



Review

Aromatase inhibitors in male: A literature review

Mohsen Korani^{a,b,*}^a Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah, University of Medical Sciences, Tehran, Iran^b Department of Biochemistry, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:

Received 19 October 2022

Accepted 31 October 2022

Available online 23 November 2022

Keywords:

Aromatase

Aromatase inhibitors

Male

A B S T R A C T

Aromatase (CYP19A1) is a monooxygenase from the family of cytochrome P450 that plays role in the androgens to estrogens conversion. Aromatase inhibitors prohibit the aromatase enzyme function. This study reviewed the different usages of aromatase inhibitors in the male gender. In this review study, all articles related to the effect of aromatase inhibitors in males were evaluated through databases such as PubMed, Web of Science, Scopus, Science Direct, Google Scholar, and Cochrane library using the keywords “aromatase inhibitors”, “infertility”, “bone metabolism”, “Breast cancer”, “obesity”, “men” and “male”. Estrogen excess in males shows a correlation with premature closure of the epiphyses. Aromatase inhibitors reduce estrogen by preventing the testosterone to estrogen conversion and have thus been used in patients with short stature or with a delay of puberty. The breast cancer cells show aromatase activity, a probable source of local estrogen for the tumor cells. The inhibition of aromatase suppresses the amounts of serum estrogen and reduces cancer cell proliferation mediated by estrogen in hormone receptor-positive breast cancer. Aromatase inhibitors have also been used in late-onset hypogonadism by lowering the levels of estrogen which is correlated with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and testosterone increase. In obese males, an augmented androgen-to-estrogen conversion happens in the adipose tissue, resulting in raised estrogen levels. Aromatase inhibitors by reducing this conversion lead to a reduction of estrogen and elevation of testosterone and FSH in males with obesity-associated hypogonadotropic hypogonadism. Furthermore, aromatase inhibitor therapy reduced the breast size in males with gynecomastia. They may affect bone metabolism.

© 2022 The Authors. Published by Elsevier España, S.L.U. This is an open access article under the license CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Inhibidores de la aromatasa en hombres: una revisión de la literature

R E S U M E N

La aromatasa (CYP19A1) es una monooxigenasa de la familia del citocromo P450 que desempeña un papel en la conversión de andrógenos a estrógenos. Los inhibidores de la aromatasa prohíben la función de la enzima aromatasa. Este estudio revisó los diferentes usos de los inhibidores de la aromatasa en el género masculino. En este estudio de revisión, todos los artículos relacionados con el efecto de los inhibidores de la aromatasa en los hombres se evaluaron a través de bases de datos como PubMed, Web of Science, Scopus, Science Direct, Google Scholar y la biblioteca Cochrane utilizando las palabras clave “inhibidores de la aromatasa”, “infertilidad”, “metabolismo óseo”, “cáncer de mama”, “obesidad”, “hombres” y “masculino”. El exceso de estrógenos en los varones muestra una correlación con el cierre prematuro de las epífisis. Los inhibidores de la aromatasa reducen el estrógeno al evitar la conversión de testosterona en estrógeno y, por lo tanto, se han utilizado en pacientes con baja estatura o con un retraso en la pubertad. Las células de cáncer de mama muestran actividad aromatasa, una fuente probable de estrógeno local para las células tumorales. La inhibición de la aromatasa suprime las cantidades de estrógeno sérico y reduce la proliferación de células cancerosas mediada por estrógeno en el cáncer de mama con receptores hormonales positivos. Los inhibidores de la aromatasa también se han utilizado en el hipogonadismo de inicio tardío al reducir los niveles de estrógeno que se correlacionan con la hormona luteinizante (LH) y la hormona estimulante del folículo (FSH) y el aumento de testosterona. En el hombre obeso, ocurre una conversión aumentada de andrógenos a estrógenos en el tejido adiposo, lo que resulta en niveles elevados de estrógenos. Los inhibidores de la aromatasa al reducir esta conversión conducen a una reducción de los estrógenos y una elevación de la testosterona y la FSH en los hombres con hipogonadismo

Palabras clave:

Aromatasa

inhibidores de la aromatasa

Masculino

* Autor para correspondencia.

