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Osteoporotic fractures in patients with untreated hyperprolactinemia vs. those taking dopamine agonists: A systematic review and meta-analysis

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Abstract

OBJECTIVE: Hyperprolactinemia is associated with bone fragility. Traditionally attributed to prolactin-induced hypogonadism, recent studies have identified increased fracture rates independent of gonadal function.

METHODS: We performed a systematic review to identify studies assessing fracture risk in patients with untreated hyperprolactinemia compared to those on dopamine agonists. MEDLINE, EMBASE, Cochrane, Web of Science and BIOSIS Previews databases were searched from inception to December 2013 for studies of hyperprolactinemia with fractures as an outcome. Two authors independently performed title and abstract searches, full-text searches, data abstraction, and quality assessment. A summary odds ratio (OR) was calculated using a random effects model.

RESULTS: Of the 197 articles identified, 2 met inclusion criteria. Both cross-sectional studies examined cabergoline use (or non-use) in patients with prolactin-secreting adenomas, with vertebral fractures as the primary outcome. For women, vertebral fractures were identified in 46% of untreated patients, vs. 20% of patients on cabergoline (OR: 0.29, 95% CI: 0.10–0.78). For men, the results were 67% in untreated, vs. 26% in cabergoline treated patients (OR: 0.18, CI: 0.03–0.94), with no difference between gonadal and hypogonadal men (p=0.8). Combining studies gave a summary odds ratio of 0.25 (CI: 0.11–0.59), I^2=0%.

CONCLUSIONS: In the limited studies available, fracture prevalence was increased in patients with untreated hyperprolactinemia compared to those on treatment, independent of gonadal function. Further studies are needed to clarify if post-menopausal women, or high-risk men, with no other indication for treatment, should be on dopamine agonists to decrease fracture risk.

ORIGINAL ARTICLE

INTRODUCTION

Hyperprolactinemia is characterized by amenorrhea, infertility, and galactorrhea in women, and decreased libido, erectile dysfunction, and gynecomastia in men (Klibanski 2010). These symptoms are secondary to prolactin-mediated suppression of gonadotropin-releasing hormone (GnRH), which in turn inhibits luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and decreases the production of estradiol and testosterone causing hypogonadism (Shibli-Rahhal & Schlechte 2009). Elevated serum prolactin levels can be the result of many different etiologies, but commonly anti-dopaminergic medications or a pituitary tumour are implicated (Mancini *et al.* 2008). In addition to the well-defined symptoms described above, it has been shown that prolactinomas, in both men and women, can cause increased bone resorption thereby leading to lower bone mineral density (BMD) (Shibli-Rahhal & Schlechte 2009). In the past, decreased BMD has been shown to be secondary to prolactin-induced hypogonadism (Greenspan *et al.* 1989); however, a recent study has shown increased fracture incidence in patients with normal gonadal function (Mazziotti, *et al.* 2011a). This study would therefore suggest that high prolactin levels could affect bone health independent of the sex hormone influence on bone metabolism. Further, in vitro studies have demonstrated prolactin receptors on osteoblasts. These studies show inhibition of osteoblast proliferation and impairment of bone mineralization with prolactin stimulation, thus providing a possible mechanism for prolactin induced bone resorption (Seriwantanachai *et al.* 2009; Coss *et al.* 2000).

Osteoporosis has been shown to affect up to one in three women, with fragility fractures as a common manifestation (Keen 2003). In men over the age of 50, up to 25% will experience a fracture due to osteoporosis (Sidlauskas *et al.* 2014). The presence of one osteoporotic fracture is a strong predictor of future fractures, conferring a close to two-fold increase in the risk of future fractures (Kanis *et al.* 2004). This has important clinical relevance to health care practice, as the morbidity and mortality associated with osteoporotic fractures are significant (Ioannidis *et al.* 2009; Johnell & Kanis 2006). Recent studies have demonstrated the increased prevalence of vertebral fractures in both men and women with prolactinomas (Greenspan *et al.* 1989; Mazziotti *et al.* 2011b), thus underscoring the importance of management of hyperprolactinemia with regards to bone disease. Current guidelines recommend the use of dopamine agonists in patients with macroadenomas, enlarging microadenomas, and symptoms of hypogonadism (Melmed *et al.* 2011); however, low BMD and osteoporosis are not currently considered indications for treatment. Similarly, it is not clear if dopamine agonist therapies should be continued on after the age of menopause in women with persistently elevated prolactin levels.

