



## REVIEW

# Hypogonadotropic hypogonadism in men due to obesity – Is there a place for aromatase inhibitors?

Andrej Belančić<sup>1</sup>, Sanja Klobučar Majanović<sup>2</sup>

<sup>1</sup>Faculty of Medicine, University of Rijeka, Rijeka, Croatia,

<sup>2</sup>Department of Endocrinology, Diabetes and Metabolic Diseases, Clinical Hospital Centre Rijeka, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

**Corresponding author:**

Andrej Belančić,  
Faculty of Medicine, University of Rijeka,  
Braće Branchetta 20, 51000 Rijeka,  
Croatia, e-mail: a.belancic93@gmail.com

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**Abstract**

High expression of adipose tissue aromatase is a common finding among severely obese men. Aromatase enhances the peripheral conversion of androgens into estrogens, which exerts estradiol-mediated negative feedback on the pituitary and results in inhibition of gonadotropin production and hypotestosteronemia. Therefore, we are scrutinizing aromatase inhibition as a potential novel therapeutic (second-line) strategy for men with hypogonadotropic hypogonadism due to obesity. Several questions remain and will be considered in this review. Could we use aromatase inhibitors to increase gonadotropin secretion and normalize the testosterone/estradiol ratio to improve fertility? Could we use them to treat/prevent gynecomastia? And finally, if we were to use aromatase inhibitors for these indications, what would be the recommended safe dose that would not trigger the potential detrimental therapy effect on bone mineralization?

**Key words:** Aromatase inhibitors; gynecomastia; hypogonadism; infertility; obesity; testosterone

## 1. Obesity and its Comorbidities

Obesity, which refers to body mass index (BMI) over 30 kg/m<sup>2</sup>, has become a serious worldwide health problem. As the prevalence of obesity increases so does the prevalence of its associated comorbidities: Hypertension, dyslipidemia, impaired glucose tolerance and diabetes mellitus, metabolic syndrome, heart diseases, cerebrovascular diseases, pulmonary abnormalities (obstructive sleep apnea and asthma), gastrointestinal abnormalities (cholelithiasis and gastroesophageal reflux disease), osteoarthritis, depression, cancer (gallbladder, esophagus, colon, thyroid, kidney, and breast), and reproductive diseases (hypogonadism, impotence, and infertility) [1,2].

## 2. Hypogonadism and Obesity - Which Came First, the Chicken or the Egg?

Male hypogonadism is a medical condition characterized by impaired production of testosterone, an anabolic steroid, which is the cornerstone of masculine growth and development during puberty. The negative correlation between total testosterone levels and BMI has previously been described [3-5]. This fact reveals the cause-effect relationship between obesity and male hypogonadism, which raises the eternal question- which came first, the chicken or the egg? Since testosterone is a hormone that promotes protein synthesis, reduces carbohydrate consumption, and reduces fat storage/promotes fat usage as a source of energy, obesity can develop as a consequence of hypogonadism (impaired testosterone levels). On the other hand, the decline in serum testosterone levels in obese men is exacerbated by suppression of the hypothalamic-pituitary-gonadal axis due to hyperestrogenemia, so hypogonadism can occur due to obesity as its complication. The increased expression of aromatase in adipose tissue triggers the peripheral conversion of testosterone and other androgens into estradiol. Increased estradiol levels suppress the production of gonadotropin-releasing hormone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) in the hypothalamus and pituitary gland, and as a consequence, the production of testosterone by the testis results in hypogonadotropic hypogonadism [6-11].