E-mail address: mohsenkorani@gmail.com.

hipogonadotrópico asociado a la obesidad. Además, la terapia con inhibidores de la aromatasa redujo el tamaño de los senos en hombres con ginecomastia. Pueden tener un efecto sobre el metabolismo óseo.

© 2022 Los Autores. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Aromatase is a member of the cytochrome P450 superfamily, a large family of enzymes that catalyzes the incorporation of oxygen into an organic molecule, titled hydroxylases.¹ A single copy of the CYP19A1 gene placed on the short arm of chromosome 15 (15q21) encoding aromatase.² Numerous tissue-specific promoters under the influence of various hormones and growth factors like gonadotropins, interleukin-6, interleukin-11, and tumor necrosis factor- α regulate the transcription of the aromatase gene.³ Human aromatase is a 58 kDa protein that converts androgens (C19), including testosterone and androstenedione, to estrogens (C18), estradiol, and estrone, in an enzymatic complex with flavoprotein, NADPH-cytochrome P450 reductase.⁴⁻⁶ Aromatase expresses by various cell types such as granulosa cells, neurons, placental cells, preadipocytes and fibroblasts, osteoblasts, Leydig and Sertoli cells, vasculature smooth muscle cells, and chondrocytes.⁴

Aromatase inhibitors

Aromatase inhibitors are a group of drugs that can stop the construction of estrogens by preventing their conversion from androgens.⁷ Aminoglutethimide and Testolactone are first-generation aromatase inhibitors. Aminoglutethimide usage for breast cancer was restricted due to many side effects.⁸ Testolactone is another first-generation aromatase inhibitor that was used for the treatment of progressive breast cancer.⁹ Formestane was the first selective steroidal inhibitor in the second generation of aromatase inhibitors. Formestane was used as second-line therapy after tamoxifen, it was confirmed to be effective with fewer side effects compared to the first-generation.¹⁰ Fadrozole was another second generation and classified as a type 2 inhibitor but due to its rapid clearance and inhibition of aldosterone synthesis in required doses its use was limited.^{11,12} The highly selective third-generation aromatase inhibitors were discovered in the 1990s that are including exemestane, anastrozole, and letrozole.⁷ They were shown to have higher efficacy, specificity, greater potency, and less toxicity than first and second generations.^{12,13}

Aromatase inhibitors have another classification, steroidal (type1) and nonsteroidal (type 2). Steroidal aromatase inhibitors such as testolactone, exemestane, and formestane inhibit the activity of aromatase by imitating the substrate androstenedione. They permanently inhibit the aromatase by covalently binding to it. Nonsteroidal aromatase inhibitors, such as aminoglutethimide, anastrozole, fadrozole, vorozole, and letrozole inhibit aromatase activity by binding to the heme iron of the aromatase, leading to competitive inhibition.¹⁴

Estradiol has a significant role in gonadotropin secretion, maintaining bone mass, and closing of the epiphyses. The extra estrogen is associated with low gonadotropin and testosterone levels and premature closure of the epiphyses and gynecomastia.¹⁵ Therefore, decreasing the levels of estrogen in males has been used as a possible treatment for disorders such as hypogonadism, and gynecomastia. Aromatase is responsible for the conversion of androgens to estrogens. Aromatase inhibitors were defined to be safe and effective for the treatment of hormone-sensitive breast cancer in men and women as well as for other disorders. This review will discuss the different usages of aromatase inhibitors in the male gender.

