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REVIEW

The metabolic role of prolactin: systematic review, meta-analysis and preclinical considerations

Giovanni Corona [a], Giulia Rastrelli[b], Paolo Comeglio[b], Federica Guaraldi[c], Diego Mazzatenta[c], Alessandra Sforza[a], Linda Vignozzi[b] and Mario Maggi [d]

[a]Endocrinology Unit[1], Medical Department, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy; [b]Andrology, Women's Endocrinology and Gender Incongruence Unit[2], Mario Serio Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [c]IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; [d]Department of Biomedical and Neuromotor Sciences (DIBINEM)4, Alma Mater Studiorum Bologna University, Bologna, Italy; Endocrinology Unit [4], Mario Serio Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy

ABSTRACT

Introduction: Hyperprolactinemia has been proven to induce hypogonadism and metabolic derangements in both genders, while the consequences of prolactin (PRL) deficiency have been poorly investigated.

Areas covered: To systematically review and analyze data from clinical studies focusing on the metabolic consequences of abnormally high prolactin levels (HPRL) and low prolactin levels (LPRL). In addition, data from preclinical studies about underlying pathophysiological mechanisms were summarized and discussed.

Expert opinion: PRL contributes to providing the correct amount of energy to support the mother and the fetus/offspring during pregnancy and lactation, but it also has a homeostatic role. Pathological PRL elevation beyond these physiological conditions, but also its reduction, impairs metabolism and body composition in both genders, increasing the risk of diabetes and cardiovascular events. Hence, hypoprolactinemia should be avoided as much as possible during treatment with dopamine agonists for prolactinomas. Patients with hypoprolactinemia, because of endogenous or iatrogenic conditions, deserve, as those with hyperprolactinemia, careful metabolic assessment.

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1. Introduction

Due to apes walking upright and to the relative increase in human cranial dimension, as compared to other mammals, the human female birth canal is relatively narrow, forcing women to have developmentally premature offspring [1,2]. Hence, long-term lactation and maternal care of the newborn are two important aspects for human species perpetuation. Several hormones facilitate these attitudes and behaviors, but the most important is prolactin (PRL) and its receptor. The PRL receptor (PRLR) is a single-pass transmembrane receptor belonging to the cytokine receptor superfamily acting through Janus Kinase (JAK) and Signal Transducer and Activator of Transcription 5 (STAT5). Interestingly, PRLR showed a burst of change in structure during primate evolution along with its ligand, PRL [3], most probably to adapt to the aforementioned scenario. PRL is a pleiotropic 199 amino acid polypeptide discovered in the early thirties of the last century and produced by many cells throughout the human body, but mainly secreted in the bloodstream from the anterior pituitary [4]. It serves many biological functions, but its main role in mammals is to favor milk production by controlling mammary gland development (mammogenesis), onset of lactation (lactogenesis), and galactopoiesis [4].

In humans [5] and chimpanzees [6] PRL levels are almost twice as high in females as in males, and increases by 10- to 20-fold during pregnancy and lactation, substantiating the important role of this hormone in maternal preparation for childbearing. Unlike other pituitary hormones or hormones from other endocrine glands, a clinical condition characterized by an isolated deficiency of PRL has been scarcely investigated. Recently, three cases of isolated PRL deficiency have been described in female subjects from one family with postpartum alactogenesis, due to a PRL gene mutation [7]. No other phenotype was apparent and fertility, along with normal menstrual cycling, was preserved [7]. The latter finding further corroborates the essential role of PRL in milk production.

In contrast to the female gender, the biological function(s) of PRL in the male are less defined and a matter of debate. In several animal models a trophic effect of PRL on growth and function of male accessory glands has been demonstrated [8,9]. Accordingly, normal circulating PRL levels in men are associated with a trophic effect on seminal vesicle volume and on its emptying activity, as well as with the amount of ejaculated volume [10].

In men, as well as in women, an abnormal increase in PRL levels (HPRL) is associated with hypogonadotropic hypogonadism due

CONTACT Giovanni Corona jocorona@libero.it Endocrinology Unit[1], Medical Department, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy
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Article highlights

- High prolactin levels are associated with worse body composition and glycometabolic profile
- Restoring normal prolactin levels in patients with hypoprolactinemia ameliorates body composition and glycometabolic profile
- Gender differences can interfere with elevated prolactin metabolic-related disturbances.
- Low prolactin levels are characterized by worse lipid profiles, higher fasting glucose and higher risk of diabetes when compared to controls.
- The clinical syndrome hypoprolactinemia is a new condition that needs further studies to define its pathological burden.

to a hyperprolactinemia-induced reduction of gonadotropin-releasing hormone (GnRH) pulsatility [11]. In addition, in women, there is a clear phenotype associated with an abnormal PRL elevation (Chiari Frommel syndrome: amenorrhea/galactorrhea) that was formerly described in the early 1950s[12]. In contrast, in men, besides the hypogonadism-related symptoms and signs, there is no hyperprolactinemia-associated phenotype, and the only, often reported, symptom is severely reduced sexual desire [13,14]. More than ten years ago we originally described, in a large cohort of men consulting for sexual dysfunction, a syndromic condition we termed 'hypoprolactinemia' (LPRL) [15]. The condition was characterized by the association between low prolactin levels with particular psychological, sexual and metabolic issues, including anxiety, premature ejaculation, increased glucose levels and diabetes [15]. However, considering the metabolic effects of PRL, there are conflicting results – obtained in both preclinical and clinical studies – showing that either low or high PRL might be associated with consistent metabolic derangements (see for review in [9,16,17]).

The aim of the present review is to describe the metabolic effects of PRL and its receptor in conditions where PRL levels were abnormally decreased or increased. We will overview, through meta-analysis, clinical results obtained in cross-sectional, longitudinal and intervention studies, focusing on studies involving either 'abnormally' high PRL levels or 'abnormally' low PRL levels. Preclinical studies from our and other laboratories will aid in the interpretation of clinical results.

