

RESEARCH

Metabolic effects of dopamine agonists in patients with prolactinomas: a systematic review and meta-analysis

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Abstract

Objectives: Recent large cohort studies suggest an association between high plasma prolactin and cardiovascular mortality. The objective of this systematic review was to systematically assess the effect of reducing prolactin with dopamine agonist on established cardiovascular risk factors in patients with prolactinomas.

Design: Bibliographical search was done until February 2019 searching the following databases: PubMed, EMBASE, WHO and LILAC. Eligible studies had to include participants with verified prolactinomas where metabolic variables were assessed before and after at least 2 weeks treatment with dopamine agonists.

Methods: Baseline data and outcomes were independently collected by two investigators. The study was registered with PROSPERO (registration number CRD42016046525).

Results: Fourteen observational studies enrolling 387 participants were included. The pooled standardized mean difference of the primary outcome revealed a reduction of BMI and weight of -0.21 (95% CI -0.37 to -0.05 ; $P = 0.01$; $I^2 = 71\%$), after treatment. Subgroup analysis suggested that the reduction of weight was primarily driven by studies with high prolactin levels at baseline ($P = 0.04$). Secondary outcomes suggested a small decrease in waist circumference, a small-to-moderate decrease in triglycerides, fasting glucose levels, HOMA-IR, HbA1c and hsCRP, and a moderate decrease in LDL, total cholesterol and insulin.

Conclusion: This systematic review suggests a reduction of weight as well as an improved lipid profile and glucose tolerance after treatment with dopamine agonist in patients with prolactinomas. These data are based on low-quality evidence.

Key Words

- ▶ prolactinoma
- ▶ dopamine agonist
- ▶ weight
- ▶ BMI
- ▶ metabolic effect

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Introduction

In recent large cohort studies, high prolactin levels within and above the normal physiological range have been associated with increased risk of cardiovascular mortality (1, 2, 3). It is speculated whether this association is mediated through prolactin-induced increase in cardiovascular risk factors including obesity, dyslipidemia and insulin resistance (4, 5, 6, 7, 8, 9, 10). In a German population-based cohort study, prolactin levels within the normal

range showed a positive correlation to all-cause as well as cardiovascular mortality (1). Furthermore, prolactin levels prospectively correlated with higher levels of low-density lipoprotein (LDL) in women, and with hypertension and incidence of diabetes in men (11). In two large cohort studies hyperprolactinemia was associated with increased incidence of cardiovascular disease and cardiovascular mortality in men only (2, 3). However, the association between prolactin and excess disease burden is not consistent: In a case-control study with 1204 cases of

hyperprolactinemia, no increased morbidity or mortality was found (12), and in a large cohort, levels of prolactin did not differ between those participants who suffered from fatal or nonfatal coronary artery disease and those who did not (13).

Prolactin receptors are widely distributed in the liver (14), endocrine pancreas (15) and in adipose tissue (16) pointing to a possible direct metabolic effect of prolactin. A number of small studies have found that prolactin levels are associated with inflammation, endothelial dysfunction, insulin resistance and dyslipidemia that could contribute to cardiovascular complications (7, 17, 18, 19, 20). Furthermore, prolactin levels correlated with insulin resistance in patients with polycystic ovary syndrome (21).

Dopamine is the natural negative regulator of prolactin release from the anterior pituitary gland, and dopamine D2 receptor agonists are the first line of treatment for most patients with prolactinoma.

A link between high prolactin levels and cardiovascular mortality would have important clinical implications. According to current guidelines (22), asymptomatic patients with hyperprolactinemia are not necessarily offered treatment; the same is true for secondary hyperprolactinemia as a side effect to widely used medications, such as antipsychotic drugs or in patients with kidney failure.

The purpose of this systematic review was to systematically assess the metabolic effects of dopamine agonist treatment in patients with prolactinomas.

Methods

Study design

A systematic review and meta-analysis. The study was registered with PROSPERO (registration number CRD42016046525).