Search strategy

In this review study, all articles related to the effect of aromatase inhibitors in males were evaluated from the year 1975 to 2021. Articles were searched through databases such as PubMed, Web of Science, Scopus, Science Direct, Google Scholar, and Cochrane library using the keywords “aromatase inhibitors”, “infertility”, “bone metabolism”, “Breast cancer”, “obesity”, “men” and “male”. Articles without full text and those which were not written in the English language were excluded. A total of 98 articles were extracted in the initial search. After reviewing the abstract of these articles, finally, 53 articles that met the necessary criteria of the present review were selected and evaluated completely.

Aromatase inhibitors for male infertility

It seems that the levels of testosterone-to-estradiol ratio in infertile males improve by treatment with aromatase inhibitors and resulting in improvements in semen parameters. Del Giudice et al. in a systematic review and meta-analysis determined that both steroidal (Testolactone) and nonsteroidal (Letrozole and Anastrozole) aromatase inhibitors improved all the assessed hormonal and seminal results with a safe tolerability profile. This study reported that aromatase therapy significantly augmented the levels of testosterone (95% CI: 1.634–7.253; s.m.d: 4.443, $P = 0.002$; $I^2 = 97.85\%$) as well as increased the T/E2 ratio from the baseline (95% CI: 5.813–10.200; s.m.d: 8.006; $P < 0.001$; $I^2 = 95.8\%$). A mean increase of 9.2×10^6 ml $^{-1}$ was achieved for sperm concentration with the baseline sperm concentration of $7.9 \pm 5.4 \times 10^6$ ml $^{-1}$ and after treatment sperm concentration of $17.2 \pm 8.1 \times 10^6$ ml $^{-1}$. Sperm motility showed a mean increase of 8.7% from the baseline (18.6% \pm 12.4%) to the end of treatment (27.4% \pm 12.5%).¹⁶ Peivandi et al. reported that the aromatase inhibitor therapy increased the FSH and LH levels in infertile males after the intervention [5.74 \pm 1.71 vs. 6.62 \pm 1.8 mIU/ml and 5.07 \pm 1.89 vs. 7.42 \pm 1.6 mIU/ml, respectively, ($P < 0.001$)]. They also reported that, testosterone (25.15 \pm 11.1 vs. 40.73 \pm 12.6 ng/ml, $P < 0.001$) and estradiol (4.8 \pm 1.66 vs. 5.99 \pm 1.51 pg/ml, $P = 0.002$) levels as well as the T/E2 ratio (5.89 \pm 2.84 vs. 7.09 \pm 2.35 $P = 0.014$) were increased significantly after the therapy. Moreover, sperm parameters including sperm concentration, forward motion, and sperm motility were improved significantly after treatment ($P < 0.001$).¹⁷ Shuling et al. also demonstrated that Letrozole improves testosterone levels by 2.5 folds ($P < 0.0001$) and repressed estradiol levels by 0.6 fold ($P = 0.0033$), hence increases the T/E2 ratio ($P < 0.0001$). Significant rises were also reported in FSH and LH (2.1 folds and 2.2 folds, respectively). Sperm concentration and total count were increased [5.5 folds ($P = 0.0068$) and 4.3 folds ($P = 0.0096$), respectively], however, no significant difference was observed in the volume of semen and motility of sperm after treatment.¹⁸ Gregoriou et al. revealed that the use of aromatase inhibitors including letrozole and anastrozole improved the serum testosterone levels from 265 \pm 25 to 513 \pm 65 ng/dL ($P < 0.001$) and T/E2 ratio from 8 \pm 0.5 to 34 \pm 5.9 ($P < 0.001$) in infertile males with low testosterone/estradiol ratios. Although, FSH and LH levels were not significantly changed after therapy. Sperm count ($\times 10^6$) (4.15 \pm 3.38 vs. 8.9 \pm 2.11, $P < 0.001$) and motility (12.35 \pm 3.89 vs. 22.85 \pm 3.38, $P < 0.001$) were also significantly increased.¹⁹