We performed a systematic review to examine if untreated hyperprolactinemia is associated with an increase in fracture risk and BMD decline compared to corrected prolactin levels through treatment with a dopamine agonist. No previous systematic reviews have been done in this area. We aimed to summarize all published studies on this subject, with fracture prevalence or BMD as a primary outcome. By defining the risk of fracture and BMD loss associated with on-going elevated prolactin levels, we hope to add clarity to the risks and benefits of medical treatment for hyperprolactinemia, and provide evidence for alternate indications for treatment of this condition.

METHODS

We performed a systematic review in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reviews of observational studies (Stroup *et al.* 2000).

Search strategy

An electronic literature search was conducted using the following electronic databases from database inception to December 2013: MEDLINE, EMBASE, Cochrane (EBMR on Ovid), Web of Science and BIOSIS Previews. Keywords and search strategy were reviewed by a research librarian with experience in systematic reviews of medical literature. A summary of the search strategy used is presented in Appendix 1; keywords included: hyperprolactinemia, prolactinoma, prolactin, fracture, bone, dopamine agonist, bromocriptine, cabergoline, lisuride, pergolide, quinagoline, and ergoline. Variations in search terms were used in different databases to reflect the respective differences in indexing. Studies deemed relevant during the review were examined for their reference list to identify potential additional studies. No language, publication date, or publication status restriction were imposed.

Eligibility criteria

We included all studies reporting either bone mineral density or fractures in adult patients with hyperprolactinemia (from any etiology). To be eligible, a study had to have a treatment group of patients on a dopamine agonist (bromocriptine, cabergoline, pergolide, quinagolide, or lisuride), and a comparison group of similar patients with untreated hyperprolactinemia. Studies that contained patients with renal or hepatic failure, or those taking estrogen replacement therapy, were excluded.

Data extraction and quality assessment

Two reviewers (CD and TK) independently screened all titles and abstracts retrieved from the literature search. Any abstract deemed potentially relevant was independently reviewed by both reviewers in full-text format,

with attention to the predefined eligibility criteria. There was perfect agreement between the two reviewers after full text review (kappa statistic = 1.0). Data was independently extracted by both reviewers using a pre-specified comprehensive data extraction form. Data extraction results were compared to ensure reliability. Primary outcomes measured included fracture incidence at any site, including morphometric or clinical fractures, and change in BMD over time at any site.

Quality of the included articles was assessed by both reviewers using the Newcastle-Ottawa Scale (NOS) 9-star system for quality assessment of observational studies (Wells *et al.* 2009). Quality rating was determined by stars achieved in each domain of the NOS, based on predetermined values, as has been done previously (McPheeters *et al.* 2012).

Statistical analysis

Odds ratio (OR) of fracture incidence was the primary measure of the intervention effect. A summary odds ratio was calculated using a random effects model, with a 95% confidence interval. Statistical heterogeneity was evaluated with the I^2 statistic, with 0% indicating no observed heterogeneity and 50% indicating substantial heterogeneity. Funnel plots were generated to visually assess for publication bias. All statistics were performed using the Cochrane Collaboration Review Manager (RevMan) [Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012].

RESULTS

Search results

Details of the literature search and selection process are outlined in Figure 1. After removal of duplicate studies, 197 articles were identified and screened based on title and abstract; 21 of which were deemed relevant and underwent full text review. Two studies met full inclusion and exclusion criteria and were included in our review and meta-analysis. A total of 13 articles were excluded due to lack of a comparison group.

Study characteristics

The characteristics of included studies are presented in Table 1. Each article was a cross sectional study of patients with hyperprolactixnemia in the setting of a known prolactin secreting adenoma. At the time of assessment, participants were classified as either being on treatment with a dopamine agonist (cabergoline), or being untreated and with no prior exposure to a dopamine agonist. The studies were similar in methodology, as they were performed by the same group of researchers, however with different sexes enrolled. Primary outcomes measured included vertebral fractures based on spine radiographs using semi-quantitative and morphometric assessment performed by a blinded operator. A total of 110 patients were included in the studies, 46 of which had no prior treatment with cabergoline.

Outcomes

Vertebral fractures were identified in 46% of untreated women with hyperprolactinemia, compared to 20% of those women on treatment with cabergoline (OR 0.29, 95% CI: 0.1–0.78). The majority of women with these vertebral fractures were also post-menopausal (22 of 25 women). In men, 67% of untreated patients with hyperprolactinemia were found to have vertebral fractures, compared to 26% of those on cabergoline (OR 0.18, 95% CI: 0.03–0.94). The prevalence of vertebral fractures was not statistically different in hypogonadal men compared to those on testosterone replacement therapy (37.5% vs. 33.3%, p=0.8). Combining these studies gave a summary measure odds ratio of 0.25 (CI 0.11–0.59), I^2=0% (Figure 2). The summary odds ratio was unchanged when calculated with a fixed effects model. We were not able to examine the effects of cabergoline on changes in BMD, as insufficient data was available. Both included studies scored well, with the highest quality rating ("Good") in each domain of the NOS, and overall score of 7/9 stars.