Study selection

Eligible studies were observational or randomized clinical trials assessing the effect of dopamine agonist treatment in patients with prolactinomas verified by MRI or CT scan. For inclusion, the studies should report on metabolic variables before and after dopamine-agonist treatment. Patients should have been treated with dopamine agonist for more than 2 weeks. Studies that included patients with other treatments for prolactinomas, for example, surgical resection or radiotherapy of the pituitary adenoma were not included. There was no age or language restriction.

Search strategy

The following bibliographical databases were searched until February 2019: PubMed, EMBASE, WHO and LILAC using the text words terms: (prolactin OR hyperprolactinemia OR prolactinoma) AND (dopamine agonist OR dostinex OR cabergoline OR bromocriptine). The search was restricted to titles.

One investigator (SB) conducted the main search. Based on title and abstract, obviously irrelevant titles were removed and the remaining studies were considered for inclusion after thorough review of the full manuscript.

Data extraction

Demographical data, baseline data of participants, study outcomes, diagnostic procedures, patient co-morbidity, hormone replacement among participants, type and duration of treatment, and results were independently collected by two investigators (SB, JF). In studies where more than one follow-up was reported, data from the latest follow-up, where the number and gender distributions of participants were reported, were included in the analysis.

Authors were contacted by mail in case of queries regarding reported data. Two requests were sent with 14-days interval if no response was received after the first request.

Outcomes

Primary outcome

The primary outcome was change in weight or body mass index (BMI) from baseline to the end of the observation.

Secondary outcomes

Secondary outcomes were waist circumference (WC), total cholesterol, low-density lipoprotein (LDL), triglycerides (TRG), fasting plasma glucose, HOMA-IR, fasting serum insulin, glycated hemoglobin (HbA1c), plasma testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), high-sensitivity C-reactive protein (hsCRP) and systolic and diastolic blood pressure.

Assessment of study quality

The risk of bias in the included studies was assessed by using the Newcastle–Ottawa Scale (NOS) for cohort studies as suggested by the Cochrane collaboration (23), which assesses selection bias, comparability and outcome modified for the current systematic review. Selection of

cases was awarded points if patients were consecutively approached for inclusion, if both genders were included in the study and if hypothyroidism was ruled out. In the outcome domain we assessed if the staff assessed weight or if weight was reported by the participants themselves, if staff were blinded to baseline weight and if attrition were less than 5% at follow-up. For each study, we assessed the above items providing each with assessment of 'yes' or 'no'. In case there was inadequate information to judge either 'yes' or 'no' we used 'unclear'. The total risk of bias score was based on one point for each 'yes' in the selection bias domain or the outcome domain. We also included whether the study was conducted prospectively or retrospectively. We considered this item as posing a risk of random error opposed to a systematic error, which was assessed in the selection bias domain and the outcome domains and did not include this item in the total score which represents an estimated pooled risk of bias. Studies with a total score of 4 or more were considered with less risk of bias.

Statistical methods

For all outcomes we reported the pooled effect estimates using the standardized mean difference (SMD). SMD is the mean difference in outcome between the post- and pre-intervention assessment divided by the pooled standard deviation (SD). The result is a unit free effect size and by convention, SMD of 0.2, 0.5 and 0.8 are considered small, medium and large effects sizes.

In case mean (\bar{x}) was not reported, we calculated the mean from median (m) and range (a – b) using the formula $\bar{x} \approx (a+2m+b)/4$, as proposed by Hozo *et al.* (24), and $SD = (b-a)/4$. In case results were reported separately for men and women, a pooled mean and SD was calculated as recommended in Cochrane Handbook for Systematic Reviews (23).

We expected some degree of heterogeneity due to differences in population, duration of treatment and dose of DA, and we *a priori* planned to use random-effects analysis to pool estimates from included studies.

P values below 0.05 were considered significant.

For data analyses, we used Comprehensive Meta-Analysis 2.0. The heterogeneity for each outcome was reported as I^2 .