In a study by Shoshany et al., in about 95% of males with hypogonadism treated with anastrozole, testosterone was significantly increased from 258.4 ± 10.8 to 509.2 ± 20.4 ng/dL ($P < 0.001$) and T/E2 ratio from 6.98 ± 0.33 to 34.5 ± 6.5 ($P < 0.001$). LH and FSH were also increased significantly (6.41 ± 0.89 vs. 10.7 ± 1.1 , $P < 0.001$ and 12.4 ± 2 vs. 19.4 ± 2.3 , $P < 0.001$, respectively). A subset of oligozoospermic males presented a significant improvement in sperm concentration from $4.7 \pm 1.2 \times 10^6$ /mL to $13.1 \pm 2.9 \times 10^6$ /mL ($P < 0.001$) and total motile count from $4.6 \pm 1.3 \times 10^6$ to $8.0 \pm 3.4 \times 10^6$ ($P = 0.008$), however, no significant change was observed for sperm motility and ejaculated seminal volume. In this subset, the rise in sperm parameters was associated with the alteration in the testosterone/estradiol ratios.²⁰ Schlegel et al. reported that treatment of infertile males with the aromatase inhibitors such as anastrozole, testolactone, and letrozole has been correlated with augmented production of sperm and return of sperm to the ejaculate in males with nonobstructive azoospermia.²¹

Raman et al. study demonstrated that infertile men with a low serum testosterone-to-estradiol ratio may be treated by an aromatase inhibitor. The testolactone treatment results in a rise in the testosterone-to-estradiol ratio (5.3 ± 0.2 versus 12.4 ± 1.1 , $P < 0.001$) accompanied by enhanced semen parameters such as sperm concentration (5.5 vs. 11.2 million/mL, $P < 0.01$), sperm motility (14.7% vs. 21.0% , $P < 0.05$), motility index (606.3 vs. 1685.2 , $P < 0.05$), and morphology (6.5% vs. 12.8% , $P = 0.05$). They showed similar effects on hormonal profiles and semen analysis using both anastrozole and testolactone. Anastrozole was as effective as testolactone for treating males with abnormal testosterone-to-estradiol ratios (7.2 ± 0.3 vs. 18.1 ± 1.0 , respectively, $P < 0.001$), excluding the Klinefelter syndrome subset that seems to be treated more efficiently by testolactone and had an increase in sperm concentration (5.5 vs. 15.6 million/mL, $P < 0.001$), semen volume (2.9 vs. 3.5 mL, $P < 0.05$), and motility index (832.8 vs. 2930.8 , $P < 0.005$).²²

In adult men, neurons in the preoptic region and the medial basal area of the hypothalamus are responsible for the secretion of gonadotropin-releasing hormone (GnRH), which regulates the secretion pattern of the gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) from the anterior pituitary gland. FSH regulates spermatogenesis via Sertoli cells in the testis while LH produces testosterone by acting on the Leydig cells in the testis. Estradiol is mainly produced through the aromatization of testosterone with the Leydig cells with a contribution of aromatase enzyme.^{14,23} Testosterone and estradiol act on the anterior pituitary and the hypothalamus through a negative feedback mechanism. It was shown that estradiol signaling through the hypothalamic-pituitary-gonadal (HPG) axis plays a significant role in regulating GnRH and gonadotropin secretion in males. The hypothalamus and pituitary gland have many estradiol receptors besides testosterone receptors. Aromatase inhibitors decrease the levels of estradiol, which counteract the estradiol's negative feedback mechanism at the pituitary gland level and consequently increase the levels of gonadotrophins, LH, and FSH, and result in a rise in serum testosterone.^{24,25}

Effect of aromatase inhibition on bone metabolism in elderly Male

Aging in males is accompanied by loss of bone mass and weakened physical function.²⁶ Estrogens and androgens play significant roles in skeletal development and maintenance in males. recent data recommended that a threshold level of bioavailable estradiol is required to avoid bone loss, and with aging, in a large number of elderly men, the levels fall below this threshold.²⁷ Aromatase inhibitors reduce estrogen production and raise androgen production in males.²⁸

