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A neutral effect of testosterone therapy on macroprolactin content in men with macroprolactinemia and late-onset hypogonadism

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ABSTRACT

Background: In the light of recent studies, macroprolactinemia seems to occur much more frequently than previously thought. In women, oral contraceptive pills exhibit a stimulatory effect on macroprolactin production. No previous study has investigated macroprolactin levels in androgen-treated hypogonadal men.
Methods: We studied 10 men with isolated macroprolactinemia and 14 men with normal prolactin levels who because of late-onset hypogonadism were treated with intramuscular testosterone enanthate. Serum prolactin, macroprolactin content, serum testosterone and gonadotropin levels were assessed at baseline and after 4 months of therapy.
Results: Although baseline levels of testosterone and gonadotropins were similar in men with and without macroprolactinemia, clinical symptoms were more severe in patients with elevated big-big prolactin levels. As expected, testosterone treatment increased serum testosterone, slightly reduced serum gonadotropins, as well as improved clinical condition in both patients with and without macroprolactinemia, with no difference between the groups. However, testosterone therapy did not affect serum prolactin and macroprolactin content, even after replacing intramuscular testosterone enanthate with oral testosterone undecanoate.
Conclusions: Our results suggest a negligible effect of testosterone replacement on macroprolactin levels in macroprolactinemic men with late-onset hypogonadism.

Introduction

In the light of recent studies, macroprolactinemia, which is characterized by markedly increased macroprolactin content, probably occurs much more frequently than previously thought. Its prevalence is estimated to be as high as 3.7% in the general population, and between 15 and 46% in hyperprolactinemic patients [1–3]. Macroprolactinemia seems to occur more frequently in elderly subjects [1]. Macroprolactin consists mainly from complexes of prolactin with IgG, but in a minority of patients macroprolactin is composed of complexes formed by IgA or IgM and prolactin, or aggregates of covalent or noncovalent polymers of monomeric prolactin, some of which have been shown to be highly glycosylated [4–6]. Because of its high molecular weight (150–170 kDa), macroprolactin cannot cross the endothelial lining and reach the cell surface receptors and therefore most patients with macroprolactinemia do not manifest clinical features related to hyperprolactinemia [7,8]. However, the complexes of prolactin and immunoglobulins (particularly low-affinity, high-capacity IgG) may intermittently dissociate releasing monomeric prolactin and induce symptoms of prolactin excess [9]. This may explain the presence of galactorrhoea, oligomenorrhoea/amenorrhoea and subfertility in some women diagnosed with macroprolactinemia [10].

Although early studies suggested a female predominance with the female–male ratio of approximately 10:1 [11], a more recent study showed no particular predilection for either sex [1]. Unfortunately, very little is known about the clinical picture of macroprolactinemia in men. In a study by Alfonso et al. [12], most men (78%) diagnosed with macroprolactinemia had erectile

Abbreviations: ADAM, androgen deficiency in aging male; FSH, follicle-stimulating hormone; Ig, immunoglobulin; LH, luteinizing hormone; LOH, late-onset hypogonadism; SD, standard deviation.

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dysfunction. According to other authors, the frequency of erectile dysfunction did not differ between patients with elevated levels of macroprolactin and men with an increase in monomeric prolactin [13,14]. The remaining symptoms of macroprolactinemia in men include diminished libido and infertility [12,14,15].

These symptoms are similar to those observed in men with late-onset hypogonadism (LOH), defined as a clinical and biochemical syndrome associated with advancing age, characterized by typical symptoms and deficiency in serum testosterone levels [16]. Because of the slow nature of testosterone decline, the resulting symptoms are less expressed than in young hypogonadal men and often characterized by great individual variability [17]. Some patients diagnosed with LOH may benefit from testosterone treatment, which improves libido, sexual function, muscle strength, mood, glycometabolic control and central obesity and therefore this therapy may be considered in patients with LOH after explicit discussion of the uncertain benefits and potential risks [18,19].

Unfortunately, no previous study has investigated the relationship between LOH and macroprolactinemia, as well as the effects of exogenous testosterone on macroprolactin levels. In our recent study [20], macroprolactin production in macroprolactinemic women was stimulated by oral contraceptive pills containing ethinyl estradiol and levonorgestrel. Therefore, this study was aimed at assessing whether intramuscular preparations of testosterone affect macroprolactin content in men in whom LOH coexisted with isolated macroprolactinemia.