Subgroup analysis

For the primary outcomes, weight and BMI, we planned to explore the potential effect of confounding variables:

duration of treatment (<6 months was short duration of treatment vs duration of treatment of ≥ 6 months), percentage of included men, prolactin levels at baseline, percentage of macroprolactinoma, the effect of study design as well as the effect of risk of bias. The division of groups for subgroup analysis was based on the median value.

Deviation from the protocol

There have been some changes from the original protocol: the duration of treatment was found to be equivalent to follow-up in the included studies; therefore, no subgroup analysis on follow-up was performed. Comorbidities were an exclusion criterion in seven studies and were not reported in five studies, and as a result of the inconsistency in this data point, a subgroup analysis on comorbidities was not performed. Only three studies reported change of testosterone levels (6, 25, 26) or estradiol levels (25, 27, 28), which is why this subgroup analysis was abandoned. Mixed treatment modalities were added as exclusion criteria to the original protocol. In the data analysis we conducted subgroup analysis by study design and risk of bias in addition to the original protocol. To improve the clinical applicability of the analysis, the effect sizes are also presented as mean difference.

Results

Study selection and characteristics

The bibliographical search was conducted until February 2019. As illustrated in Fig. 1, we included 14 observational studies assessing the effect of dopamine agonist therapy on metabolic variables in 387 patients with prolactinomas (4, 5, 6, 7, 8, 25, 26, 27, 28, 29, 30, 31, 32, 33).

As shown in Table 1, nine of the included studies were prospective (5, 7, 8, 26, 27, 28, 29, 30, 32), three studies (4, 25, 33) were retrospective and in two studies the design was not clearly stated (6, 31). As shown in Table 2, study participants were treated with cabergoline (CAB) in eight studies (4, 5, 7, 25, 26, 27, 30, 33), bromocriptine (BRC) in two studies (28, 31) and in four studies participants received either CAB or BRC (6, 8, 29, 32).

The median percentage of male participants was 23% (range, 0–100%). The median of mean age was 37 years (range, 27–42 years). The median percentages of study participants with macroprolactinoma were 31.5% (range, 13–78%). The range of mean plasma prolactin was 2514–43,693 mU/L and the median follow-up time was 6 months (range, 3–60 months). The median number

Prisma Flow Chart

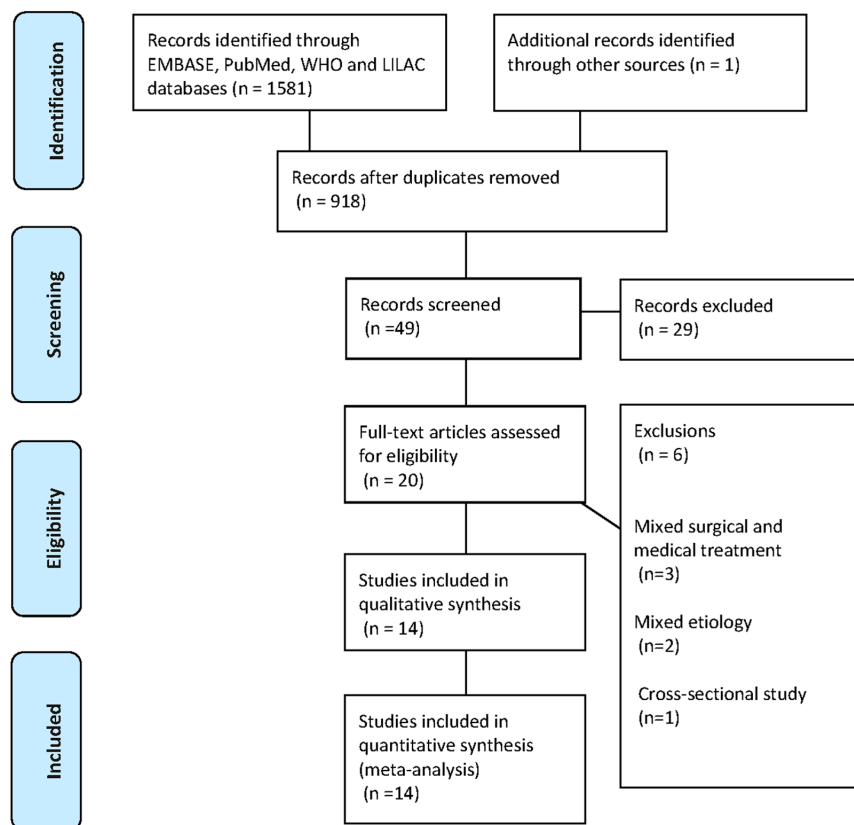


Figure 1
Prisma flow chart.