Dias et al. in a study evaluated the effects of aromatase inhibition versus testosterone in older males with low testosterone and demonstrated that aromatization of testosterone is vital for preserving bone mineral density (BMD) in older men with low testosterone levels.²⁶

Burnett-Bowie et al. reported that aromatase inhibition increases the levels of testosterone, declines the levels of estradiol, and seems to reduce bone mineral density. They suggested that aromatase inhibitors do not improve skeletal health in older males with low or normal testosterone levels.²⁹

Leder et al. showed that although short-term administration of aromatase inhibitor (anastrozole) reduces the levels of serum estradiol in an elderly male with slight hypogonadism, this intervention does not impact bone metabolism in 12 weeks. This may be a result of the concomitant rise in testosterone production, the modest impact on estradiol production, or a combination of both factors. They showed that this therapy is improbable to affect bone metabolism and may verify to be valuable in normalizing testosterone production in older men.²⁸

The effect of aromatase inhibitors in obese males

Adipose tissue is the main estrogen-producing nongonadal tissue. In the adipocyte differentiation process, PPAR γ regulates the aromatase expression. During obesity, the rise of pro-inflammatory factors in adipocytes caused by obesity will result in greater transcription of the CYP19 gene encoding aromatase in adipocytes, which in turn results in augmented expression of aromatase in adipocytes.³⁰

In obese males, the amplified expression of the aromatase enzyme in the adipose tissue results in a great conversion of androgens to estrogens which leads to hypogonadotropic hypogonadism.³¹

In a study by Colleluori et al., it was found that aromatase inhibitors accompanied by weight loss develop the hormonal profile (had higher testosterone and lower estradiol) of obese hypogonadal males with no significant side effects.³¹

Loves et al. showed that despite a significant increase in serum testosterone and a decrease in estradiol levels, low-dose aromatase inhibition had no somatic or psychological impacts in males with obesity-related hypogonadotropic hypotestosteronemia.³² In another study by Loves et al. aromatase inhibitor (Letrozole < 2.5 mg) once per week formed a constant normalization of serum total testosterone in obese males with obesity-related isolated hypogonadotropic hypogonadism.³³ Boer et al. also showed that Letrozole normalizes serum testosterone in intensely obese males with hypogonadotropic hypogonadism.³⁴ Zumoff et al. reported that the administration of the aromatase inhibitor testolactone (one g per day for six weeks) reversed the hypogonadotropic hypogonadism of obese males.³⁵

Aromatase inhibitor and male breast cancer

Male breast cancer is a scarce incidence. Treatment of male breast cancer is normally inferred from data on the treatment of female breast cancer. Now, first-line use of aromatase inhibitors is a standard strategy in hormone-sensitive metastatic breast cancer in females.³⁶ Aromatase inhibitors are widely used for treating metastatic male breast cancer patients.³⁷

In a pooled analysis by Zagouri et al., it was reported that aromatase inhibitors may play a significant role in the treatment of metastatic male breast cancer. Particularly, its administration with a gonadotropin-releasing hormone (GnRH) analog appears to raise the rate of clinical advantage and may be more effective.³⁸ Kuba et al. also showed that aromatase inhibitors with or without luteinizing hormone-releasing hormone (LH-RH) agonists suggest an effective treatment strategy for hormone receptor-positive metastatic male breast cancer.³⁹ Lauro et al.'s study demonstrated that a combination of letrozole and GnRH analog is a safe and effective therapy for hormone-receptor-positive, metastatic breast cancer in male patients.⁴⁰ Arriola et al. report a case of a metastatic breast cancer male patient who was treated with letrozole and attained a clinical response related to a reduction in blood oestradiol levels.⁴¹ In another study by Chen et al., it was found that the efficacy of aromatase inhibitors and tamoxifen was comparable in early male breast cancer patients and the aromatase inhibitors

activity was associated with a significant reduction in estradiol level. They also suggested that some patients may develop secondary resistance.⁴²