## 3. Diagnosing Male Hypogonadism and Solving the Eternal Mystery assessing the Cause and the Consequence

Hypogonadism is associated with a significantly reduced quality of life, since the decreased testosterone levels in adult males are accompanied by a variety of unpleasant symptoms and severe conditions: Impaired sex drive and performance (low libido, erectile dysfunction, and ejaculation disorders), testicular atrophy, infertility, decrease in beard and body hair growth, osteopenia/osteoporosis, decrease in muscle mass, visceral obesity, gynecomastia, increased sweating, anemia, dyslipidemia, insulin resistance, fatigue, lack of concentration, and depression [12]. For establishing the diagnosis of hypogonadism, two parameters have to be fulfilled: The presence of hypotestosteronemia and the presence of its signs and symptoms. However, the cutoff value for determining hypotestosteronemia varies depending on the guidelines of a particular society: The Endocrine Society (total testosterone <10.4 nmol/L), European Association of Urology, and International Consultation for Sexual Medicine (total testosterone <12.1 nmol/L) [13-15]. Sex hormone-binding globulin (SHBG) levels affect the interpretation of total testosterone results and SHBG levels may be low in the setting of obesity, thus necessitating the measurement of free/bioavailable testosterone for a reliable diagnosis of secondary hypogonadism in obese men. Moreover, LH and FSH values are required for further evaluation of primary/hypergonadotropic (elevated LH and FSH) and secondary/hypogonadotropic hypogonadism (decreased or normal LH and FSH). Obesity, as previously explained, is a potential cause of secondary/hypogonadotropic hypogonadism. However, obesity could also be the consequence of hypogonadism/hypotestosteronemia. The clinical diagnosis of obesity-related hypogonadism can only be made if other causes of secondary hypogonadism have been systematically excluded. Male secondary hypogonadism may result from hypothalamic-pituitary lesions, disorders and genetic dysfunction, examples being hyperprolactinemia, pituitary adenomas, Kallmann syndrome, and hemochromatosis. Serum levels of pituitary hormones, iron saturation, and magnetic resonance imaging of the pituitary should be obtained to screen for hypothalamic or pituitary

disease. To improve the cost-effectiveness of the diagnostic algorithm, it has been proposed that pituitary imaging should be performed if severe secondary hypogonadism (serum testosterone <5.2 nmol/L), panhypopituitarism, persistent hyperprolactinemia, or symptoms or signs of tumor mass effect, such as headache, visual impairment, or visual field defect, are present [13].

#### 4. Treatment of Hypogonadotropic Hypogonadism in Men Due to Obesity

In patients with hypogonadism, reduced quality of life in general and particularly the quality of sex life sometimes result in the loss of livelihood and separation of couples [12]. Hence, the adequate and early treatment of hypogonadism is desirable. The treatment of hypogonadotropic hypogonadism due to obesity is primarily based on weight reduction (exercise and energy-restricted diets) and anti-obesity drugs (orlistat, naltrexone/bupropion, liraglutide, etc.). According to the American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for the medical care of patients with obesity, men with hypogonadism and obesity who are not seeking fertility should be considered for testosterone therapy in addition to lifestyle intervention, since testosterone in these patients results in weight loss, decreased waist circumference, and improvements in metabolic parameters [16]. Testosterone can be administered by intramuscular injection (200–300 mg of testosterone enanthate every 2–3 weeks, 200 mg of testosterone cypionate every 2 weeks, or 1000 mg of testosterone undecanoate administered every 10–14 weeks) or transdermally (5–10 g of 1% testosterone gel applied in the morning over a covered area of non-genital skin such as shoulders, arms, or abdomen) to improve a hypogonadal man's sense of well-being, muscle strength, bone density, and sexual function. However, testosterone use can also provoke several severe adverse effects such as: Deterioration in mood with aggressiveness or anger, erythrocytosis, inducing or worsening obstructive sleep apnea, worsening symptoms of benign prostatic hyperplasia, growth of pre-existing prostate cancer, decreased urinary flow rates, acne and oily skin, and reduced sperm production and fertility [13,17]. Thus, regular follow-up is mandatory. Biochemical measurements (PSA, hematocrit, liver function tests, and serum testosterone levels) should be performed at 3 and