2. Methods

A comprehensive systematic review was performed using Medline, Embase and Cochrane search. In particular, two separate literature searches until 31 March 2022 for published English-language articles were performed. The first literature search was conducted to evaluate the influence of HPRL and its treatment on body composition and metabolic controls using the following search string: ('high'[All Fields] AND ('prolactin'[MeSH Terms] OR 'prolactin'[All Fields] OR 'prolactins'[All Fields] OR 'prolactin s'[All Fields] OR 'prolactine'[All Fields] OR 'prolactinic'[All Fields] OR 'hyperprolactin*' [All Fields]) AND ('glucose'[MeSH Terms] OR 'glucose'[All Fields] OR 'glucoses'[All Fields] OR 'glucose s'[All Fields] OR 'glycemia' [All Fields] OR 'weight' [All Fields] OR 'lipid' [All Fields] OR 'cholesterol' [All Fields] OR 'triglycerides' [All Fields] OR 'waist circumference' [All Fields] OR 'fat' [All Fields]). 'high'[All Fields] AND ('prolactin'[MeSH Terms] OR 'prolactin'[All Fields] OR 'prolactins'[All Fields] OR 'prolactin s'[All Fields] OR 'prolactine'[All Fields] OR 'prolactinic'[All Fields]) AND ('glucose'[MeSH Terms] OR 'glucose'[All Fields] OR 'glucoses'[All Fields] OR 'glucose s'[All Fields]). The second search was performed to investigate the contribution of reduced PRL levels (LPRL) on the same parameters evaluated in the first search using the following search string; ('reduced'[All Fields] OR 'low'[All Fields] OR 'hypo'[All Fields]) AND ('prolactin'[MeSH Terms] OR 'prolactin'[All Fields] OR 'prolactins'[All Fields] OR 'prolactin s'[All Fields] OR 'prolactine'[All Fields] OR 'prolactinic'[All Fields] OR 'hyperprolactin*' [All Fields]) AND ('glucose'[MeSH Terms] OR 'glucose'[All Fields] OR 'glucoses'[All Fields] OR 'glucose s'[All Fields] OR 'glycemia' [All Fields] OR 'weight' [All Fields] OR 'lipid' [All Fields] OR 'cholesterol' [All Fields] OR 'triglycerides' [All Fields] OR 'waist circumference' [All Fields] OR 'fat' [All Fields]).('reduce'[All Fields] OR 'reduced'[All Fields] OR 'reduces'[All Fields] OR 'reducing'[All Fields]) AND ('prolactin'[MeSH Terms] OR 'prolactin'[All Fields] OR 'prolactins'[All Fields] OR 'prolactin s'[All Fields] OR 'prolactine'[All Fields] OR 'prolactinic'[All Fields]) AND ('glucose'[MeSH Terms] OR 'glucose'[All Fields] OR 'glucoses'[All Fields] OR 'glucose s'[All Fields]). When indicated, further papers were retrieved from available meta-analyses.

Preclinical data were obtained from a previously published series of rabbits fed a regular or a high- fat diet [HFD] and undergoing or not physical exercise [18–22]. Animal handling complied with the Institutional Animal Care and Use Committee of the University of Florence, Florence, Italy in accordance with the Italian Ministerial Law # 116/92.

Clinical data were derived from a consecutive series of more than 3000 patients seeking medical care at the University of Florence as previously described [15,23].

A meta-analytic approach was applied to evaluate the influence of HPRL and its treatment as well as the contribution of LPRL to metabolic and body composition parameters (Supplementary Appendix # 1 and 2). In particular, we included all studies analyzing the effects of HPRL or LPRL on body composition and glycometabolic parameters. Specifically, only those studies dealing with HPRL due to PRL secreting pituitary micro and macroadenomas were considered. Conversely, those trials considering HPRL due of other causes or a mixed population were excluded from the analysis. The search was restricted to English-language articles and human studies.

3. Results

3.1. Metabolic consequences of (abnormal) PRL increase

3.1.1. Clinical evidence

3.1.1.1. Observational studies. Out of 434 retrieved articles, 17 were included in the analysis ([15,24–39]; Supplementary Figure S1, Panel A). In particular, 15 studies included patients with hyperprolactinemia (HPRL) due to pituitary PRL-secreting adenomas, and 2 a mixed population of patients with HPRL due to PRL-secreting adenomas or as a consequence of other causes of elevated PRL levels. The characteristics of the

Table 1. Characteristics of trials included in the study.

Study	N° of HPRL subjects	N° of control subjects	Mean age (years)	BMI (Kg/m^2)	Male (%)	Aetiology of HPRL	% macroadenomas	PRL levels (mU/ml)
Greenman et al., 1998 [24]	42	36	37	31.3	57	Pituitary secreting adenomas	59.5	37.984
Yavuz et al., 2003 [25]	16	20	31	26	100	Pituitary secreting adenomas	0	3.287
Tuzcu et al., 2003 [26]	30	30	25.9	23	100	Mixed HPRL	6.6	1.764
Serri et al., 2006 [27]	15	20	39.8	25.9	50	Pituitary secreting adenomas	13.3	1.880
Naliato et al., 2007 [28]	11	14	34.6	27.6	0	Pituitary secreting adenomas	-	24.846
Corona et al., 2009 [15]	13	65	47.8	27.5	0	Pituitary secreting adenomas	-	-
Erem et al., 2010 [29]	22	20	38.8	27.3	54.5	Pituitary secreting adenomas	63.6	9.870
de Assunção et al., 2012 [30]	20	40	33.9	28.6	80	Pituitary secreting adenomas	80	4.440
Reuwer et al., 2012 [31]	10	10	35	25.6	80	Pituitary secreting adenomas	-	1.428
Corona et al., 2014 [32]	14	70	61.3	27.4	100	Mixed HPRL	-	-
Jiang et al., 2014 [33]	31	60	29.7	23.6	74.2	Pituitary secreting adenomas	31.3	9.267
Breyer de Freitas et al., 2015 [34]	23	28	48.3	35	78.3	Pituitary secreting adenomas	70	1.229
Delibasi et al., 2015 [35]	44	32	38,7	30,7	82	Pituitary secreting adenomas	25	1.867
Medic-Stojanoska et al., 2015 [36]	19	20	30,45	24,5	100	Pituitary secreting adenomas	30	2.892
Pala et al., 2015 [37]	20	16	27,3	24,2	95	Pituitary secreting adenomas	21	2.491
Peric et al., 2016 [38]	29	57	34	31	65,5	Pituitary secreting adenomas	-	3.121
Posawetz et al., 2021 [39]	21	30	37	31,3	33,3	Pituitary secreting adenomas	57,1	5.201

BMI = body mass index; PRL = prolactin; HPRL = hyperprolactinemia.

retrieved trials and type of outcomes considered are reported in Table 1 and Supplementary Table S1. The retrieved studies included 380 and 568 individuals with HPRL and control groups, respectively. The mean age, baseline PRL and body mass index (BMI) of enrolled patients were 37.2 years, 7437 mU/L and 27.3 kg/m^2, respectively. Among the population considered, the prevalence of women was higher when compared to men (61.8 vs 38.2%) and PRL-secreting pituitary macro-adenomas were present in about 1/3 of the considered studies (mean 38.1%; Table 1). The criteria used for the definition of HPRL differ among the studies.

I^2 for BMI was 30.2, p = 0.116. Funnel plot and Begg-adjusted rank correlation test suggested no major publication bias (Kendall's τ: −0.213; p = 0.232). When compared to controls, patients with HPRL showed worse body composition: higher BMI, waist circumference and body fat; (see also Figure 1, Panel A and Supplementary Figure S2, panels A-C). In addition, higher total and low-density lipoprotein (LDL)-cholesterol as well as higher triglyceride levels were observed in patients with HPRL when compared to controls (see also Figure 1, Panel A and Supplementary Figure S2, Panels D-F). Furthermore, a trend towards lower HDL-cholesterol in patients with HPRL was also observed (see also Figure 1, Panel A and Supplementary Figure S2, Panel G). Finally, when glucose profile was analyzed, subjects with HPRL were characterized by higher HOMA index and insulin levels although no difference in fasting glucose levels was observed (see also Figure 1, Panel A and Supplementary Figure S2; Panels H-L).

