetes, and insulin resistance (2, 7–10), suggesting a role for reduced PRL levels in the pathophysiology of metabolic diseases. As a proof of concept, PRL treatment in mice and rats with streptozotocin (STZ)-induced diabetes or diet-induced obesity improves their metabolic profile (2, 11, 12), whereas PRLR null mice with STZ-induced diabetes or diet-induced obesity show a more severe disease phenotype (2, 13). Moreover, mice lacking PRLR in the liver become insulin resistant, whereas insulin resistant obese mice (db/db mice lacking leptin receptors) overexpressing the PRLR in the liver show improved insulin sensitivity (14).

In addition, PRL action is required to deal with the metabolic challenges of pregnancy, a state characterized by hyperphagia, excessive adiposity, and physiological insulin resistance to redirect nutrients towards the fetus (15–17). Pregnant mice null for the PRLR in the pancreas, specifically in β-cells, develop gestational diabetes (18–20), due to deficient pancreatic β-cell hyperplasia and hyperinsulinemia (21).

Moreover, PRL reduces metabolic alterations in lactating pups nursed by dams consuming a high fat diet (HFD) during lactation. The obeseogenic milk from HFD-fed dams has 50% less PRL compared to the milk from dams fed a chow diet (22). Pups consuming the obeseogenic-hypoprolactinemic milk develop obesity, excessive adiposity, severe insulin resistance, and fatty liver at weaning; whereas when their HFD-fed mothers or themselves receive exogenous PRL during lactation, metabolic alterations are ameliorated (22). These findings support PRL in maternal milk exerting beneficial metabolic effects in lactating pups, and low PRL levels in milk contributing to the maternal obeseogenic diet-induced metabolic disease in pups.

**Elevated prolactin levels as a mechanism to counteract metabolic alterations in humans**

Low PRL levels associate with a higher prevalence of type 2 diabetes (T2D), insulin resistance, glucose intolerance, metabolic syndrome (MS), adipose tissue (AT) dysfunction, β-cell dysfunction, non-alcoholic fat liver disease (NAFLD), and cardiovascular events, whereas moderately high PRL levels correlate with metabolic protection in all these instances (Table 1).

Moderately high PRL levels (16–35 μg/L) associate with lower prevalence of T2D and even predict a reduced incidence of T2D 10 years later (23). PRL levels in the 4th quartile correlate with lower incidence (23, 25, 29) or prevalence (24, 26–28, 30, 42) of T2D (Table 1), and PRL levels are inversely related to fasting glucose levels and glycosylated hemoglobin (HbA1c) values (4, 25, 26, 28, 31, 35, 36) in both men and women. Consistently, high serum PRL in pregnancy predicts a lower risk of postpartum prediabetes/diabetes (29), and in women with gestational diabetes mellitus, lower PRL levels at 6 to 9 weeks postpartum associate with a higher future risk of developing T2D in a 10-year follow up (30) (Table 1). T2D and other metabolic alterations derive from insulin resistance, i.e., the inability of insulin to activate a normal insulin response on its target cells.

Moderately elevated PRL levels associate with increased insulin sensitivity in men (2, 3, 5, 26, 31), women (3, 5, 26, 31, 33, 34) and even children (32) (Table 1).

Insulin resistance can derive from AT dysfunction and occur in parallel to β-cell dysfunction. High PRL levels associate with reduced AT dysfunction and predict smaller adipocytes (reduced hypertrophy) in visceral AT (2, 3, 5, 6, 34), the type of fat that, in excess, associates with metabolic alterations and disease severity (43–46). Regarding β-cell function, pregnant women with high PRL levels have a lower postpartum risk of developing diabetes and β-cell dysfunction (29), and women with polycystic ovary syndrome (PCOS) with PRL levels in the 4th quartile show lower prevalence of β-cell dysfunction (33) (Table 1).

The MS represents a group of alterations that elevate the risk of cardiovascular disease, stroke, and T2D, and consists of high blood pressure, hyperglycemia, abdominal obesity, and abnormal cholesterol and triglyceride levels (47). Moderately high PRL levels associate with lower prevalence of MS in children (32) and in adult patients suffering from certain conditions, such PCOS in women (38), and sexual dysfunction (SD) in men (36, 37). Also, high PRL levels in men with SD are associated with protection from major cardiovascular events (40). However, in the general adult population a correlation between PRL and MS has not been found (3, 25). When only dyslipidemia is evaluated, an inverse association occurs between PRL levels and total cholesterol, LDL cholesterol, and triglyceride levels (4, 5, 38, 39).