6 months after commencing testosterone therapy and then annually thereafter. Moreover, in patients with severe heart failure, kidney disease, liver disease, or occasionally among elderly patients, testosterone treatment may lead to fluid retention that requires dose adjustments or diuretic therapy [13,17]. As some patients are not adequate candidates for testosterone therapy (those with confirmed/suspected prostate cancer, hematocrit >50%, breast cancer, benign prostatic hyperplasia, untreated/severe obstructive sleep apnea, and untreated/severe heart failure), and especially those who are planning offspring in the future (since testosterone therapy can reduce sperm production and fertility), plausible second-line therapy should be proposed and implemented as an integral part of hypogonadism therapeutic guidelines. The main purpose of this review article is to discuss the strengths and limitations of aromatase inhibitors and to conclude if there is a potential place for them as second-line therapy for men with hypogonadotropic hypogonadism due to obesity.

#### 5. Aromatase Inhibitors for Male Hypogonadotropic Hypogonadism Due to Obesity

Aromatase is an enzyme in adipose tissue that is responsible for the peripheral conversion of androgens into estrogens. Its overexpression results in hyperestrogenemia, which consequently leads to gynecomastia, low gonadotropin levels, hypotestosteronemia, and premature closure of the epiphyses [18,19]. By contrast, aromatase deficiency caused by CYP19 gene mutation is associated with low bone mineral density, unfused epiphyses, high gonadotropin levels, and hypertestosteronemia [20–22]. Therefore, several questions remain such as: Could we use aromatase inhibitors to increase gonadotropin secretion, normalize the testosterone/estradiol ratio, and improve fertility? Could we use them to treat/prevent gynecomastia? And finally, if we were to use aromatase inhibitors for these indications, what would be the recommended safe dose that would not trigger the potential detrimental therapy effect on bone mineralization?

Steroidal aromatase inhibitors block enzyme activity by mimicking the substrate androstenedione, while non-steroidal inhibitors (letrozole and anastrozole) inhibit the aromatase activity by binding with the heme iron of the enzyme. Third-generation aromatase inhibitors

(letrozole and anastrozole) are potent and specific since they only block the aromatase enzyme and do not block other steroidogenic enzymes, which is not the case with first- and second-generation inhibitors. Moreover, they are well tolerated and their use does not appear to be associated with significant side effects since they do not suppress estradiol levels completely. Their administration inhibits the aromatase enzyme close to 100%; however, it only decreases the estradiol/testosterone ratio by 77% [23,24]. This incomplete suppression can be considered as advantageous since it prevents excessive reduction of estrogen levels and thus potential adverse effects [25].

The available reported experience with aromatase inhibition suggests that adverse effects are dose-dependent and that major harmful effects are unlikely if the dose is accurately adjusted according to the serum testosterone and estradiol levels. A weekly anastrozole dose of 2–7 mg was used in the study by Leder et al., and no harmful effects on bone turnover or bone mineral density were observed [26]. Mauras et al. conducted a 10-week study (4 late-pubertal boys and 4 young adults) with anastrozole at a weekly dose of 7 mg, and no adverse effects on bone density, body composition, or muscle strength were reported [27]. On the contrary, anastrozole at a weekly dose of 14 mg triggered a decrease in bone formation markers and increase in bone resorption markers, so this high dose should be avoided due to possible harmful effects on bone turnover [28]. When it comes to letrozole, Trunet et al., in their open dose-finding study, conducted on healthy non-obese male volunteers (age 20–48 years), explored the effects of single doses of letrozole ranging from 0.02 to 30 mg. A reduction in estrogen levels and increase in LH and testosterone levels were achieved with a single minimal (0.02 mg) dose of letrozole; however, the effect lasted for 48 h. Moreover, the effect of a single dose of 0.5 mg lasted for 72 h [29]. Furthermore, Loves et al. reported, in their open uncontrolled 6-month pilot study conducted on 12 severely obese men (BMI >35 kg/m<sup>2</sup>), that letrozole at a dose of 2.5 mg once a week was an acceptable starting dose for men with obesity-related hypogonadotropic hypogonadism [30]. According to available data, we believe that the potential recommended starting dose

of letrozole, in most cases of male obesity-related hypogonadotropic hypogonadism, should be 0.5 mg administrated once every 3 days or 2.5 mg once a week according to the study by Loves et al.