3.1.1.2. Interventional studies. Data on several parameters derived after medical therapy of HPRL due to pituitary-PRL secreting adenomas were available in 18 studies (Table 2 and Supplementary Table S2 [25,27,36,37,39–52];). Dopamine agonist treatment (DAT) was administered in different doses and formulations. Only DAT was used in 18 studies whereas a combination of DAT and surgery [52] or testosterone replacement therapy (TRT [46];) was used in one study respectively (Table 2 and Supplementary Table S2). The characteristics of the retrieved trials and type of outcomes considered are reported in Table 2 and Supplementary Table S2. The retrieved studies included 499 patients with mean age, baseline PRL and BMI of 35.9 years, 13,747 mU/L and 27.4 kg/m^2, respectively. Similar to what was reported for cross-sectional studies, among the population considered, the prevalence of women was higher when compared to men (63.9 vs. 35.1%) and the mean follow-up was 78.3 weeks (Table 2). The criteria used for the definition of HPRL differ among the studies.

I^2 for BMI was 77.02, p < 0.0001. Funnel plot and Begg-adjusted rank correlation test suggested no major publication bias in both types of studies (Kendall's τ: 0.110; p = 0.537). DAT resulted in amelioration of BMI (Figure 1,

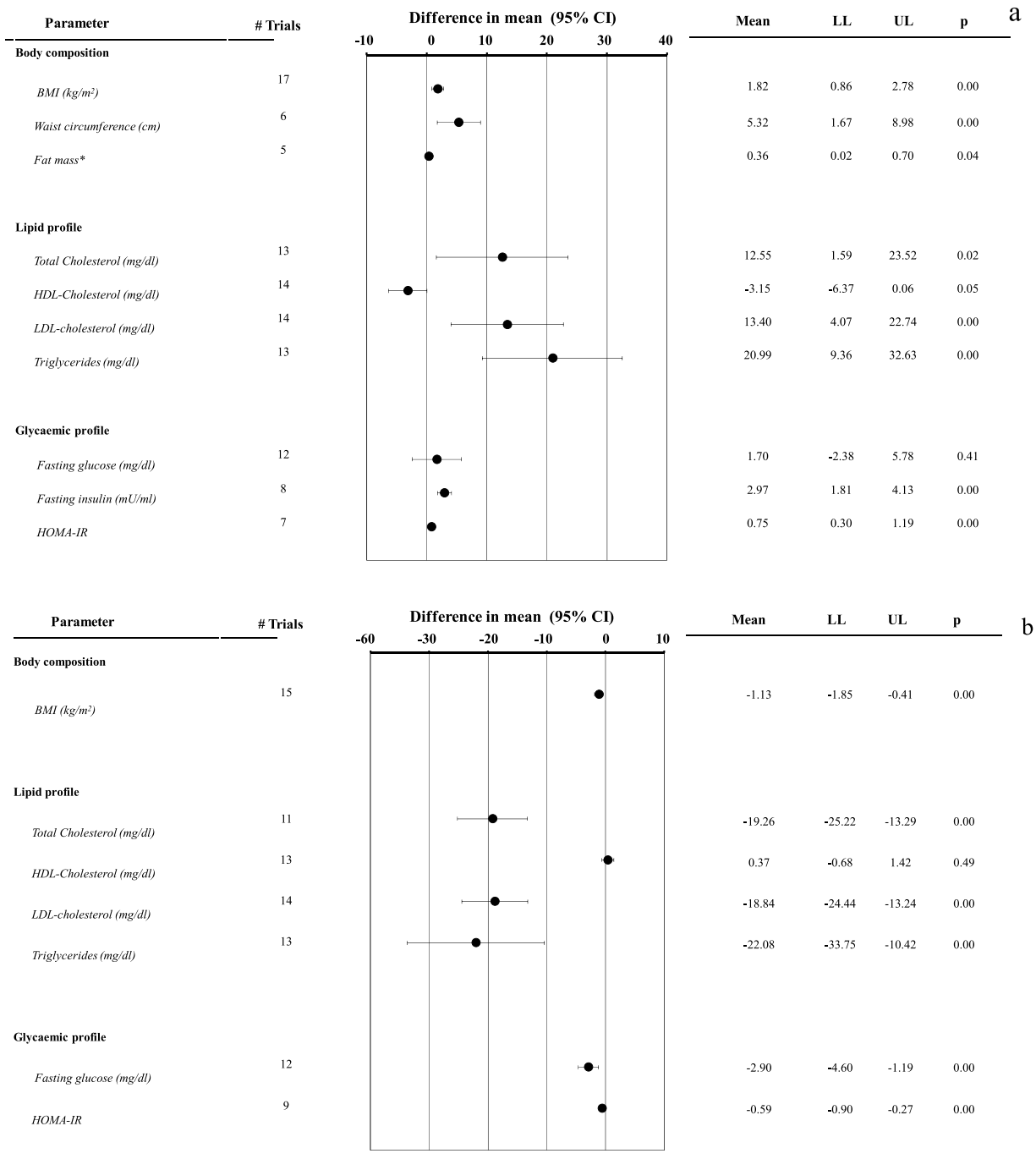

Figure 1. *Panel a*: Overall differences in several body composition and glycometabolic parameters between patients with hyperprolactinemia and controls. *Panel b*: Overall differences in several body composition and glycometabolic parameters after dopamine agonist treatment in patients with prolactin secreting adenomas. BMI = body mass index; HDL = high density lipoprotein; LDL = low density lipoprotein; HOMA-IR = Homeostasis model assessment: insulin resistance. LL = lower levels; UL = upper levels. *reported as standardized mean.

Panel B and Supplementary Figure S3, Panel A) although no differences in patient's weight were observed (not shown). When lipid profile was considered, DAT resulted in an improvement of total and LDL cholesterol as well as triglyceride levels (Figure 1, Panel B and Supplementary Figure S3, Panels B-D). Conversely, no effect on HDL cholesterol was detected (Figure 1, Panel B and Supplementary Figure S3, Panel E). Similar to what was observed for lipid profile, DAT also induced an improvement in fasting glycaemia and HOMA index (Figure 1, Panel B and Supplementary Figure S3, Panels F-G). Interestingly, a meta-regression analysis showed that both total cholesterol and fasting glucose improvement were higher in those studies enrolling a larger number of female

Table 2. Characteristics of trials included in the study.