Another parameter closely linked to metabolic disease is a proinflammatory environment. In subjects with obesity, moderately high PRL levels associate with lower levels of interleukin 6 in children (32) and tumor necrosis factor-α (TNF-α) in adults (4).

Most studies in humans show that moderately high PRL levels are not associated with obesity itself, the exception being a study in children (32). This observation can be explained by the fact that some subjects with obesity remain metabolically healthy (metabolically healthy obesity - MHO), or at least show fewer metabolic alterations. Indeed, subjects having MHO have
increased circulating PRL levels as compared to those with metabolically unhealthy obesity (MUHO) (4–6). Moreover, logistic regression analysis showed PRL as an independent predictor of MHO (6). Patients with obesity and high PRL (HP) levels displayed reduced blood glucose, total and LDL cholesterol, triglyceride, and TNFα levels than patients with obesity and normal PRL (NP) levels. Also, after sleeve gastrectomy, patients in the HP group showed reduced PRL levels, whereas those in the NP group have increased PRL levels (4). Similarly, patients with OW/OB with higher PRL levels had a better metabolic profile than those with lower PRL values. Interestingly, PRL levels decreased once metabolic parameters improved following bariatric surgery (5) (Table 1). These studies support that increased PRL levels are protective against metabolic diseases and return to basal values after the metabolic challenge is resolved (Figure 1).

Another metabolic disease associated with low PRL levels is NAFLD. Patients with NAFLD show lower PRL levels than control subjects and those with severe hepatic steatosis have even lower PRL values than patients with a mild to moderate disease (41) (Table 1). Moreover, PRL levels are part of a mathematical model to diagnose the presence and severity of NAFLD (48).

The association between low PRL levels and higher prevalence of metabolic diseases also stands for postmenopausal women and middle-aged and elderly men (23, 36), implying its independence from gonadal status. Because PRL levels may decrease with aging, it remains to be determined whether the HomeoFIT-PRL range differs between young vs. middle-age or elderly individuals.

**The right prolactin levels for metabolic maintenance and protection – not too much and not too little**

While low and very high PRL levels have deleterious metabolic consequences, a specific range of PRL values is beneficial for metabolism. This PRL range includes levels in the normal physiological range (7 to 25 µg/L) but also levels above (25 to 100 µg/L). The latter, previously claimed as hyperprolactinemia, have been defined as HomeoFIT-PRL (Homeostatic Functionally Increased Transient Prolactinemia) (1), since they occur in response to physiological or pathological challenges and respond to it by favoring metabolic homeostasis (Figure 1).

**TABLE 1** Moderately high PRL serum levels associate with lower incidence of metabolic disease.

| Metabolic disease                  | Population | PRL level associated with lower disease incidence or prevalence (µg/L) |
|-----------------------------------|------------|---------------------------------------------------------------------|
| T2D                               | Women      | >15.8 (23), 18.4 (24)                                                |
|                                   | Women & men| >12.9 (25), >11.5 (26), Q4 (27, 28)                                  |
|                                   | Pregnancy  | >115 Lower postpartum risk (29)                                      |
|                                   | Women w/GDM| >78.7 postpartum, lower risk of future T2D (30)                     |
| Insulin resistance                | Men        | ≥12.0 (2)                                                            |
|                                   | Women & men| ≥12.0 (3), >11.5 (26)                                                |
|                                   | Children   | >14.9 (33), Inverse association with PRL levels (34)                 |
|                                   | Women w/PCOS| Inverse association with PRL levels (5)                               |
|                                   | Women & men w/obesity| Inverse association with PRL levels (31)                             |
| Fasting glucose levels & HbA1c   | Women w/T1D| Inverse association with PRL levels (35)                              |
|                                   | Women & men w/obesity| 19.2 (6)                                                            |
|                                   | Men        | 30.5 (4), >11.5 (26), >12.9 (25), Q4 (28)                            |
|                                   | Women w/PCOS| Inverse association with PRL levels (31)                              |
|                                    | Women & men w/obesity| 19.2 (5, 6)                                                          |
|                                    | Children   | 7.9 (32)                                                            |
|                                    | Men w/SD   | >11.1-35 (36), Inverse association with PRL levels (37)              |
|                                    | Women w/PCOS| >7.0 (38)                                                           |
| Adipose tissue dysfunction        | Men & men  | ≥12.0 (3)                                                            |
|                                    | Men w/PCOS| ≥12.0 (2)                                                            |
|                                    | Women & men w/obesity| Inverse association with PRL levels (34)                             |
| Metabolically unhealthy obesity   | Women & men w/obesity| 19.2 (5, 6)                                                          |
|                                    | Women & men| 30.5 (4)                                                            |
| Beta cell dysfunction             | Pregnancy  | >115 Lower postpartum risk (29)                                      |
|                                    | Women w/PCOS| >14.9 (33)                                                          |
| Dyslipidemia                      | Women & men| 30.5 (4)                                                            |
|                                    | Women & men w/obesity| Inverse association with PRL levels (5)                              |
|                                    | Women w/PCOS| >7.0 (38), >15.9 (39)                                                |
| Major CVE                        | Men w/SD   | > 12 – 35 (40)                                                      |
| NAFLD                             | Women & men| >12.8 (41)                                                          |