DISCUSSION

In this systematic review of the literature, we were only able to identify two studies that compared the fracture risk associated with hyperprolactinemia in those

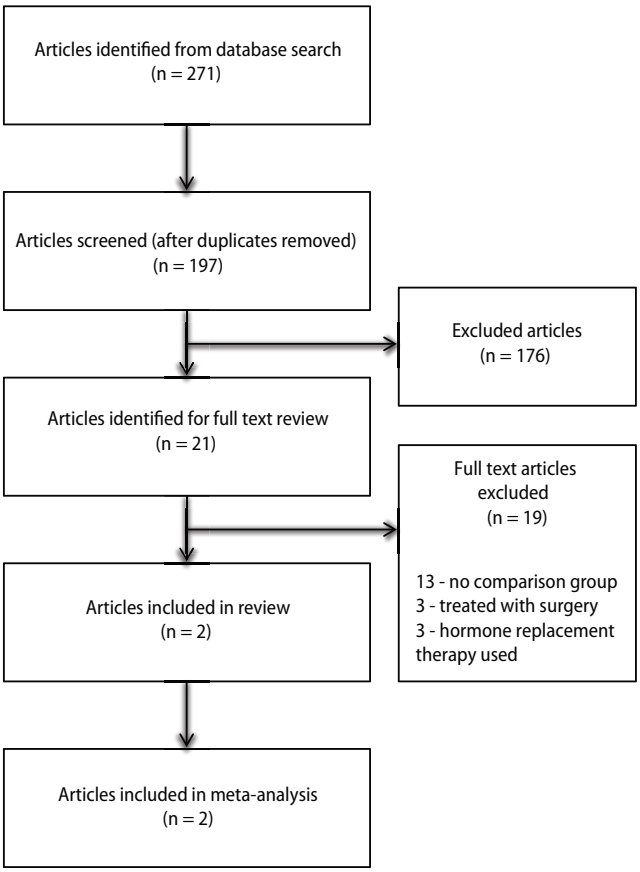

Fig. 1. Flow diagram of study selection.

Tab. 1. Characteristics of studies included in meta-analysis, including quality assessment.

Study	Participants	Intervention	Comparison	Outcomes	Quality assessment
Mazziotti *et al.* 2011, Italy	-32 males with hyperprolactinemia secondary to prolactin secreting adenoma -median duration of disease 4 years (1-10) -median age 47.0 years (22-79) -mean serum prolactin 98 ng/mL (3.3-1800)	cabergoline (n= 23)	no treatment (n=9)	-vertebral fractures, measured by AP and lateral X-rays -semi-quantitative and morphometry assessment by a single blinded operator	-NOS: 7/9 -"Good" rating in Selection, Comparability, Outcome
Mazziotti *et al.* 2011, Italy	-78 females with hyperprolactinemia secondary to prolactin secreting adenoma -median duration of disease 5 years (2-30) -median age 45.5 years (20-81) -mean serum prolactin 77 ng/mL (4-1490)	cabergoline (n=41)	no treatment (n=37)	-vertebral fractures, measured by AP and lateral X-rays -semi-quantitative and morphometry assessment by a single blinded operator	- NOS: 7/9 -"Good" rating in Selection, Comparability, Outcome

*Prolactin normal range: 4–15 ng/mL in men, <25 ng/mL in women; NOS: Newcastle-Ottawa Scale; AP: anteroposterior

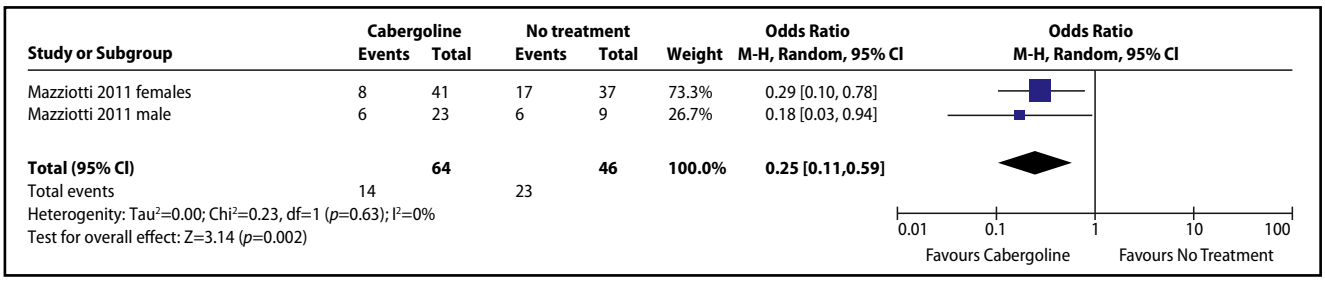

Fig. 2. Meta-analysis results of vertebral fractures with cabergoline compared to no treatment.