of participants that reached normoprolactinemia at follow-up was 97% (range, 56–100%) (4, 5, 6, 7, 8, 26, 27, 28, 29, 30, 32).

Because of heterogeneity in reported data, it has not been possible to compare the data regarding treatment dosage: In two studies the dosage was not reported (8, 29); two studies reported the initial dosage (27, 30), two studies reported a range of doses administered, without reporting a median dose (28, 31); one study reported the accumulated dose of 108 mg CAB administered over a mean period of 56.9 ± 46 months (33) and four studies reported doses administered in different periods of the studies (4, 5, 7, 26).

Raw data are presented in Supplementary Tables 3, 4, 5, 6, and 7 (see section on [supplementary data](#) given at the end of this article).

In the nine studies reporting obesity at baseline, the median percentage of participants with overweight at baseline was 47% (range, 19–97%) (5, 6, 7, 8, 26, 27, 29, 30, 31). The median fasting glucose levels at baseline were 5.2 mmol/L (range, 4.4–6.5), and median HbA1c was 35.5 mmol/mol (34.4–36.8). The median mean value of LDL at baseline was 3.3 mmol/L (range, 2.8–3.7). Only 3 of 14 studies reported on baseline levels of sex hormones.

The prevalence of comorbidities was not reported, or participants with comorbidities were excluded, in 12 studies.

Assessment of risk of bias in included studies

None of the included studies had a control group and the comparability item was left out. No participants were lost to follow-up in 9 of 14 studies (4, 5, 25, 26, 28, 30, 31, 32, 33), in four studies 7–40% of participants were not included in final analysis (6, 8, 27, 29), and in one study this item was unclear (7). Based on our modified NOS bias assessment, we found that eight studies had a high risk of bias, and five studies had a lesser risk of bias in the 13 studies that reported on the primary outcome. Risk of bias for the primary outcome is presented in [Table 1](#).

Primary outcome: the effect of dopamine agonist therapy on weight or body mass index

At follow-up, 12 studies reported change in BMI, one study reported change in weight exclusively and, finally, one study reported neither change in weight nor BMI. Therefore, 13 studies with 360 participants were available for analysis. The standardized mean change in BMI and

Table 1 Risk of bias in included studies for the primary outcome – ‘change in weight’.

