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Prolactinomas and menopause: any changes in management?

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Abstract

Purpose Treatment goals in prolactinomas are to correct hypogonadism, restore fertility and control tumor mass in case of macroadenomas. According to current guidelines, medical treatment of asymptomatic postmenopausal women is not indicated. The purpose of this study was to review the current literature pertaining to biological behavior of prolactinomas during menopause, likelihood of successful dopamine agonist withdrawal during this period and possible prolactin-mediated increased morbidity that could modify current management.

Methods A comprehensive literature search including papers published until July 2019 was conducted using PubMed and Medline databases.

Results Women with prolactinomas entering menopause have a higher chance of prolactin normalization of treatment compared with women in their reproductive years. Although most prolactin secreting adenomas diagnosed during menopause are large, they respond well to dopamine agonist treatment. Data directly linking hyperprolactinemia with an increased risk of cancer and cardiovascular and metabolic morbidity are inconsistent. There is no data indicating that correction of hyperprolactinemia improves clinical outcomes in asymptomatic patients bearing microadenomas.

Conclusion There is no evidence that justifies changing current recommendations to withhold medical treatment of microprolactinomas in asymptomatic post-menopausal women. Macroprolactinoma patients should be treated according to standard clinical practice.

Keywords Prolactin · Pituitary adenoma · Prolactinoma · Menopause · Osteoporosis · Breast cancer

Introduction

Prolactinoma is the most commonly occurring pituitary adenoma [1–4]. Prevalence rates according to epidemiological studies from several countries are between 35 and 54.3 cases per 100,000 inhabitants. Tumor size and clinical presentation of prolactinomas are clearly gender and age dependent. These differences were readily apparent in the population-based study performed nationwide in Iceland, in which 75% of prolactinoma patients were female. The estimated prevalence in women was 41.3/100,000, compared with 13/100,000 in men. Women were younger at diagnosis (median age 32 year vs. 47 year in men) and 72.3% of them had microadenomas. In contrast, 63.8% of male patients harbored macroadenomas [4].

The higher prevalence of prolactinomas in women of reproductive age and its decline with menopause conforms to the well-recognized stimulatory effect of estrogen on prolactin secretion and lactotroph proliferation [5]. This estrogen-driven effect underlies the high prolactin levels and pituitary enlargement during pregnancy [6], as well as the physiological decline of prolactin levels in post-menopausal women [7, 8]. In this paper, we will address effects of the estrogen deprived milieu of menopause on biological behavior and medical management of prolactinomas diagnosed prior or following menopause onset. Further, data linking hyperprolactinemia to increased risk of malignancy, metabolic and cardiovascular morbidity that could possibly modify current management will be reviewed.

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Gender-related differences in prolactin secreting tumors

Oligomenorrhea, amenorrhea, galactorrhea and infertility are the usual presenting symptoms leading to the diagnosis of prolactinomas in women of reproductive age. Because these are mostly microadenomas, young women rarely present with local mass-related effects. Although symptoms of prolactin-induced hypogonadism are common in men, they present commonly with compression signs such as headaches and visual dysfunction secondary to a large tumor [9]. The significantly higher prevalence of macroprolactinomas in men has been attributed to a possible delay in diagnosis, linked to men's reluctance in reporting sexual function impairment. This hypothesis implies that growth of small undiagnosed tumors is the basis of macroadenoma preponderance in men [10]. This is not supported by the natural history of microprolactinomas, that rarely grow if left untreated [11, 12]. Further, no differences in tumor size are found according to age of diagnosis and duration of symptoms in either sex [13], suggesting that a delay in diagnosis does not explain the higher rate of large tumors in men. Prolactin secreting tumors in males had a higher number of mitoses and Ki-67 index compared with tumors from female patients irrespective of tumor size [14]. When the comparison was restricted to macroprolactinomas, still the Ki-67 immuno-reactivity index was higher in tumors from male patients [14]. Interestingly, estrogen receptor (ER) α expression score, as analyzed by immunohistochemistry, was significantly lower in men and was inversely correlated with tumor size and proliferative activity. Low ERα expression was also a hallmark of dopamine agonist-resistant, invasive and proliferative tumors [14].