Study	N°	Follow up (weeks)	Mean age (years)	BMI (Kg/m^2)	Female (%)	Aetiology of HPRL	PRL levels (mU/ml)
Doknic et al., 2002 * [40]	12	96	-	30.4	0	Pituitary secreting adenomas	71.362
Doknic et al., 2002 [40]	11	96	-	24.4	100	Pituitary secreting adenomas	11.395
Korner et al., 2003 [41]	16	54	-	30	38	Pituitary secreting adenomas	-
Yavuz et al., 2003 [25]	16	16	31.1	26.3	100	Pituitary secreting adenomas	3.287
Serri et al., 2006 [26]	15	12	39.8	28.9	50	Pituitary secreting adenomas	1,880
Steele et al., 2010 [42]	29	460	18	27.9	96.6	Pituitary secreting adenomas	10.238
Berinder et al., 2011* [43]	6	26	44.5	25.1	0	Pituitary secreting adenomas	26,460
Berinder et al., 2011 [43]	8	26	44.5	25.1	100	Pituitary secreting adenomas	1.512
dos Santos Silva et al., 2011 [44]	22	26	38	29.5	85.7	Pituitary secreting adenomas	3.129
Auriemma et al., 2013 [45]	61	240	34.4	27.6	78.7	Pituitary secreting adenomas	16.5756
Ciresi et al., 2013 [47]	43	24	34	29.6	85.7	Pituitary secreting adenomas	3.715
Barbosa et al., 2014 [48]	21	52	33.7	25.6	81	Pituitary secreting adenomas	3.024
Auriemma et al., 2015 [46]	30	104	42	31,7	100	Pituitary secreting adenomas	42.588
Medic-Stojanoska et al., 2015 [36]	20	26	27,3	24,2	94	Pituitary secreting adenomas	28.920
Pala et al., 2015 [37]	19	16	30,45	24	100	Pituitary secreting adenomas	2.491
Schwetz et al., 2017 [49]	53	36	40	27,9	41,5	Pituitary secreting adenomas	4.633
Khalil et al., 2020 [50]	32	12	36	28,9	43,8	Pituitary secreting adenomas	12.851
Andereggen et al., 2021 [51]	30	207,6	48	28,6	43	Pituitary secreting adenomas	17.976
Pirchio et al., 2021 [52]	17	52	33,9	-	29,4	Pituitary secreting adenomas	28.452
Pirchio et al., 2021** [52]	17	52	33,9	-	41,2	Pituitary secreting adenomas	5.229
Posawetz et al., 2021 [39]	21	10	38,1	24,8	33,3	Pituitary secreting adenomas	5.202

BMI = body mass index; PRL = prolactin; HPRL = hyperprolactinemia. * only men; ** combined medical and surgical therapy

patients (Figure 2, Panels A and B). Conversely, the effects on BMI were more evident in those studies enrolling a larger amount of males (Figure 2, Panel C).

3.1.2. Preclinical evidence

Meta-analyses of available clinical trials investigating metabolic derangements associated with an excess of PRL levels essentially indicate that, in humans, an abnormal PRL increase – as observed in prolactinomas – is associated with weight gain, dyslipidemia and insulin resistance, but not with an overt diabetes mellitus. In addition, treating hyperprolactinemia is associated with weight loss and amelioration of the lipid profile. Interestingly, glycometabolic control is apparently unaffected by the excess of PRL. Overall, these findings suggest a direct effect of increased PRL on changing metabolism, most probably to favor storing energy for childbearing and lactation. The HPRL-associated weight gain could be due to either an increase in fat storing or to an increase in food intake. As stated before, the main PRL role in humans is favoring mammogenesis, lactogenesis and galactopoiesis during pregnancy and breastfeeding. Hence, it can be hypothesized that if an increased PRL has any role in metabolism, it is to store enough extra energy resources to ensure optimal nutrition to the offspring. In fact, it has been demonstrated that the daily additional energy need for breastfeeding in humans is around 700 kcal [53] and therefore represents a highly demanding metabolic state.

3.1.2.1. PRLR and adipogenesis. Many preclinical studies, summarized by Lopez-Vicchi et al [16], have demonstrated that PRL favors adipogenesis. For example, PRLR deficient mice showed one half of total abdominal fat mass and one third of fat mass expressed as a percentage of body weight, when compared to wild type mice with a final 10% reduction in body weight [54]. This phenotype was more apparent in female than in male mice [54]. In addition, PRLR gene expression increased by 90-fold during in vitro adipocyte differentiation from preadipocytes [55]. Hence, PRLR might have a direct role in regulating fat mass.

During the last 10 years, we have been investigating rabbit models characterized by alterations of visceral fat mass obtained by dieting (high fat diet, HFD, with or without testosterone), hormonal (chemical castration with a GnRH analog with or without testosterone) or pharmacological (metformin, tadalafil) manipulations [18–22]. Figure 3, panel B shows the effect of the different treatments [18–22] on visceral fat accumulation expressed as percentage of body weight (VAT/BW). Figure 3, Panel A also shows the relationship between VAT/BW and gene expression of PRLR. Even after adjusting for total testosterone and glucose tolerance (area under the curve of an oral glucose tolerance test), there is a highly significant, positive correlation ($\beta = 0.298$, $p < 0.0001$, $n = 131$) between VAT/BW mass and PRLR. Interestingly, at ANCOVA and post-hoc Bonferroni test we also found no significant differences in PRLR expression among the aforementioned different experimental groups, after adjusting for VAT/BW modification (all $p > 0.05$, data not shown). Hence, the expression of PRLR mRNA in VAT is affected more by the amount of VAT accumulation than by its experimental manipulations. Among 122 VAT genes previously investigated [18–22] – involved in inflammation, white and brite adipogenesis, glucose and lipid metabolism, lipid droplet formation, signal transduction and hormone receptors – we found a significant association between the expression of PRLR and the majority of them ($n = 72$, 59%). Supplementary Table S3 reports Spearman coefficients for several of these associations. Overall these associations, along with the other experimental observations [16], support an important role of PRLR in adipose tissue remodeling and lipid metabolism. It is important to note that the expression of PRLR in VAT is associated with genes playing apparent opposite roles in metabolism, such as the two main adipokines adiponectin and leptin, or genes devoted to lipid formation (acetyl-CoA carboxylase, diacylglycerol O-acyltransferase 2 and sterol regulatory element-binding