Materials and methods

The study population consisted of 10 men (50–79 years old) with isolated macroprolactinemia and LOH. To be admitted to the study, they had to meet the following criteria of isolated macroprolactinemia: the prolactin recovery less than 40% and post-polyethylene glycol serum prolactin levels less than 20 ng/mL. In turn, LOH was defined as total testosterone level below 3.0 ng/mL on two different occasions combined with the presence of the following symptoms: decreased frequency of morning erection, erectile dysfunction and decreased frequency of sexual thoughts. These patients were compared with 14 age-, sex- and serum-lipid matched men with LOH with normal prolactin and macroprolactin levels. We excluded patients with coexisting prolactinomas or other pituitary tumors, impaired renal or hepatic function, thyroid disorders, uncontrolled diabetes, prostate cancer, severe lower urinary tract symptoms (the American Urological Association International Prostate Symptom Score exceeding 19), baseline prostate-specific antigen >4 ng/mL (or >3 ng/mL in men at high risk of prostate cancer), breast cancer, myocardial infarction, acute coronary event, unstable angina, coronary revascularization procedure or stroke within 6 months preceding the study, heart failure (classes II–IV according to the New York Heart Association Functional Classification), hematocrit exceeding 50%, untreated obstructive sleep aspnea (defined as at least 5 apnea and hypopnea events per hour of sleep combined with excessive daytime sleepiness or fatigue) and with poor compliance. We also excluded patients treated with other drugs known either to affect serum prolactin and hypothalamic–pituitary–gonadal axis activity steroid hormone levels or known to interact with testosterone.

The study protocol was approved by the local review board. Before enrollment, both groups of patients were informed about the benefits and harms of androgen therapy and gave written, informed consent to participate in the study. All enrolled patients were treated for 4 months with testosterone enanthate, which was administered intramuscularly at the dose of 100 mg once weekly. Patients who were already taking other drugs kept their pharmacologic schedule constant. After completing the study protocol, in 6 patients with macroprolactinemia and 8 men with LOH and normal prolactin levels intramuscular testosterone enanthate was on their request replaced with oral testosterone undecanoate (120 mg daily in three divided doses) and these patients were assessed again after the following 4 months.

At the beginning and at the end of the study, the participants were invited to complete the *Androgen Deficiency in the Aging Male* (ADAM) questionnaire, consisting of 10 questions describing the most common symptoms of androgen deficiency [21]. They were asked to rate their answers for each of the questions on a scale from 1 (terrible) to 5 (excellent). The minimum score obtained with this questionnaire could be 10, whereas the maximum is 50.

Venous blood samples were drawn from antecubital vein, after a 12-h overnight fast, in a quiet temperature controlled room (24–25 °C) between 8.00 and 9.00 a.m. (to avoid possible circadian fluctuations in the parameters studied) before and after 4 months of intramuscular treatment. Blood samples of patients treated later with oral testosterone were also obtained after 4 months after replacing intramuscular with oral testosterone.

Serum prolactin and total testosterone levels were determined before and shortly after polyethylene glycol precipitation by the enzyme-linked immunosorbent assay using reagents obtained from DRG (Instruments GmbH, Marburg, Germany). To perform polyethylene glycol precipitation, 250 μL of sera was mixed with an equal volume of 25% cold polyethylene glycol 6000 dissolved in phosphate buffered saline (Sigma-Aldrich, St. Louis, MO, USA, 137 mmol/L sodium chloride, 10 mmol/L sodium phosphate, pH 7.4) and incubated for 10 min. After vortex mixing for 30 s, the suspension was clarified by centrifugation at 3000 × *g* for 30 min, before prolactin measurement. To correct for the dilution with polyethylene glycol, the post-polyethylene glycol prolactin concentration was determined by multiplying the prolactin result by 2. Prolactin recovery was calculated as follows: serum prolactin after polyethylene glycol precipitation/serum prolactin before polyethylene glycol precipitation × 100. Macroprolactinemia was diagnosed if the prolactin recovery was less than 40% (polyethylene glycol precipitation ratio greater than 60%). LH and FSH levels were measured by the immunochemiluminescence method (Siemens Healthcare Diagnostics, Inc., Deerfield, IL, USA). Serum levels of creatinine were assayed using the Jaffe method (Roche Diagnostics, Basel, Switzerland). The estimated glomerular filtration rate was calculated using the Modification Diet in Renal Disease Study equation. The intra- and interassay coefficients of variation for the assessed variables were less than 5.1 and 8.6%, respectively.

The Kolmogorov–Smirnov test was used to analyze the normal distribution of the variables. Quantitative data without a normal distribution (prolactin, macroprolactin, testosterone, DHEA-S, FSH and LH) were natural log-transformed to normalize their distributions prior to statistical analysis. Between-group comparisons were performed by the *t* test for independent samples. Student's paired *t* test was used to compare differences between the means of variables within the same treatment group. The χ^2 test was employed to compare the proportional data. Correlations were calculated using Kendall's tau test. Values of $p < 0.05$ were considered statistically significant.

Results

Both groups were similar as regard to age, weight, medical background and clinical characteristics. Patients with macroprolactinemia exhibited higher levels of total prolactin ($p < 0.001$) and macroprolactin ($p < 0.001$), as well as the lower total ADAM score than patients with normal prolactin levels. The mean values of serum androgens, FSH and LH were all comparable between the study groups (Table 1).