Severe obesity is accompanied by enhanced peripheral androgen aromatization, hence increased serum estradiol and low testosterone levels. Modulation of serum estradiol levels, by administering an aromatase inhibitor, has beneficial effects since it is associated with an increase in FSH, LH, and testosterone levels [23,24,31,32]. A randomized double-blind 12-week study by Leder et al. showed that anastrozole administration at a daily dose of 1 mg resulted in doubling of the mean bioavailable testosterone [33]. A similar effect of anastrozole on testosterone levels was demonstrated in a 1-year randomized, double-blind, placebo-controlled trial conducted by Burnett-Bowie et al., however, in the absence of concomitant effects on body composition and strength [34]. In contrast, normalization of testosterone levels associated with the positive effects on weight loss has been reported by Vermeulen et al. [35]. Aromatase inhibition has also been reported to result in a three-fold increase of FSH in eugonadal men and may potentially stimulate spermatogenesis [23,24,36]. Moreover, a beneficial effect of aromatase inhibitors on sperm concentration and motility has been demonstrated in several uncontrolled studies [37–39]. Cakan et al., in their study with anastrozole, conducted on idiopathic oligoasthenoteratozoospermic men, demonstrated the increased pregnancy rate in comparison to the group without the addition of the aromatase inhibitor [40]. Roth et al. reported a case of a 29-year-old man that presented with infertility and hypogonadism in the setting of morbid obesity, who was successfully treated with aromatase inhibitors. Testosterone was given as the initial therapy; however, after 4 months of unsuccessful treatment and a significant decrease in sperm concentration, testosterone was replaced with anastrozole. Aromatase inhibition led to a decrease in serum estradiol concentration and normalization of the patient's LH, FSH, and testosterone levels and resulted in normalization of spermatogenesis and fertility [41]. To conclude, aromatase inhibitors have been successfully used to correct hypotestosteronemia and improve fertility in subfertile oligospermic men. Its

positive effect on semen quality and quantity followed by increased frequency of pregnancies has also been reported [38-40].

Aromatase inhibitors are frequently prescribed for hormone-sensitive breast carcinoma in women since they have proved to be safe and effective in the reduction of tumor estrogen concentrations. This raises the question as to whether they are also effective when it comes to treating gynecomastia in obese men. Gynecomastia is a result of an imbalance between androgen and estrogen activity, so the use of aromatase inhibitors would inhibit the peripheral conversion of androgens into estrogens. Following this idea, Plourde et al. used anastrozole daily for 6 months to treat pubertal gynecomastia, but their research did not show a significant improvement in comparison to placebo [42]. According to the review by Maidment, a similar response to placebo of anastrozole and tamoxifen was reported in a number of observational studies [43]. Thus, aromatase inhibitors should not be considered as a first-line treatment for gynecomastia.

## 6. Conclusion - Is There a Place?

After we pointed out the strengths and limitations, we believe that aromatase inhibitors should be considered as a potential second-line therapy in certain cases of male hypogonadotropic hypogonadism due to obesity. There is growing evidence that aromatase inhibition successfully raises serum testosterone levels and improves fertility in subfertile oligospermic men. Moreover, the positive effect on semen quality and quantity followed by increased frequency of pregnancies has also been reported. Therefore, we suggest aromatase inhibitors as a plausible second-line therapy for infertility in the setting of obesity-related hypogonadotropic hypogonadism. To conclude, there is certainly a place for aromatase inhibitors; however, the spectrum of indications for their use is not wide ranging.

### Authors contribution

AB gave the idea for the article, reviewed the previously published literature, contributed in writing the manuscript and manuscript preparation. SKM reviewed the previously published literature, contributed in writing the manuscript, guided the overall manuscript composition, and gave the final approval.

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