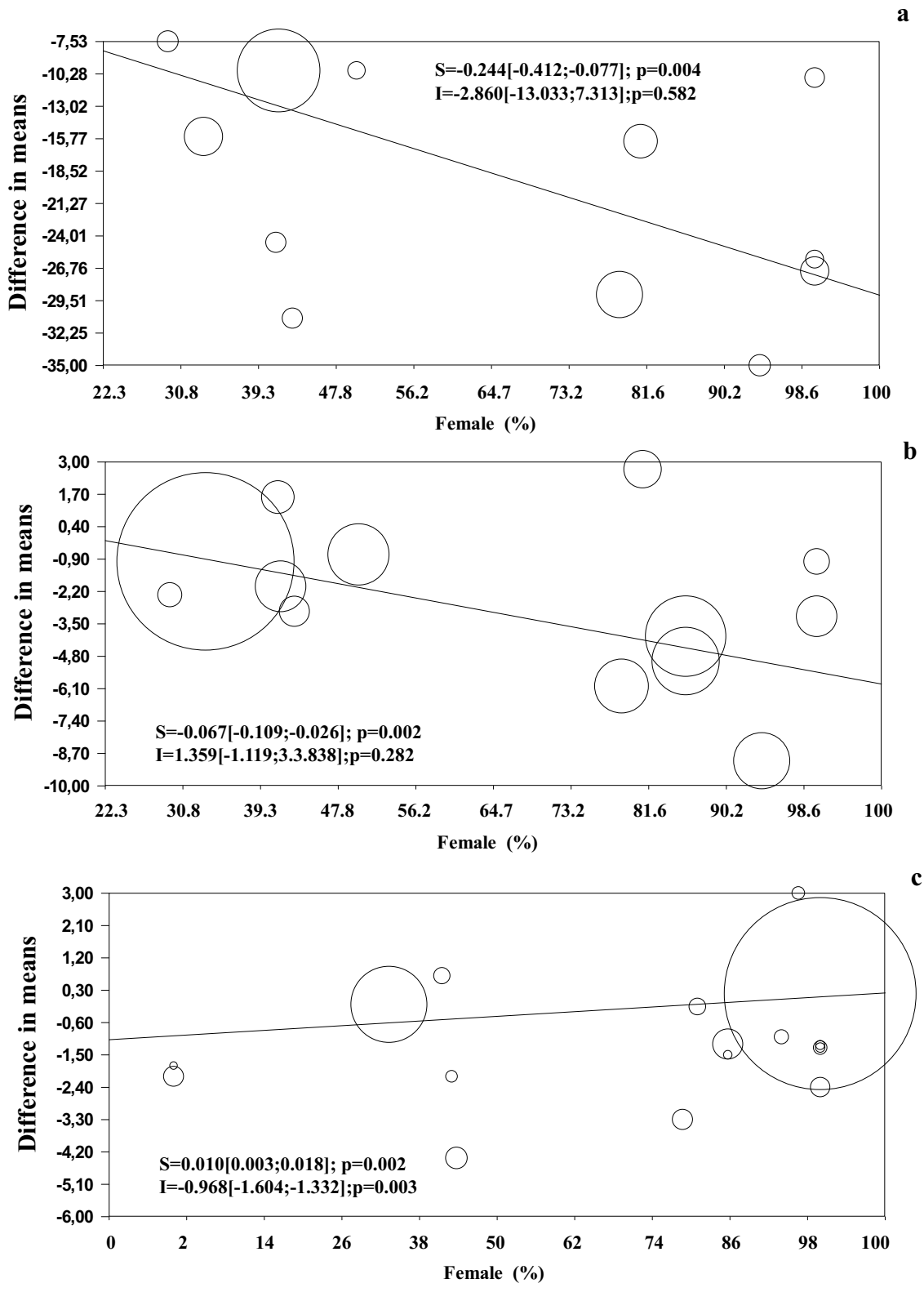

Figure 2. Effects of dopamine agonist treatment in patients with pituitary prolactin secreting adenomas on fasting total cholesterol (a; mg/dl), fasting glucose (b; mg/dl) and body mass index (c; kg/m^2) according to female prevalence within the studies.

protein 2) or degradation (hormone-sensitive lipase, lipoprotein lipase).

3.1.2.2. PRLR and food intake. Weight gain due to high PRL could also be ascribed to an increase in food intake. In fact, several pharmacological manipulations aimed at increasing PRL levels in preclinical models are associated with overfeeding, most probably due to a central effect (reviewed in [16]). PRL and its receptor are present in discrete brain regions, including the hypothalamus [16,56]. In particular, within the hypothalamus,

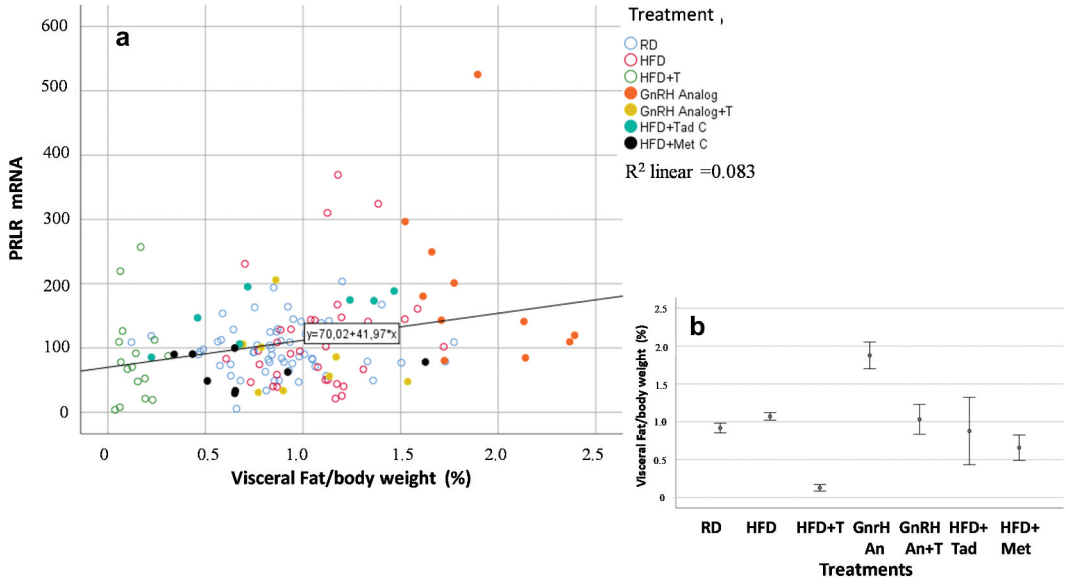

Figure 3. Panel a. Association between visceral fat accumulation (visceral fat/body weight %) and expression of PRL receptor (PRLR) mRNA in different experimental groups of rabbits as in references (18–22). Different colors in open and closed circles indicate the different treatments. Panel b. Effect of the different treatments on visceral fat accumulation expressed as visceral fat/body weight (%). RD = regular diet, control (18–22); HFD = high-fat diet (18–22); GnRH An = GnRH analog triptorelin pamoate (21); GnRH An+T = GnRH analog triptorelin pamoate plus testosterone (21); HFD+Tad = high-fat diet + tadalafil (18); HFD+Met = high-fat diet + metformin (19). Data are derived from the aforementioned references and calculated per the $2^{-\Delta\Delta Ct}$ comparative method, using the 18S ribosomal RNA subunit as the reference gene for normalization. Results are expressed as percentage-change vs. the RD group.