Clinical studies within the last 12 years showing an inverse association between PRL circulating levels and risk, prevalence or incidence of metabolic diseases. Abbreviations: Q, quartile; T2D, type 2 diabetes; GDM, gestational diabetes mellitus; PCOS, polycystic ovary syndrome; T1D, type 1 diabetes, HbA1c, glycosylated hemoglobin; MS, metabolic syndrome; SD, sexual dysfunction; CVE, cardiovascular event; NAFLD, non-alcoholic fatty liver disease.
In healthy individuals, PRL levels are usually within the classical normal range <25 μg/L. However, some physiological challenges elevate PRL in a transient manner, such as intense exercise, acute stress, sleep, and sexual arousal (49). These conditions together with reproductive states (pregnancy and lactation) can be categorized as conditions that trigger a homeorhetic response, meaning the orchestrated or coordinated control of body metabolic tissues necessary to maintain a physiological state (defined by Bauman and Currie) (50). Moreover, the association between moderately elevated PRL levels and a beneficial metabolic phenotype supports elevated PRL levels in obesity as part of a homeorhetic response occurring both, under physiological and pathological challenges (Figure 1).

Altogether, PRL levels ranging from 7 to 100 μg/L are beneficial for metabolism. PRL values are in the lower end of this range under healthy physiological conditions (outside reproductive states); however, in the context of a metabolic challenge they are likely to increase towards maintaining metabolic homeostasis and return to basal when the stressor/challenge is eliminated. Conversely, patients experiencing a metabolic challenge, such as obesity, that are unable to respond by increasing PRL levels, are more prone to suffer from metabolic alterations than those upregulating their PRL levels (Figure 1).

Elevated PRL levels derived from prolactinomas are not part of a response to a metabolic challenge, they result from a diseased state (tumor) and are not considered HomeoFIT-PRL (and are usually above 100 μg/L). It is expected that normalization of PRL levels in subjects with prolactinomas associate with a healthier metabolic profile, if the PRL levels achieved by the treatment remain in the healthy range (>7 μg/L).

**Mechanisms mediating the beneficial metabolic action of prolactin**

PRL actions favoring metabolism are the result of its pleiotropic action reflected by the presence of the PRLR in almost every tissue in the body, including the main metabolic organs—pancreas, liver, adipose tissue, muscle, intestine, and hypothalamus—where beneficial metabolic actions and mechanisms of PRL have been described (51, 52).

**Pancreatic β-cells**

PRL stimulates the proliferation and survival of β-cells (53, 54), promotes glucose-induced insulin secretion (53), stimulates pancreas development during the perinatal stage (55), and is essential for β-cell expansion during pregnancy (18, 19, 56). The mechanisms that mediate PRL effects on β-cells involve increased osteoprotegerin synthesis, leading to the inhibition of receptor activator of NF-κB ligand pathway, an inhibitor of β-cell proliferation (57); increased survivin levels (58), elevated expression of the transcription factors Foxm1 and MafB, increased cyclin activity, and higher islet serotonin production.