Taken together, it follows that macroprolactinomas in men have an inherently more aggressive behavior, irrespective of the age at diagnosis.

Prolactinomas diagnosed in the post-menopausal period

Prolactinomas diagnosed during the post-menopausal period are rare. Tumor induced menstrual disturbances that lead to the diagnosis in young patients cannot be detected in women already amenorrheic as a function of menopause. Tumors may remain unrecognized; therefore the true prevalence of prolactinomas during the menopausal period cannot be accurately determined. Although large tumors presenting with symptoms related to tumoral mass effects on adjacent structures are readily detected, microadenomas and small intrasellar macroadenomas are probably underdiagnosed due to the lack of endocrine manifestations. This assumption is supported by the high prevalence of previously undiagnosed pituitary adenomas found in autopsy series [15], the majority of which are prolactinomas. In a large series comprising 3048 autopsy cases carefully analyzed, 334 pituitary tumors were identified, 39.5% of which had positive prolactin immunostaining [16]. These were very small tumors with a median size of 1.2 mm (0.1–6 mm).

Three small clinical case series encompassing 37 women diagnosed after menopause were identified [17–19] (Table 1). Mean age at diagnosis was 60.8 years. The vast majority had macroadenomas, one quarter of which were giant tumors. Still, 19% of tumors were diagnosed incidentally (mean diameter 17 ± 8.4 mm vs. 28.2 ± 12 mm in symptomatic patients, $p = 0.054$). Headaches and visual deterioration (37.8%) were the most common symptoms leading to diagnosis. Two patients presented with apoplexy. It is important to highlight the fact that 12 patients had a history of secondary amenorrhea at an early age that was not investigated. Six patients in the 1997 report [17] had a mean duration of amenorrhea of 31.8 ± 5.6 years, thus reaching the period during which the first prolactin radioimmunoassays became available. Four additional women had undergone hysterectomy, thus precluding an earlier diagnosis based on

Table 1 Prolactinomas diagnosed during menopause

	N	Mean age (range)	Micro/macro/giant	Amenorrhea before 40	Visual compromise	Prolactin normalization	Tumor shrinkage
Maor and Berezin (1997) [17]	6	57.5 (49–68)	1/5/0	6/6	0	6/6	5/6
Shimon et al. (2014) [18]	14	63.6 (61–76)	1/10/3	3*/14	6/14	10/14	13/14
Santharam et al. (2017) 24	17	63 (52–78)	1/12/4	7*/17	8/17	15/16**	16/16
Total	37	60.8 (49–78)	3/27/7 (8.1/73/18.9) %	16/37 (43%)	14/37 (37.8%)	31/36 (86%)	34/36 (94.4%)

*Two after hysterectomy

**One untreated patient

menstrual disturbances. It emerges that 43% of women in this cohort could have been diagnosis at an earlier age. As in male subjects, one could hypothesize that the high rate of macroprolactinomas in menopausal women are related to a diagnosis delay. We would expect these tumors to be larger than those in which there were no elements suggestive of a missed diagnosis in the clinical history. Nevertheless, there were no differences in tumor size between the former (26.3 ± 12.8 mm) and later (26.7 ± 12 mm) scenarios. Hence, as in male patients, it seems that macroprolactinomas diagnosed during menopause have inherently higher proliferative characteristics. Despite these initially aggressive features, prolactin normalization and tumor shrinkage were achieved respectively in 86% and 94.4% of patients (Table 1).

Evolution of prolactinomas diagnosed in the pre-menopausal period

A physiologic decrease in prolactin levels occurs after menopause [20], with an overall linear correlation between estradiol and prolactin levels [21]. The question of whether the hypoestrogenic environment of menopause affects the natural course of prolactinomas arises. The literature on this topic is not abundant. Some reports include patients in whom the definitive presence of a microadenoma could not be ascertained accurately, as imaging was performed before MRI, and in some cases, before CT scans were routinely available. Karunukaran and colleagues [22] reported in 2001 a significant decrease of prolactin levels in 11 untreated women with microprolactinomas entering menopause. Five of them (45%) experienced complete normalization of prolactin levels. In contrast, only 7% of premenopausal women remained normoprolactinemic after a trial of dopamine agonist (DA) treatment interruption. Recently, three groups studied the effect of DA withdrawal in women with prolactinomas entering menopause.

