Letrozole normalizes serum testosterone in severely obese men with hypogonadotrophic hypogonadism

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Background: Morbid obesity is associated with increased estradiol production as a result of aromatase-dependent conversion of testosterone to estradiol. The elevated serum estradiol levels may inhibit pituitary LH secretion to such extent that hypogonadotrophic hypogonadism can result. Normalization of the disturbed estradiol-testosterone balance may be beneficial to reverse the adverse effects of hypogonadism.

Aim: To examine whether aromatase inhibition with Letrozole can normalize serum testosterone levels in severely obese men with hypogonadotrophic hypogonadism.

Patients and Methods: Ten severely obese men, mean age 48.2 ± 2.3 (s.e.) years and body mass index 42.1 ± 2.6 kg/m², were treated with Letrozole for 6 weeks in doses ranging from 7.5 to 17.5 mg per week.

Results: Six weeks of treatment decreased serum estradiol from 120 ± 20 to 70 ± 9 pmol/l (p = 0.006). None of the subjects developed an estradiol level of less than 40 pmol/l. LH increased from 4.5 ± 0.8 to 14.8 ± 2.3 U/l (p < 0.001). Total testosterone rose from 7.5 ± 1.0 to 23.8 ± 3.0 nmol/l (p < 0.001) without a concomitant change in sex hormone-binding globulin level. Those treated with Letrozole 17.5 mg per week had an excessive LH response.

Conclusion: Short-term Letrozole treatment normalized serum testosterone levels in all obese men. The clinical significance of this intervention remains to be established in controlled, long-term studies.

Keywords: aromatase inhibition, male hypogonadism, obesity

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Introduction

Severe obesity may cause hypogonadism in men [1–6]. The first reports describing this phenomenon suggested that the reduction in total testosterone was mainly the result of a decrease in sex hormone-binding globulin (SHBG) [1–3]. Later studies, however, demonstrated a significant decrease in total as well as free testosterone [4–7]. Subsequently, adrenal androgens were also found to be decreased [8,9]. In addition to the decrease in androgen levels, there is an increase in serum oestrogens. Both estrone and estradiol concentrations are significantly higher than in age-matched non-obese men [3,5,7]. Hypothalamic and pituitary function appear to be suppressed, as LH levels are inappropriately low for the degree of hypogonadism [7,10,11,12]. The combined result of these findings can be described as hyperestrogenic hypogonadotrophic hypogonadism (HHH).

The changes in androgen and oestrogen levels are proportional to the degree of obesity [6–8]. The key abnormality is an increase in estradiol production, which is a result of an aromatase-dependent conversion of gonadal and adrenal androgens to estradiol and estrone [3]. This process occurs predominantly in fat tissue. The ensuing elevation of serum oestrogens exerts an inhibitory effect on pituitary LH secretion to such extent that hypogonadotrophic hypogonadism may result

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[7,11,13–18]. Estrogen-mediated pituitary inhibition causes a marked decrease in LH-pulse amplitude [7,11,14]. In addition, there is evidence that oestrogens reduce hypothalamic gonadotropin-releasing hormone (GnRH)-pulse frequency [18].

The clinical implications of HHH, the question of whether it needs treatment, as well as the preferred method of treatment all remain to be established. Administration of testosterone is unlikely to normalize the androgen–oestrogen balance in obese men, because it will further enhance the increased estradiol production. As aromatase-dependent androgen conversion appears to be the key abnormality, we decided to examine the potential efficacy of Letrozole. Letrozole is a selective, non-steroidal, reversible aromatase inhibitor that blocks the conversion of androstenedione to estrone and of testosterone to estradiol. It does not affect adrenal corticosteroid or aldosterone synthesis. In healthy male volunteers, oestrogen-suppressive and testosterone-raising effects have been observed with doses as low as 0.02 mg [19].

**Patients and Methods**

Ten severely obese men, body mass index (BMI) 42.1 ± 2.6 kg/m² (mean ± s.e.m.), with a diagnosis of acquired and isolated hypogonadotropic hypogonadism were included in the study. Their mean age was 48.2 ± 2.3 years. All subjects initially presented themselves with a request for medical or surgical treatment of obesity. Biochemical hypogonadism was detected because assessment of gonadal status was recently included in the screening procedure for men with a BMI > 35 kg/m² applying for bariatric surgery. Hypogonadism was defined as a serum testosterone of less than 10 nmol/l in blood samples taken between 8:00 and 10:00 h, on Wednesday. All hormone assays were performed with commercially available assays (Roche Diagnostics, Mannheim, Germany). Reference ranges provided by the manufacturer are: total testosterone 10–28 nmol/l, estradiol < 160 pmol/l (detection limit 40 pmol/l), LH 2.0–9.0 U/l and FSH 1.5–12.4 U/l. SHBG was measured with a commercial kit from DPC, Los Angeles, CA, USA (reference range 13–71 nmol/l).

Results are shown as mean values and s.e.m. After confirmation of normal distribution, results of treatment were analysed by paired t-test. A p value less than 0.05 was considered to be statistically significant.

**Results**

Six weeks of Letrozole treatment decreased serum estradiol from 120 ± 20 to 70 ± 9 pmol/l (p = 0.006). LH increased from 4.5 ± 0.8 to 14.8 ± 2.3 U/l (p < 0.001) and FSH rose from 8.1 ± 2.0 to 21.0 ± 4.3 U/l (p < 0.001). Total testosterone rose from 7.5 ± 1.0 to 23.8 ± 3.0 nmol/l (p < 0.001), without a concomitant change in SHBG (27.3 ± 6.3 vs. 24.3 ± 4.2 nmol/l, p = 0.89). The estradiol–testosterone ratio declined from 19.1 ± 5.4 to 2.9 ± 0.3 pmol/nmol (p < 0.005).