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**FIGURE 1**
Elevated prolactin levels are part of a homeorhetic response upon metabolic challenges. A challenged metabolic state can be either physiological or pathological, in both cases a homeorhetic response includes elevated prolactin (PRL) levels, allowing a series of metabolic adaptations to deal with the physio-pathological demand. In a physiological challenge, such as pregnancy, lactation, or stress, this response leads to a new physiological set point (green arrows), whereas in a pathological challenge, such as obesity, it leads to a milder disease or protection from disease risk (yellow arrows, left side of figure). If the homeorhetic response fails, PRL levels do not rise and remain low instead, leading to altered physiological states (i.e., gestational diabetes mellitus, GDM, lactation insufficiency, LI, anxiety) (yellow arrows, right side of figure), or to aggravated disease with higher disease risk or prevalence (red arrows, right side of figure). MS, metabolic syndrome, T2D, type 2 diabetes, NAFLD, non-alcoholic fatty liver disease; MUHO, metabolically unhealthy obesity. Created in BioRender.com.
via Tph1 synthesis, all promoting β-cell proliferation (18, 56). Also, PRL leads to the inhibition of extrinsic and intrinsic apoptosis pathways (54) and improved glucose sensitivity through increased glucokinase and glucose transporter 2 expression (19, 59, 60) (Figure 2).

Liver

PRL regulates liver growth (61) and liver metabolic function. Increased PRLR expression in liver stimulates both liver and systemic insulin sensitivity, whereas reduced hepatic PRLR expression results in tissue and whole-body insulin resistance (14). Also, PRL reduces hepatic lipid accumulation by inhibition of the expression of the fatty acid transporter CD36 and the lipid synthesis enzyme, SCD1 (41, 62). Consistently, there is an inverse association between PRL levels and hepatic CD36 expression, and the PRLR decreases in the liver of patients with NAFLD (41). Thus, PRL prevents fatty liver disease. Mechanistically, the activation of STAT5 downstream of the PRLR mediates the insulin sensitizing effects of PRL (14). PRLR interacts with IRS1 (63) and promotes the phosphorylation of AKT (64), two key members of the insulin signaling pathway. Upregulating the hepatic PRLR in combination with systemic insulin treatment enhances the phosphorylation of the insulin receptor and of AKT in mouse liver, whereas reducing the expression of the PRLR by adenovirus-shRNA impairs insulin-induced liver phosphorylation of IR and AKT (14) (Figure 2). Moreover, the PRLR is regulated by the level of hepatic insulin resistance/sensitivity, i.e., it is downregulated in insulin resistant conditions and upregulated in insulin sensitive states (14).

Adipose tissue

PRL acts on the AT to regulate lipid metabolism and promote adipogenesis and healthy AT expansion (65). PRL inhibits lipid uptake via reduced lipoprotein lipase activity in human fat (66) and inhibits lipolysis in rat and human AT (67). PRL contributes to adipocyte differentiation in the adipocyte cell lines NIH-3T3 and 3T3-L1, by stimulating the activation of STAT5, and of the adipogenic transcription factors C/EBPb and PPARγ (68, 69). PRL is essential for brown fat formation and activity in newborn mice, and for brown preadipocyte differentiation (70). The PRLR is present in AT from rodents and humans and PRL is secreted by human AT (65, 66, 71), while obesity decreases PRL release from human fat (67). In PRLR null mice, there is either decreased or no change in fat mass (2, 72–74) depending on age, fat depot, and genetic background. C57BL/6 PRLR null mice fed an HFD, show increased adiposity and exacerbated adipocyte hypertrophy in AT (2). In obese rats, PRL treatment stimulates the healthy expansion of AT by promoting adipocyte hyperplasia and reducing visceral adipocyte hypertrophy, via increased expression of transcription factors PPARγ and Xbp1s, both favoring adipogenesis and insulin sensitivity (2) (Figure 2).

Hypothalamus

PRL promotes insulin sensitivity, at least in part, by central actions on the hypothalamus. Increased PRLR expression in the hypothalamus stimulates whole body insulin sensitivity, whereas reduced PRLR expression results in insulin resistance and glucose intolerance (75). PRL effects on the hypothalamus lead to vagal signals that promote increased liver insulin sensitivity (75). Also, in 90% pancreatectomized rats, intracerebroventricular infusion of PRL increases liver insulin sensitivity, inhibits β-cell apoptosis, and reduces body weight and adiposity by increasing hypothalamic dopamine levels and leptin signaling (76) (Figure 2).