Study	Random error		Selection bias			Outcome		Total points	Notes
	Prospective	Consecutive enrollment	Both genders	Hypothyroidism ruled out	Weight assessment by staff	Blinded to baseline weight	<5% missing data		
Auriemma 2014 (5)	Yes	Yes	Yes	Yes	Yes	Unclear	No	4	Assessment from 3 to 6 months interval from baseline not included in report. 25/95 patients excluded due to treatment duration <12 months
Auriemma 2015 (26)	Yes	Yes	No	Yes	Yes	Unclear	No	3	Assessment from 3 to 6 months interval not included in report. 7/45 patients not included due to treatment duration <12 months
Barbosa 2014 (33)	Yes	Unclear	Yes	Yes	Yes	Unclear	No	3	10/35 patients not included due to discontinuation of dopamine agonist therapy due to irregular supply. Exclusion criteria: chronic disease
Berinder 2011 (6)	Unclear	Unclear	Yes	No	Yes	Unclear	Yes	2	Exclusion criteria: diabetes and dyslipidemia
Ciresi 2013 (4)	No	Yes	Yes	Unclear	Yes	Unclear	No	3	Patients receiving hypoglycemic agents at baseline were excluded. One patient had diabetes, 13 patients with metabolic syndrome
Docknic 2002 (30)	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	4	52% of included patients were men
Inancil 2013 (29)	Yes	Unclear	No	Yes	Yes	Unclear	Yes	3	Exclusion criteria: CVD, diabetes and hypertension
Medic-Stojanovska 2015 (31)	Yes	Unclear	No	Yes	Yes	Unclear	Yes	3	Exclusion criteria: CVD, diabetes mellitus
Pala 2015 (27)	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	5	Only 1 male patient. Exclusion criteria: Diabetes, dyslipidemia
Silva 2011 (8)	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	4	10/35 patients excluded due to discontinuation of DA therapy. 2 diabetes, Exclusion criteria: Acute or chronic diseases
Schwetz 2017 (25)	No	No	Yes	Unclear	Yes	Unclear	Yes	3	Patients failing to demonstrate normoprolactenemia at follow-up were excluded from analysis
Serri 2006 (7)	Yes	No	Yes	Unclear	Yes	Unclear	Yes	4	7/15 patients were male. Exclusion criteria: CVD, HT, diabetes
Yavuz 2003 (28)	Yes	Unclear	No	Unclear	Yes	Unclear	Yes	2	No comorbidities
Iglesias ^a 2016 (32)	No	Unclear	No	Unclear	N/A	N/A	No	0	

^aIglesias *et al.* did not report weight changes in response to dopamine receptor antagonist treatment.



Table 2 Background characteristics and study data.

Study	n	Country	Follow-up, months	Drop out, %	Age, mean \pm s.d.	Male, %	Macroprolactinoma, %	Treatment ^a	Overweight or obese at baseline, %	Baseline prolactin, mU/L mean \pm s.d.	Baseline BMI, mean \pm s.d.
Schwetz 2017 (25)	53	Austria	9	0	39 \pm 17	58	59	CAB	-	7607 \pm 4414	27.9 \pm 5.9
Iglesias 2016 (32)	27	Spain	57	0	39 \pm 13	100	74	CAB	-	43693 \pm 27401	31.3 \pm 5.1
Auriemma 2015 (26)	32	Italy	24	0	42 \pm 5	100	78	CAB	97	42996 \pm 93443	31.7 \pm 3.9
Auriemma 2014 (5)	61	Italy	60	0	34 \pm 10	21	33	CAB	64	16733 \pm 5073	27.6 \pm 5.3
Barbosa 2014 (33)	21	Brazil	6	40	-	-	23	CAB, BRC	69	9080 \pm 7034	29.3 \pm 15.4
Ciresi 2013 (4)	43	Italy	12	0	34 \pm 11	19	-	CAB	-	3715 \pm 5718	25.57 \pm 5.18
Inancil 2013 (29)	21	Turkey	6	0	30 \pm 10	0	14	CAB	19 ^b	3201 \pm 1230	27.1 \pm 5.9
Berinder 2011 (6)	14	Sweden	6	7	40 \pm 14	43	43	CAB, BRC	21 ^b	M:26809(2617-204,255) /F: 1511(1043-2787)	25.8 \pm 7.8
Silva 2011 (8)	22	Brazil	6	37	42 \pm 35	23	18	CAB, BRC	62	5720 \pm 3621	29.2 \pm 15.3
Serri 2006 (7)	15	Canada	3	-	39 \pm 13	47	13	CAB	47 ^b	20,160 \pm 18,780	29 \pm 6
Doknic 2002 (30)	23	Serbia	6	0	37 \pm 3	52	65	BRC	39 ^c	42,682 \pm 37,429	27.5 \pm 3.4
Medic 2015 (31)	20	Serbia	4	0	30 \pm 7	0	30	CAB, BRC	-	2919 \pm 1102	24 \pm 6.4
Pala 2015 (27)	19	India	6	32	27 \pm 6	5	21	CAB	37	2514 \pm 2232	24.2 \pm 4.0
Yavuz 2003 (28)	16	Turkey	6	0	31 \pm 10	0	-	BRC	-	3318 \pm 1637	26.3 \pm 5.3

^aCabergoline (CAB); Bromocriptine (BRC)

^bBMI > 30.