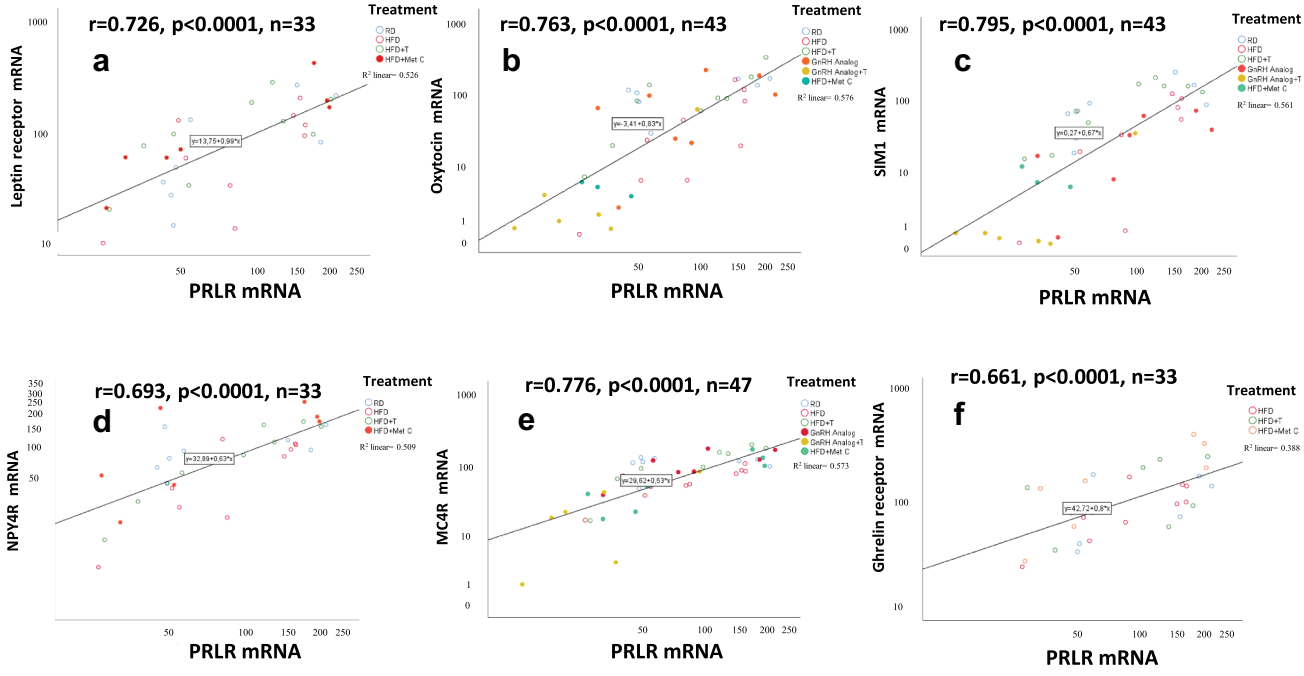

Figure 4. Association between expression in the preoptic area of the hypothalamus of prolactin receptor (PRLR) mRNA and the indicated genes involved in the regulation of food intake. In each panel the number of experimental observations, the correlation coefficients and the level of significance are reported. Different colors in open and closed circles indicate the different treatments. Note the log scales. SIM1 = Single-minded homolog 1; NPY4R = Neuropeptide Y receptor Y4; MC4R = Melanocortin 4 receptor. Data are derived from references (20–21, 60–62) and calculated per the $2^{-\Delta\Delta Ct}$ comparative method, using the 18S ribosomal RNA subunit as the reference gene for normalization. Results are expressed as percentage-change vs. the RD group.

PRLR is expressed in several nuclei, such as the ventromedial (VMN), the arcuate, the supraoptic, the paraventricular (PVN) and in the medial preoptic area (mPOA). The PVN is a region that is critical not only for maternal behavior but also for energy balance. This nucleus is endowed with receptors for anorexigenic stimuli – i.e. melanocortin 4 receptor (MC4R) and leptin receptor – and contains anorexigenic peptides such as oxytocin, which, beside its anorexigenic property [57], is of crucial relevance in maternal behavior and pair bonding [58]. The development of PVN is dependent on a transcription factor, Single-minded 1

(SIM1), whose haploinsufficiency causes hyperphagia and severe obesity even in humans [59].

By using data on the preoptic area of the hypothalamus from previous studies in rabbits [20,21,60–62] we now report (Figure 4) a very close association between PRLR gene expression and SIM1, and oxytocin (Figure 4, Panels C and B; respectively). In addition, PRLR in the hypothalamus is also very closely associated with other sensors of the metabolic state, such as leptin and ghrelin receptors (Figure 4 Panels A and F; respectively) and receptors for neurotransmitters deeply implicated in human food intake disorders, such as MC4R and the neuropeptide Y receptor Y4 (NPY4R) (Figure 4 Panels D and E; respectively). Some lines of evidence suggest that the major function of PRLR in the hypothalamus is to induce a state of leptin insensitivity, therefore decreasing anorexigenic (e.g. MC4R) and increasing orexigenic (e.g. NPY4R) neuron activity, as summarized by Lopez Vicchi et al [16].

3.1.2.3. PRLR and insulin secretion. Taken together, the preclinical data could offer a sufficient explanation of why in the present meta-analysis PRL excess is associated with weight gain, insulin resistance and dyslipidemia. The proof of this concept is that treating hyperprolactinemia with dopaminergic agents is associated with a decrease in body weight and amelioration of the lipid profile. Interestingly, the HPRL-related weight gain is in one way associated with insulin resistance but in the other way not with a state of overt diabetes. This most probably because PRLR in the pancreas positively regulates β-cell expansion, glucose entry within the β-cells and glucose-stimulated insulin secretion [16]. These conditions are crucial in guaranteeing euglycemia during pregnancy, a state characterized by insulin resistance. Accordingly, loss of function of PRLR in the β-cells is associated with elevated blood glucose, lowered β-cell mass and gestational diabetes [63]. In

Table 3. Characteristics of trials included in the study.

Study	N°	Mean age (years)	BMI (Kg/m^2)	Female (%)	Type of population	Mean PRL levels (mU/ml)	Reduced PRL definition	Lowest PRL levels (mU/ml)
Cross-sectional data								
Corona et al., 2009 [15]	1040	52	313	0	Erectile dysfunction	159	I vs. IV quartile	113
Reuwer et al., 2009* [64]	1004	64.5	26.7	0	Population based	210.2	I vs. III tertile	178,5
Reuwer et al., 2009 [64]	583	66.3	26.5	100	Population based	195.9	I vs. III tertile	165,3
Carrero et al., 2012** [65]	457	52	26	48	Chronic kidney diseases	669.9	Median	714
Carrero et al., 2012 [65]	173	52	25.1	48	Hemodyalisis	452.8	Median	426,3
Ballach et al., 2013*[66]	1966	52.1	27.3	0	Population based	102.9	I vs. IV quartile	-
Ballach et al., 2013 [66]	2027	49.5	26.1	100	Population based	136.5	I vs. IV quartile	-
Wang et al., 2013 [67]	1034	60	25.1	0	Population based	184.8	I vs. IV quartile	134,4
Wang et al., 2013 [67]	1343	60.5	25.6	100	Population based	210.4	I vs. IV quartile	141,5
Corona et al., 2014 [32]	1448	60	27.8	0	Population based	180.6	I vs. IV quartile	119,7
Glintborg et al., 2014 [68]	1034	30	27.4	100	PCOS	573	Median	573
Wang et al., 2016* [69]	309	60.5	24.9	0	Population based	179.9	I vs IV quartile	138,4
Wang et al., 2016 [69]	447	61.1	25.2	100	Population based	187.3	I vs IV quartile	144,5
Chahar et al., 2017* [70]	90	52.8	24.4	0	People presenting for check-up at medicine outpatient facility	206	I vs IV quartile	151,2
Chahar et al., 2017 [70]	60	55.9	24.9	100	People presenting for check-up at medicine outpatient facility	224.3	I vs IV quartile	159,6
Ruiz-Herrera et al., 2017 [71]	27	37.7	27.2	0	Surgery involving access to the abdominal cavity	254.5	<249 mU/L	249
Ponce et al., 2020 [72]	40	38.9	28.9	50	Surgery involving access to the abdominal cavity	312.3	<252 mU/L	252
Yang et al., 2021 [73]	390	28.8	24.2	100	PCOS	159	I vs. IV quartile	180
Longitudinal data								
Ballach et al., 2013* [66]	1966	52.1	27.3	0	Population based	102.9	I vs. IV quartile	-
Ballach et al., 2013 [66]	2027	49.5	26.1	100	Population based	136.5	I vs. IV quartile	-
Wang et al., 2016* [69]	309	60.5	24.9	0	Population based	179.9	I vs. IV quartile	138.4
Wang et al., 2016 [69]	447	61.1	25.2	100	Population based	187.3	I vs. IV quartile	144.5
Li et al., 2018 [74]	1966	52.7	25.4	100	Female registered nurses	102.9	I vs. IV quartile	168