Mallea-Gil et al. [23] report on 29 DA treated, normoprolactinemic patients (22 micro- and seven macroprolactinomas) in whom treatment was withdrawn at menopause. Tumors were already undetectable in nine microprolactinoma patients at treatment interruption, and seven additional tumors could not be identified in subsequent imaging. Six of seven macroprolactinomas were reported to have disappeared or decreased in size after menopause. The percentage of patients in whom prolactin levels increased after withdrawal of DA treatment was not reported, but in two microprolactionoma patients treatment was resumed because of increasing PRL levels.

Santharam et al. [24] reported outcomes of DA agonist withdrawal in patients entering menopause (n = 30, 24 micro- and 6 macroprolactinomas) compared with treatment interruption during the premenopausal period (n = 28, 23 micro- and five macroprolactinomas). In post-menopausal women, prolactin levels remained normal in 69% of women who were normoprolactinemic compared with 25% of women who were hyperprolactinemic at the time of treatment withdrawal. Interestingly, in univariate Cox regression analysis, tumor size at diagnosis, visible adenoma in MRI, prolactin levels before treatment interruption, and duration of DA treatment did not predict recurrence of hyperprolactinemia in this group. Prolactin levels remained normal in 50% of post-menopausal and in 29% of premenopausal women after treatment withdrawal (HR 0.316, 95% CI 0.0–0.98). Tumor enlargement was detected in only two menopausal patients after treatment interruption, both of whom had increasing prolactin levels during follow up.

Finally, Indirly et al. [25] summarized outcomes of DA withdrawal from 62 women with microprolactinomas, in 14 of whom treatment was interrupted after menopause. In 4/14 (29%) post-menopausal and in 35/48 (73%) pre-menopausal women an increase in prolactin levels was detected after treatment withdrawal (OR 0.149 95% CI 0.04–0.55 for recurrence in postmenopausal women). Similar to findings in the Santharam study [24], prolactin levels before withdrawal, treatment duration and complete adenoma regression were not correlated with recurrence risk in a multivariate analysis. Hence, the menopausal status per se was the main factor determining outcomes of DA withdrawal. This is in contrast with results from recent papers and meta-analysis showing an overall higher likelihood of remission in patients with microprolactinomas, longer treatment duration, and no evidence of tumor in MRI [26, 27].

Taken together, women with prolactinomas entering menopause had a higher chance of prolactin normalization off treatment compared with women in their reproductive years, possibly reflecting estrogen effects on lactotroph proliferation and prolactin secretion.

Prolactinomas at menopause: should they be treated?

Treatment goals of prolactinomas in men and in women of reproductive age are straightforward:

(1) Correction of hypogonadism achieved through normalization of prolactin levels. For women, this means restoration of regular menses, libido and fertility, as well as resolution of galactorrhea, when present. In men, treatment leads to normalization of sexual function and fertility. In both genders, resolution of hypogonadism prevents long term deleterious effects of a prolonged state of sexual hormone deficiency, such as osteoporosis, and increased risk for cardiovascular morbidity [28, 29].

(2) Tumor mass reduction, particularly in macroprolactinomas causing mass-effect related complications such as visual dysfunction.

Medical treatment with DA is extremely effective in achieving both goals. Normalization of prolactin levels may be achieved in roughly 92% of patients with microprolactinomas and 77% of patients with macroprolactinomas. Furthermore, mass reduction of 20% or more is achieved in over 80% of tumors [30]. Surgery is reserved for large tumors requiring immediate decompression, or in cases of resistance or intolerance to DA treatment.