treated with a dopamine agonist to those who remain untreated. Although limited by the dearth of information available, the studies identified show a 75% decrease in fracture prevalence in patients with hyperprolactinemia treated with cabergoline.

Traditionally, the effect of hyperprolactinemia on bone loss is thought to be mediated through its suppression of the hypothalamic-pituitary-gonadal axis by inducing a hypogonadal state, as seen in studies showing decreased BMD and increased bone turnover in both amenorrheic women with hyperprolactinemia (Klibanski & Greenspan 1986; Schlechte *et al.* 1987; Shaarawy *et al.* 1999) and in hypogonadal men (Greenspan *et al.* 1986). Both studies used in this review, through subgroup analysis, were able to show that prolactin's effect may be independent of gonadal status. The first study in women with prolactin secreting adenomas did not show a difference in fracture prevalence when comparing amenorrheic to eugonadal women. Prolactin's importance was further supported, as there was a higher prevalence of fractures in post-menopausal women with hyperprolactinemia compared to post-menopausal women with normal serum prolactin levels. Similar findings were seen in the second study, where the prevalence of vertebral fractures in men was not significantly different in patients on long-term testosterone replacement compared to those with untreated hypogonadism. Thus, independent of sex hormones, hyperprolactinemia exhibited an increased fracture risk seen in both studies.

Current guidelines limit treatment of hyperprolactinemia to those with macroadenomas, or patients with symptoms of hypogonadism (Melmed *et al.* 2011). The negative effects of prolactin itself on bone health have largely been unaddressed. This is especially important for those post-menopausal women with elevated prolactin levels, who are already vulnerable for osteoporotic fractures given their physiological hypogonadal state. The results of this review suggest that bone protection may warrant further attention as another indication for dopamine agonist treatment in patients with hyperprolactinemia. Specifically, patients with concurrent osteoporosis or fracture history, post-menopausal women, or hypogonadal men, may benefit from dopamine agonist therapy. Previous studies support these conclusions, showing improvements in BMD values and bone turnover markers with dopamine agonist therapy (Klibanski & Greenspan 1986; Di Somma *et al.* 1998).

Our review was fortunate to include two studies that were both high quality, with no statistical heterogeneity given that the studies were performed by the same research group with similar methodology. Through

strict eligibility criteria, we were able to control many confounding factors that may affect the results of this study, including the effects of estrogen replacement therapy on bone protection. However, in doing so the number of studies eligible for inclusion in our review and meta-analysis was small. Due to the limited research in this area limited, as evident by the sparse number of articles retrieved, our review was unable to overcome this limitation. As well, both studies included were cross sectional; thus leaving the possibility of unaccounted for confounding variables. Similarly, the small sample size employed by both studies limits the strength and generalizability of any conclusions.

In summary, there is very little research available looking at the bone protective effects of dopamine agonist therapy in patients with hyperprolactinemia. From the literature that is available, treatment with a dopamine agonist seems to confer a protective effect on bone, leading to a decreased prevalence of vertebral fractures in patients with hyperprolactinemia, independent of gonadal status. With the high rates of osteoporosis in our society, and the high costs, morbidity and mortality associated with osteoporotic fractures, further studies are warranted in this area.

Conflicts of interest

All authors have no conflicts of interest

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Appendix 1. Search strategy used for electronic databases.

MeSH terms used	Hyperprolactinemia; Prolactinoma; exp Prolactin; exp Fractures, Bone; Bone Density; Bone Resorption; Dopamine Agonists; Bromocriptine; Lisuride; Pergolide; Ergolines
Additional terms in EMBASE	exp Fracture; Bone Atrophy; Osteolysis; Dopamine receptor stimulating agent; bromocriptine mesilate; cabergoline; lisuride maleate; quinagolide; ergoline derivative
Keywords	Hyperprolactinemia OR prolactinoma OR prolactin Fracture* OR (bone ADJ2 (densit* OR disease* OR health*)) (used "NEAR/2 in WoS/Biosis) Dopamine agonist* OR bromocriptine OR cabergoline OR lisuride OR pergolide OR quinagolide OR ergoline*