^cBMI > 27.

F, female; M, male.

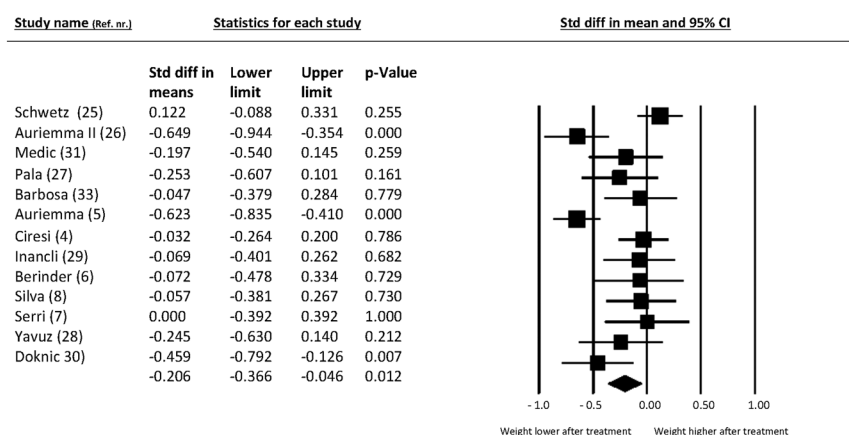


Figure 2
Change in weight/BMI after dopamine receptor agonist treatment in patients with prolactinomas.

weight was -0.21 SMD (95% CI -0.37 to -0.05 ; $P=0.01$) at follow-up compared to baseline values. For the 12 studies that only reported on BMI, the mean reduction in BMI after treatment was -1.17 BMI points (95% CI -1.99 to -0.38). The forest plot is presented in Fig. 2 and inspection of funnel plot (not shown) for primary outcome did not suggest publication bias.

Heterogeneity and subgroup analysis of primary outcome

The primary outcome was associated with an I^2 of 71% suggesting substantial heterogeneity. Subgroup analysis suggested that the reduction of weight was -0.09 SMD (95% CI -0.16 to 0.06 ; $P=0.35$; $I^2=0\%$) in studies with low prolactin levels at baseline compared to -0.33 SMD (95% CI -0.58 to -0.09 ; $P=0.008$; $I^2=72\%$) in studies with high prolactin levels at baseline. As shown in Supplementary Table 1, no other subgroup analyses explained the observed heterogeneity.

Secondary outcomes

After treatment with DA, the pooled SMD suggested a small decrease in WC, a small-to-moderate decrease in TRG, fasting glucose levels, HOMA-IR, HbA1c and hsCRP, and a moderate decrease in LDL, total cholesterol and insulin (Supplementary Table 2). There was no change in blood pressure, a small increase in LF and FSH, no increase in estrogen and estradiol and a large increase in testosterone after treatment.

Adverse events from treatment

Adverse events were reported in 4 of 14 studies. In one study, 24% of the patients had a transient gastrointestinal intolerance to DA treatment (29). In another study

non-specified transient side effects occurred in 21% (8). One study reported that no participants experienced adverse events (7) and in one study 87.5% of participants experienced nausea, dizziness and sleep disturbances during treatment (28). None of the studies reported serious adverse events.

Discussion

In this systematic review, we included 14 observational studies assessing the effect of DA treatment on metabolic variables in 387 patients with prolactinoma. For the primary outcome, weight and BMI, DA treatment significantly reduced body weight, with a weight reduction of 0.2 SMD. In addition, DA treatment was associated with small-to-moderate effects on all secondary endpoints except blood pressure, estrogen and estradiol. Too few studies reported on harmful events to provide any firm conclusions regarding this aspect of DA treatment in patients with prolactinomas.