The effects of aromatase inhibitors on short stature in males

In males besides females, estrogen is a critical regulator of the maturation of bone, growth plate fusion, and longitudinal growth cessation. Thus, a rise in predicted adult height (PAH) may be attained in short boys by blocking estrogen biosynthesis.⁴³

In a study by Mauras et al., it was shown that anastrozole rises predicted adult height of short adolescent males treated with growth hormone in a randomized placebo-controlled trial while preserving normal pubertal development after 2 to 3 years.⁴⁴ In a study by Hero et al. aromatase inhibitor, letrozole decreased the rate of bone maturation and increased the predicted adult height in boys with idiopathic short stature by blocking estrogen biosynthesis.⁴³ Neely et al. compared letrozole and anastrozole for height amplification in short pubertal males and reported that letrozole was more effective in hormonal manipulation than anastrozole. Comparable first-year growth velocities were reported, but development in PAH was superior in the anastrozole group.⁴⁵ In a study by Salehpour et al. in constitutional delay of growth and puberty (CDGD) teenage boys with predicted short stature it was found that letrozole rises PAH more than oxandrolone and improves pubertal stage and bone mineralization fewer.⁴⁶ Dunkel et al study demonstrated that treatment with the aromatase inhibitors letrozole and anastrozole efficiently postpones bone maturation and rises predicted adult height in boys with CDGP, growth hormone deficiency, and idiopathic short stature. Long-term follow-up data for treatment with letrozole for one year during adolescence propose that the attained gain in predicted adult height furthermore leads to taller final adult height.⁴⁷ Miller et al. evaluated the height outcomes in boys with growth hormone deficiency and idiopathic short stature who were treated concurrently with growth hormone and aromatase inhibitor therapy and reported that the use of aromatase inhibitor therapy with growth hormone in males looked to be related to continuing growth over two years, and aromatase inhibitor therapy probably increased growth potential as shown by continued height standard deviation score (HSDS) increase with decreased mean bone age/chronological age ratio (BA/CA) after aromatase inhibitor therapy commencement.⁴⁸

Use of aromatase inhibitors as treatment for gynecomastia

Gynecomastia may occur in boys during puberty and in adult males. The main cause of the development of gynecomastia is an imbalance of estrogen to androgen levels. Therefore, most of the treatments have been based on lowering the estrogen level.⁴⁹ In a cohort study by Mauras et al., anastrozole was reported as an effective aromatase inhibitor in adolescent males. It showed rapid absorption and slow elimination kinetics in oral administration. It also reduced breast size.⁵⁰ In another study on two monozygotic twins with Peutz-Jeghers syndrome with prepubertal gynecomastia, it was shown that treatment with anastrozole (1 mg per day) diminished gynecomastia.⁵¹ Rhoden et al. demonstrated that testosterone-induced gynecomastia was treated with the anastrozole aromatase inhibitor successfully.⁵² In Kara et al. study it was found that aromatase inhibitor testolactone administration for 1 year decreased the breast diameter from 7 to 3 cm. They suggested waiting for the aromatase inhibitors' effect on gynecomastia before decision-making for mastectomy.⁵³

Conclusion

Aromatase, an estrogen synthetase, is the main enzyme in the biosynthesis of estrogen. Estradiol has an essential role in bone mass gaining, gonadotrophin secretion, and closing of the epiphyses. Estrogen increase has been correlated with premature closure of the

epiphyses, low levels of gonadotrophin and testosterone, and gynecomastia. Therefore, lowering estrogen levels in males using aromatase inhibitors can be a potential treatment for related disorders. In this study, we assessed the effectiveness of the use of aromatase inhibitors in some male disorders. The study revealed that aromatase inhibitors are effective in the treatment of male infertility by rising the testosterone-to-estradiol ratio accompanied by enhancing the semen parameters. It was determined that aromatase inhibitors can normalize the serum testosterone levels in obese males with obesity-related hypogonadotropic hypogonadism. Aromatase inhibitors are suggested as an effective treatment strategy for hormone receptor-positive metastatic male breast cancer. They were shown to be effective in the treatment of short stature in boys as well. Moreover, aromatase inhibitor therapy reduced the breast size in males with gynecomastia. They may affect bone metabolism.