Individual responses of LH, FSH, total testosterone and estradiol are shown in figure 1. In the first four subjects, treated with Letrozole 2.5 mg daily, the LH response was considered excessive. The mean LH level after 6 weeks was 22.2 ± 1.6 U/l, i.e. exceeding the upper normal limit by more than 100%. In the next six patients treated with 2.5 mg of Letrozole, three times a week, the mean LH level rose to only 10.0 ± 1.6 U/l. Despite the small number of subjects in the low-dose group, the changes in LH (p = 0.02), FSH (p = 0.005), estradiol (p = 0.03), testosterone (p < 0.001) and the estradiol–testosterone ratio (p < 0.001) remained statistically significant. Moreover, mean testosterone levels before and after six weeks were comparable for the high- and low-dose regimens (before treatment, 7.8 ± 2.4 vs. 7.4 ± 0.8
nmol/l and, after treatment, 26.5 ± 7.8 vs. 22.0 ± 0.7 nmol/l). The subject that was included because of his very high estradiol level belonged to the group treated with 2.5 mg of Letrozole daily. He showed a decrease in serum estradiol from 263 to 122 pmol/l, and this was associated with an excessive rise in total testosterone from 13 to 49 nmol/l. None of the other subjects developed supra-physiological testosterone levels. Letrozole did not cause complete oestrogen depletion. In the high-dose group, the lowest estradiol level after treatment was 40 pmol/l; in the low-dose group, the lowest level was 49 pmol/l. Adverse effects were not reported.

**Discussion**

The results of this open-label pilot study indicate that obesity-related HHH in men can be treated effectively with aromatase inhibitor. All 10 subjects responded similarly and showed a normalization of serum testosterone after 6 weeks of treatment. Although the number of patients is far too small for firm conclusions, the data do suggest that Letrozole in a daily dose of 2.5 mg is too high. All four subjects treated with this dose showed a supraphysiological LH response. Considering the observation that two out of six subjects in the low-dose group also had a LH response exceeding the upper normal limit, the optimal dose may even be lower than 7.5 mg/week.

In general, our experience with Letrozole confirms the earlier observations of Zumoff [5] who in 1988 was the first to describe the effects of the aromatase inhibitor testolactone in four obese men. Recently, they repeated the experiment in six obese men and reached the same conclusion [20]. In contrast to Letrozole, Testolactone is a steroidal aromatase inhibitor.
Exact figures on the prevalence of HHH in obesity are not available at present. There are, however, indications that it is likely to be high. Estradiol production correlates linearly with increasing fat mass and may be increased up to fivefold in morbid obesity [3]. In addition, there is a negative correlation between BMI on one hand and total, free and non-SHBG-bound testosterone levels on the other hand [6]. In obese adult men with BMI’s ranging from 21 to 95 kg/m², mean total testosterone decreased by 0.26 nmol/l per unit increase in BMI [6]. A comparably strong relationship was found between BMI and free testosterone levels [6].

A substantial overlap of serum estradiol levels between obese and non-obese men has been described in several studies [1,5,8]. Similarly, in our study, most estradiol levels were in the upper half of the general reference range, with only one single value exceeding the upper normal limit. This does not imply that the term hyperestrogenism is incorrect. The production of estradiol is fuelled by testosterone, and therefore, the actual testosterone values must be taken into account when interpreting serum estradiol levels in men. Due to inhibitory effects of oestrogens on LH secretion, testosterone levels will decline which will cause a new equilibrium at a lower serum estradiol and testosterone level. In fact, for a better understanding of the relative increase of oestrogen levels in obese men and as an estimate of aromatase activity, it might be useful to employ the estradiol–testosterone ratio. In the present study, the estradiol–testosterone ratio decreased sixfold.

The results of aromatase inhibition are interesting in that they create the possibility of treating obesity-related HHH. It appears to be a more logical choice than testosterone replacement therapy. There is only limited and short-term experience with testosterone treatment in overweight and mildly obese eugonadal men. These studies suggest that androgens can have beneficial effects on fat mass, body fat distribution, insulin sensitivity, LDL cholesterol level and blood pressure [21–25]. We were unable to find controlled studies on testosterone treatment in severely obese HHH men. Although testosterone treatment may normalize serum testosterone in these men, it is also likely to raise serum estradiol levels into the supraphysiological range. This might antagonize some of the effects of testosterone [21].

Aromatase inhibition in men may carry some risks. In theory, the main risk of long-term aromatase inhibition in men is oestrogen deficiency. The potential consequences of oestrogen deficiency can be inferred to some extent from two reports describing males with undetectable oestrogen levels because of congenital aromatase deficiency. The main finding was premature osteoporosis [26–29]. In our study, the lowest estradiol level was 40 pmol/l, achieved with 2.5 mg of Letrozol daily. Whether this is a safe level or not remains to be established. Comparison with age-matched normal values and also a thorough evaluation of Letrozole’s metabolic effects will be essential to define the safety limits of treatment.

In conclusion, this pilot study indicates that the aromatase inhibitor Letrozole can normalize the estradiol–testosterone balance in obese men with HHH. The clinical significance of this intervention remains to be evaluated in controlled, long-term studies.

References