A reduction in body weight was observed in 11 of 13 included studies; however, the effect was most prevalent in studies with high prolactin levels at baseline. In concurrence with previous reports (17, 34, 35) the included studies had a high prevalence of obese participants at baseline which suggest an association between prolactin and obesity. There are several hypotheses, which may explain the observed reduction of weight after DA treatment in patients with hyperprolactinemia. One possible mechanism could be a direct effect of DA on metabolism. Randomized clinical trials of patients with type 2 diabetes and obesity suggest that quick-release BRC lowers HbA1c and fasting plasma glucose; however, in these studies a neutral effect on weight and lipid profile were observed (36, 37, 38).

Hyperprolactinemia causes hypogonadotropic hypogonadism and the observed effect on weight may be a result of restoration of eugonadism. It is well established that obesity can cause male hypogonadotropic hypogonadism. By contrast, it is debated whether hypogonadism induces obesity. Some studies have shown that low testosterone levels reduce the fat-to-muscle ratio, but do not alter body weight (39, 40, 41, 42). In opposition to these results a RCT (43) and two observational studies examining changes in body weight in male patients with hypogonadism before and after initiation of testosterone treatment found a mean decrease in BMI of approximately four BMI points (44, 45, 46). For women obesity has been associated with higher levels of estrogens (41, 47) but to our knowledge no studies looking at weight change related to treatment of secondary hypogonadism in women has been published.

A direct effect of prolactin on adipocytes and lipid metabolism cannot be excluded, since prolactin receptors have been identified on adipose tissue (48). However, one *in vitro* study on human adipocytes from women in the fertile age found that prolactin inhibited lipid storage outside breast tissue (16), thereby not supporting a link between obesity and prolactin. It should be emphasized that the design of the included studies in the present meta-analysis does not allow any conclusions on possible causal mechanisms between weight reduction and DA treatment.

For the secondary outcomes, we found improvement in all cardiovascular risk factors except blood pressure, estrogen and estradiol. We found a small decrease in WC, a small-to-moderate decrease in TRG, fasting glucose levels, HOMA-IR, HbA1c and hsCRP, and a moderate decrease in LDL, total cholesterol and fasting insulin levels.

DA treatment has a neutral effect on lipid profile (37). However, the favorable effect of quick-release BRC on glucose metabolism has led to the approval of BRC for treatment of type 2 diabetes by the FDA (49), and studies have found that BRC as add-on therapy in patients with type 2 diabetes lowers HbA1c (weighted mean difference, -6.52 mmol/mol; 95% CI -8.07 to -4.97) (37, 50, 51) which likely explains the observed effect on the glucose tolerance.

Reversal of hypogonadism might be contributing to the improvement in both lipid profile and glucose tolerance, but study results are conflicting: in a randomized double-blind trial allocating men with hypogonadism ($n=220$) and type 2 diabetes or metabolic syndrome to testosterone supplementation or placebo; no consistent improvement was found in lipid profile or WC, but there was significant reduction in HOMA-IR (43). In two registry-based studies ($n=255$ and $n=561$) investigating

males with hypogonadism, a significant reduction in total cholesterol, LDL, TRG, HbA1c, fasting blood glucose and CRP after testosterone treatment (44, 52).

There are several important limitations to the current review. No randomized trials were included, and all the reported outcomes were associated with moderate-to-large heterogeneity. The strength of this review is that more than half of the included studies were prospective and the thorough and systematic approach regarding search strategy as well as data extraction and data synthesis. Furthermore, the protocol was made available in a publicly accessible database (Prospero) prior to data collection and analysis.

Today, large patient populations such as patients with renal failure and those receiving antipsychotic medication are not offered treatment for hyperprolactinemia. In case the findings from this systematic review could be replicated in studies of a higher evidence level, the clinical implications are potentially large.

Conclusion

This systematic review suggests a reduction of weight as well as an improved lipid profile and glucose tolerance after treatment with dopamine agonist in patients with prolactinomas. These data are based on low quality evidence.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/ERC-19-0292>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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