Considering the first treatment goal, i.e., correction of hypogonadism, it becomes irrelevant for women who have already reached menopause. In contrast, macroprolactinomas should obviously be treated irrespective of menopausal status, in view of their aggressive biological behavior as described above.

The remaining question is whether hyperprolactinemia per se may lead to adverse clinical outcomes, in which case it should be treated even if patients are asymptomatic.

Is untreated hyperprolactinemia deleterious in post-menopausal women?

Prolactin's central role is to induce mammary cell proliferation and lactogenesis, as the only clear adverse clinical effect of prolactin deficiency is failure of post-partum lactation. Notwithstanding, prolactin is a pleiotropic hormone with a broad range of physiologic roles in multiple species, including regulation of metabolic homeostasis, immune function, hemostasis, skin biology, and bone metabolism, among others [31]. Many of prolactin's roles are related to adaptation of the organism to the increased metabolic demands of pregnancy and lactation. It induces a state of positive energy balance by increasing appetite, fat depots and weight gain [32]. Furthermore, it is involved in calcium homeostasis, regulation of glucose metabolism, and expansion of pancreatic β-cell mass [33]. Such adaptive functions could become maladaptive outside the realms of normal pregnancy and lactation.

In experimental rodent models, prolactin recapitulates pregnancy effects, but not in its adaptive context. Exogenous prolactin administration to female rats increases food intake in a dose dependent manner [34], and endogenous hyperprolactinemia secondary to selective lactotroph D2R knockout induces hyperphagia, weight gain, fat mass and adipocyte size [35].

In humans, hyperprolactinemia has been associated with weight gain and metabolic syndrome. Greenman and colleagues reported that a history of recent weight gain was present in approximately one third of their cohort of prolactinoma patients [36]. DA treatment was associated with significant weight loss in 40% of patients, being more pronounced in males. Recent weight gain was also reported by 62% of patients with hyperprolactinemia studied by Colao et al., the vast majority of whom had prolactin secreting tumors [37]. Prolactinoma patients treated with cabergoline experienced improvement in insulin sensitivity and lipid profile, and a decrease in waist circumference, inflammation markers and carotid intima thickness [38, 39]. The mechanisms by which DA treatment leads to improvement in metabolic parameters is not clearly understood and is probably multifactorial, taken that it was not related with BMI changes or the degree of prolactin suppression [38, 39]. Nevertheless, there is no data indicating that hyperprolactinemia increases cardiovascular morbidity, or that normalization of prolactin levels by medical treatment prevents cardiovascular events.

A possible association between prolactin levels, platelet aggregation [40] coagulation factors [41] and the risk of venous thrombosis has been suggested with conflicting results [42]. Based on these data, the incidence of thromboembolic events in patients with prolactinomas was explored, in comparison with clinically nonfunctioning pituitary tumors. There were no differences in the incidence of deep vein thrombosis, pulmonary embolism and cerebrovascular events between the two patient groups, suggesting that hyperprolactinemia is not a risk factor for thromboembolic events [43].

Interestingly, prolactin levels within the normal range were found to be inversely correlated with the risk for diabetes in a large population-based study [44]. The relationship between serum prolactin concentrations and type 2 diabetes risk was also assessed in 8615 women in the Nurses' Health Study. The HR for type 2 diabetes was 0.73 (95% CI 0.55, 0.95) in the highest compared with the lowest quartile of prolactin levels, irrespective of menopausal status [45]. Furthermore, no association was found between prolactin levels and cardiovascular risk factors in the Framingham Heart Study [46], and prolactin levels did not predict future coronary heart disease in a case control study [47].