BMI = body mass index; PRL = prolactin; * only men; ** Chronic kidney diseases. PCOS: Polycystic ovarian syndrome

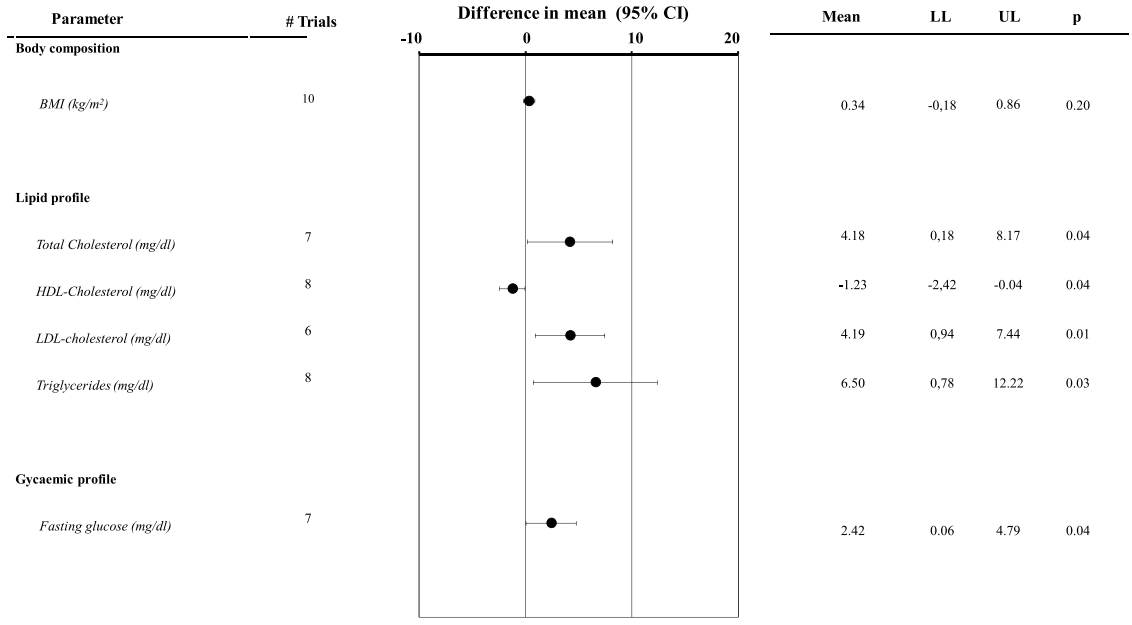

Figure 5. Overall differences in several body composition and glycometabolic parameters in patients with or without reduced prolactin levels. BMI = body mass index; HDL = high density lipoprotein; LDL = low density lipoprotein. LL = lower levels; UL = upper levels.

fact, an increased insulin secretion during pregnancy could compensate for a relative insulin insensitivity, as is also the case for obesity. Accordingly, treating hyperprolactinemia is associated with an increase in insulin sensitivity and a decrease in fasting glucose.

3.2. Metabolic consequences of (abnormal) PRL decrease

3.2.1. Clinical studies

Cross-sectional data on the comparison between subjects with or without reduced levels of PRL were present in 12 out of 615 studies (Supplementary Figure S1, Panel B, Table 3 and Supplementary Table S4 [15,32,64–73]. In addition, 3 studies [66,67,74] longitudinally evaluated the effects of reduced PRL levels and risk of developing type 2 diabetes mellitus. The characteristics of the retrieved trials and type of outcomes considered are reported in Table 3 and Supplementary Table S4. Cross-sectional studies included 7102 patients with mean age, baseline PRL and BMI of 51.9 years, 262.2 mU/L and 26.4 kg/m^2, respectively (Table 3). Longitudinal studies considered 13,364 subjects with mean age, baseline PRL and BMI of 55.2 years, 151.7 mU/L and 25.8 kg/m^2, respectively (Table 3). The criteria used for the definition of LPRL differ among the studies (Table 3).

I^2 for BMI related to cross-sectional data was 85.9, $p < 0.0001$. Funnel plot and Begg-adjusted rank correlation test suggested no major publication bias in both types of studies (Kendall's τ: 0.154; $p = 0.443$). No differences in BMI were observed when subjects with reduced PRL (LPRL) were compared to controls (Figure 5 and Supplementary Figure S4, Panel A). Conversely, subjects included in cross-sectional studies, and with LPRL, showed worse lipid profiles and higher fasting glucose when compared to controls (Figure 5 and Supplementary Figure S4, Panels B-F). In line with these data, the age-adjusted risk for having diabetes, as derived from cross-sectional data, was increased in subjects with LPRL when compared to controls (OR = 1.60[1.43;1.79]; $p < 0.0001$; see also Supplementary Figure S4; Panel G). Similar risk was observed when longitudinal studies were considered (OR = 1.30[1.11;1.52]; $p < 0.0001$ for LPRL vs. controls; see also Supplementary Figure S4, Panel H). Similar data were derived from a series of more than 3000 patients seeking medical care for sexual dysfunction at our unit (Supplementary Figure S5).

3.2.2. Preclinical evidence

As discussed above, increased PRL levels during childbearing has an important role in favoring pregnancy-induced adaptation of glucose metabolism through an induction of maternal insulin resistance compensated by proliferation and increased activity of pancreatic beta cells, with a final result of an increase in β-cell division and an enhanced glucose sensitivity of insulin secretion. These processes favor a maternal-to-fetal gradient of glucose to allow an equilibrated nutrient passage through the glucose-permeable placenta [75]. Recent experiments indicated that targeted deletion of PRLR in the pancreas, but not in the hypothalamus, during mouse pregnancy is associated with gestational diabetes [76,77]. PRLR actions on β-cell proliferation seem to be mediated by a JAK- and STAT5-dependent stimulation of Pbk, a protein kinase that is crucial for basal β-cell division [78].