Prolactin elevating drugs in the treatment of metabolic diseases

Several drugs elevate PRL circulating levels, mainly those that act as dopamine D2 receptor blockers, including first- and second-generation antipsychotics and medications treating gastrointestinal symptoms, antidepressants, antihypertensives, and others (77, 78). The use of antipsychotics has been associated to the development of metabolic alterations; however, a recent meta-analysis, evaluating the metabolic actions of 18 antipsychotics in around 26,000 patients with schizophrenia (79), showed a large variation in the metabolic side-effects of antipsychotics. Some drugs had clear adverse effects increasing body weight, triglyceride levels, cholesterol levels, and glucose levels (olanzapine, clozapine, and quetiapine), while others showed neutral or even positive metabolic outcomes, with very mild or no effects on body weight and triglyceride levels, and some reducing LDL cholesterol and glucose levels (aripiprazole, brexpiprazole, cariprazine, lurasidone, ziprasidone and amisulpiride). Regarding the effect of these drugs on PRL levels (77), some of the drugs exerting beneficial metabolic actions present a moderate to high risk for elevating PRL levels (77), whereas the drugs causing adverse metabolic actions have minimal to moderate risk for elevating PRL levels (77). This and other studies (80, 81) support those metabolic adverse effects derived from treatment with antipsychotic drugs not being associated with elevated PRL levels. Attention on drugs that exert beneficial metabolic effects by elevating PRL to HomeoFIT-PRL levels with negligible adverse actions is warranted.

One example is amisulpiride, a D2/D3 antagonist shown to reduce glucose levels in humans (79) and in diet-induced obese mice (82). The proposed beneficial metabolic action of
amisulpiride at low doses involves increasing dopaminergic activity by preferentially blocking presynaptic D2/D3 receptors (83). Also, amisulpiride seems to stimulate insulin secretion by pancreatic β-cells (82). Therefore, given the positive metabolic effects of amisulpiride at low doses and its capacity to increase PRL levels, it is worth testing whether this and other benzamides can improve metabolic outcomes in obesity conditions.

Another benzamide, levosulpiride, is being tested in a clinical trial on patients with diabetic retinopathy and diabetic macular edema to elevate PRL levels and favor its conversion into vasoinhibin, the antiangiogenic, anti-vasopermeability PRL-derived fragment (84). The results of this clinical study raise the possibility to explore the potential therapeutic benefits of levosulpiride on obesity-derived metabolic alterations.

The fact that bromocriptine quick release (Cycloset), a PRL-lowering drug, is an FDA-approved treatment for T2D questions the association between low PRL levels and high prevalence of T2D. This controversy can be explained by the fact that dopamine and PRL act through different mechanisms to promote metabolic homeostasis. There is a morning surge of...
dopaminergic activity in the central nervous system that lowers insulin resistance and hyperglycemia, and this surge is reduced in patients with T2D (85). Accordingly, by counteracting such reduction, treatment with bromocriptine benefits glucose homeostasis. Also, bromocriptine increases glucose tolerance in diet-induced obese mice that are PRL deficient (86). Whether normalizing PRL levels in bromocriptine-treated patients leads to further metabolic improvements is unclear and needs to be investigated.

Conclusions and future perspectives

PRL is present in the circulation throughout life and, particularly in humans, its levels are comparable between sexes, highlighting the role of PRL in physiology beyond reproduction. PRL senses the metabolic status of an individual, and upon physiological and pathological metabolic challenges its levels rise as part of an homeorhetic response, allowing organisms to adequately adjust to such demands. On the other hand, the inability to elevate PRL levels in challenged conditions aggravates metabolic diseases and alters physiological outcomes.

Key questions remain to be addressed such as: 1) What are the signals that increase PRL levels in metabolically healthy individuals and what prevents such elevations in metabolically unhealthy individuals? 2) Does the pharmacological elevation of PRL levels in metabolically unhealthy individuals improve their health outcomes? 3) Are changes in PRL (either decreased or elevated levels) in metabolic diseases part of a larger cascade of altered responses? and, if so, what is the upstream or leading regulator of the cascade? 4) What and how is the PRLR regulated in different physio-pathological conditions and a tissue-specific manner?

Future studies should focus on answering these questions, evaluating the benefit of PRLR-specific agonists, and carefully testing whether the current D2 receptor antagonists at low doses may be useful in the treatment of metabolic diseases due to their PRL-elevating properties. Understanding the underpinnings of PRL actions on metabolism in physiological and pathological conditions will help target this hormone to improve health outcomes.

Author contributions

YM wrote manuscript. XR-H prepared figures. XR-H, DV-C, GR-H, GE and CC reviewed, edited, and approved manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the 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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