Hypogonadism is a well-recognized risk factor for bone loss. Fittingly, patients with hypogonadism secondary to hyperprolactinemia have a high incidence of osteoporosis and fragility fractures [48, 49]. A direct detrimental effect of prolactin on bone has been suggested by an in vitro study using the human pre-osteoblast SV-HFO cell line. Incubation with prolactin caused a decrease in osteoblast proliferation and mineralization, but no effect on osteoblast activity [50]. It is uncertain if these in vitro results occur also in vivo, or if they can be translated to a clinical setting. That steroid hormone deficiency rather than prolactin excess is the main mediator of bone loss in hypogonadal women was well demonstrated by Klibanski et al., who measured bone density in women with hypothalamic or hyperprolactinemic

amenorrhea, in comparison with healthy women and eumenorrheic hyperprolactinemic patients [51]. Bone density was low in patients with amenorrhea, irrespective of the etiology, compared with patients with hyperprolactinemia with normal menses and healthy women. Hence, correction of hyperprolactinemia in post-menopausal women is not expected to improve bone health.

Another area of concern is the possible association between prolactin action and increased risk of malignancy. Autocrine or paracrine activation of the prolactin receptor by locally produced extra-pituitary prolactin has been implicated in tumorigenesis of breast and prostate cancer [52]. Some [53] but not all [54, 55] epidemiologic studies have found that circulating prolactin levels in the higher end of the normal range constitute a risk factor for breast cancer. A recent metanalysis [56] encompassing seven studies involving 12,275 and 6388 breast cancer cases, identified an overall higher relative risk of breast cancer—1.16 (1.04,1.29)—between the highest versus the lowest prolactin levels. The positive association was restricted to postmenopausal women with ER + /PR + , in situ and invasive cancer. An important limitation of these studies is that outcomes were based on a single prolactin measurement. Further, in the Nurses' Health Study [53], which was the largest study included in the metanalysis, median prolactin levels differed by only 0.3–0.5 ng/ml between breast cancer patients and controls. This difference may be significant from an epidemiologic perspective but probably not when considering treatment of hyperprolactinemic women. The prevalence of breast cancer was not increased in large cohorts of women with hyperprolactinemia from the Netherlands [57] and Scotland [58] compared with the general population. Interestingly, an overall increased risk for cancer was identified in a population-based cohort study from Sweden, but there was no increased risk for breast cancer. Upper gastrointestinal cancer risk was higher in both genders, risk for hematopoietic malignancy was increased in women, while there was a decrease in prostate cancer risk in men [59]. Importantly, there is no data indicating that lowering circulating prolactin levels decreases the risk of cancer. As dopamine does not regulate the extra-pituitary prolactin promoter, it is not expected that treatment with DA would affect its levels.

The association of hyperprolactinemia with morbidity and all-cause mortality was explored in the PROLEARS (Prolactin, Epidemiology, Audit and Research Study) study, a population-based cohort in Tayside, Scotland spanning 26 years [58]. 1204 patients with hyperprolactinemia were identified, in 331 of which high prolactin levels were related to a pituitary disorder, 598 were drug induced, 79 were secondary to hypothyroidism and the remaining cases were idiopathic. The comparison group consisted of 5888 age- and sex- matched patients, with a total follow-up time of 70,836 person-years. Non-fatal cardiovascular disease, diabetes, bone fractures and infectious diseases were increased in drug-induced hyperprolactinemia patients but not in prolactin secreting pituitary tumors, compared with controls. There was no association between the degree of hyperprolactinemia and morbidity. Considering that anti-psychotics are the main drug class that raises prolactin levels, it is unlikely that hyperprolactinemia per se is the direct cause for the increased morbidity found in this patient sub-group. Weight gain and diabetes, well recognized side effects of this type of medication, together with unhealthy behaviors such as smoking and inactivity, which are more prevalent among patients using anti-psychotic drugs, are probable mediators of the increased morbidity found in this population. There was no increase in cancer risk in the patient's group.

Conclusions

Current data support the Endocrine Society Guidelines of 2011 [60] on the management of hyperprolactinemia, in that DA withdrawal may be safely attempted in patients with microprolactinomas at the time of menopause. Similarly, there is no evidence to support treatment of hyperprolactinemia in asymptomatic postmenopausal women with microprolactinomas, while macroprolactinoma patients should be treated according to standard clinical practice.

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Compliance with Ethical Standards

Conflict of interest Yona Greenman declares that she has no conflict of interest.

Research involving animal and human participants This article does not contain any studies with human participants or animals performed by any of the authors.

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