These preclinical findings can help in understanding why a lower stimulation of PRLR, from a reduced PRL level, could be associated with increased fasting glucose along with a propensity to develop overt diabetes, as demonstrated by clinical studies. Other metabolic derangements, such as dyslipidemia, might be explained by the aforementioned diabetic propensity and by the fact that PRLR is present in adipose tissue. In fact, as shown in Supplementary Table S3, PRLR is not only associated with genes favoring lipid formation (see

above) but also with enzymes that catalyze the hydrolysis of fats (hormone-sensitive lipase, lipoprotein lipase).

4. Conclusions

Data derived from clinical evidence as detected by a meta-analytic approach support the role of PRL as a metabolic hormone involved in supporting and storing the required substances to favor mammogenesis, lactogenesis and galactopoiesis during pregnancy and breastfeeding. Pre-clinical data further corroborate the latter findings. However, it is important to emphasize that several limitations should be recognized and the data derived from the meta-analysis, here reported, should be interpreted with caution. First of all, all the meta-analyzed data were obtained from observational studies, which present an important risk of bias due to the lack of completeness of follow-up and the accrual of missing data [79]. In addition, specific sub-analyses limited to only male or female populations were available only in a limited number of studies. Significant heterogeneity among studies was detected, which reflects the differences observed in population characteristics and in the type of DA preparations and dosages used. It is well known that levels of PRL have a high variability because of its pulsatile release and due to its regulation by a large number of physiological factors, including estrogen levels. Additionally, PRL concentrations tend to be altered based on the phase of the menstrual cycle, and contraceptive use. Unfortunately, information on all these factors were available only in a limited number of the studies included and no further analyses were possible.

The concept of LPRL as a clinical entity was introduced quite recently [32] and only few studies have investigated this condition either in males or females. The criteria used for the definition of both HPRL and LPRL differ among the studies. The characteristics of control groups differ among studies. Subjects in the HPRL group tend to be younger than those included in the LPRL group, which represents a further source of bias. The magnitude of observed differences between HPRL/LPRL and controls derived from our meta-analysis is quite small, suggesting that other factors may well play a possible role. Finally, no information on the effect of increasing PRL in patients with LPRL is available. Hence, the reproducibility of our data warrants caution.

5. Expert opinion

The clinical studies summarized here essentially indicate that PRL is not only a reproductive but also a metabolic hormone. This is likely because the two functions are intimately interconnected, also considering that reproductive function is a costly process in terms of energy consumption. Pregnancy and lactation are a clear example and in these particular conditions PRL and its receptor play an important role: in one way storing and in the other one delivering nutrients to the fetus and the newborn. Accordingly, preclinical studies reviewed elsewhere [9,16,17], and the results presented here, indicate that PRLR is expressed in tissues regulating not only food intake (hypothalamus) and fat handling (adipose tissue) but also insulin secretion, such as in the pancreas. Hence, it is not surprising that in conditions that mimic the pregnancy-induced PRL increase – i.e. any pathological hyperprolactinemic state – there is increased body weight, increased waist circumference and fat accumulation, along with insulin resistance. The increase in fat mass associated with prolactinoma might also be due to the concomitant HPRL-induced hypogonadotropic hypogonadism, at least in males. In fact, in males, T deficiency is associated with an increase in fat mass [80]. Treating prolactinoma is associated with a reduction of BMI, a reduction in glycemia and an amelioration of dyslipidemia, along with a reduction of insulin resistance. It is interesting to note that meta-regression analysis of clinical studies indicates that the positive effects of prolactinoma therapy on fasting glucose and lipids are more apparent in females than in males, whereas the opposite trend was observed for BMI. These observations are in line to what reported in pre-clinical models [54]. Recent data indicate that DAT is able to restore normal T levels in no more than 2/3 of patients with macroprolactinomas [81]. Available guidelines indicate adding on TRT to DAT when the latter therapy alone is not able to completely restore normal T levels [82,83]. Data from the general population [80,84,85] as well as from patients with T2DM or MetS [22,86], have shown that TRT can clearly modify body composition, by reducing fat mass and improving lean mass, however its role on lipid profile and glycometabolic control is more conflicting [87–89]. Hence, the more limited effects on fasting glycaemia and total cholesterol observed in males in the present study after DAT can be explained, at least partially, by the persistence of reduced T levels at the end-point. Unfortunately, the latter information was available only in one study [39], included in our analysis, which confirmed mean reduced T levels at follow-up.

The hyperprolactinemia-induced increase in circulating lipid and glucose do not lead to a state of overt diabetes, because insulin secretion is also increased, most probably due to a PRL-induced stimulation in β-cell secretory response and β-cell mass. The latter may overcome the state of insulin resistance, as usually observed in normal pregnancy. Accordingly, low maternal PRL during pregnancy predicts postpartum prediabetes/diabetes [90], most probably because the compensatory stimulation of insulin secretion is insufficient. In line with this evidence, the present meta-analysis shows that low PRL is associated with overt diabetes in cross-sectional studies and with the risk of developing diabetes in longitudinal studies.

Soto-Pedre et al. [91], reported that high PRL due to pituitary microadenomas was not associated with an increased overall mortality, whereas a higher mortality risk was observed in patients with macroadenomas and in those with drug-induced and idiopathic hyperprolactinemia. Other studies supported high CV risk related to HPRL in males but not in females [92,93]. In particular, a recent retrospective observational study including a total of 3,633 patients with

a median follow-up time of 5.3 years showed that hyperprolactinemia was associated with a higher CV mortality and morbidity risk in males but not in females [93]. The same study also documented that the adjustment for the use of anti-psychotic medication attenuated the observed risk [93]. The specific underlying mechanisms supporting the latter gender difference have yet to be better elucidated. The higher risk observed in patients with macro-adenomas, which are usually characterized by higher PRL circulating levels, suggests a possible role of reduced T levels in the stratification of HPRL-induced CV risk [94]. Conversely, the association with the use of anti-psychotic medications points out other possibilities revised elsewhere [95,96]. Conversely to what was observed for HPRL, low PRL was associated with increased major adverse CV events in high-risk subjects [23] and with a higher incidence of left ventricular altered geometry and hypertrophy during five years of follow-up in the SHIP (Study of Health in Pomerania) population-based study [97].

Based on the available data, it is our expert opinion that the real problem for PRL-associated metabolic derangements is a decreased and not an increased circulating PRL. In fact, a physiological hyperprolactinemia, as observed during pregnancy and lactation, has a homeostatic significance, allowing for correct energy distribution between the mother and the fetus/offspring. In other words, PRL is not a diabetogenic hormone, but actually shows anti-diabetogenic effects. Accordingly, its deficiency is associated with an increased risk of diabetes and cardiovascular events. The clinical syndrome hypoprolactinemia is a puzzling, new condition that needs further studies to define its pathological burden. Further studies are advisable to better clarify our hypothesis.

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ORCID

Giovanni Corona http://orcid.org/0000-0002-9894-2885
Mario Maggi http://orcid.org/0000-0003-3267-4221

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