Availability of data and material

Not applicable.

Ethics approval

Not applicable.

Consent for publication

Not applicable.

Funding

There is no funding for the present study.

Authors contribution

MK has done all sections of the study.

Declaration of Competing Interest

There is no conflict of interest for the present study.

Acknowledgment

There is no acknowledgment of the present study.

References

1. Simpson ER, Mahendroo MS, Means GD, Kilgore MW, Hinshelwood MM, Graham-Lorence S, et al. Aromatase cytochrome P450, the enzyme responsible for estrogen biosynthesis. *Endocr Rev.* 1994;15(3):342–55.
2. Simpson ER, Michael MD, Agarwal VR, Hinshelwood MM, Bulun SE, Zhao Y. Cytochromes P450 11: expression of the CYP19 (aromatase) gene: an unusual case of alternative promoter usage. *FASEB J.* 1997;11(1):29–36.
3. Simpson ER, Davis SR. Minireview: aromatase and the regulation of estrogen biosynthesis—some new perspectives. *Endocrinology.* 2001;142(11):4589–94.
4. Czajka-Oraniec I, Simpson ER. Aromatase research and its clinical significance. *Endokrynol Pol.* 2010;61(1):126–34.
5. Simpson ER, Clyne C, Rubin G, Boon WC, Robertson K, Britt K, et al. Aromatase—a brief overview. *Annu Rev Physiol.* 2002;64:93–127.
6. Conley A, Hinshelwood M. Mammalian aromatases. *Reproduction.* 2001;121(5):685–95.
7. Bruggemeier RW, Hackett JC, Diaz-Cruz ES. Aromatase inhibitors in the treatment of breast cancer. *Endocr Rev.* 2005;26(3):331–45.
8. Santen RJ, Santner S, Davis B, Veldhuis J, Samojlik E, Ruby E. Aminoglutethimide inhibits extraglandular estrogen production in postmenopausal women with breast carcinoma. *J Clin Endocrinol Metab.* 1978;47(6):1257–65.
9. Cocconi G. First generation aromatase inhibitors—aminoglutethimide and testolactone. *Breast Cancer Res Treat.* 1994;30(1):57–80.
10. Dowsett M, Coombes RC. Second generation aromatase inhibitor—4-hydroxyandrostenedione. *Breast Cancer Res Treat.* 1994;30(1):81–7.

11. Steele RE, Mellor LB, Sawyer WK, Wasvary JM, Browne LJ. In vitro and in vivo studies demonstrating potent and selective estrogen inhibition with the nonsteroidal aromatase inhibitor CGS 16949A. *Steroids*. 1987;50(1-3):147-61.
12. Trunet PF, Mueller P, Girard F, Aupetit B, Bhatnagar AS, Zognbi F, et al. The effects of fadrozole hydrochloride on aldosterone secretion in healthy male subjects. *J Clin Endocrinol Metab*. 1992;74(3):571-6.
13. Tominaga T, Adachi I, Sasaki Y, Tabei T, Ikeda T, Takatsuka Y, et al. Double-blind randomized trial comparing the non-steroidal aromatase inhibitors letrozole and fadrozole in postmenopausal women with advanced breast cancer. *Ann Oncol*. 2003;14(1):62-70.
14. Tan RB, Guay AT, Hellstrom WJ. Clinical use of aromatase inhibitors in adult males. *Sex Med Rev*. 2014;2(2):79-90.
15. de Ronde W, de Jong FH. Aromatase inhibitors in men: effects and therapeutic options. *Reprod Biol Endocrinol*. 2011;9:93.
16. Del Giudice F, Busetto GM, De Berardinis E, Sperduti I, Ferro M, Maggi M, et al. A systematic review and meta-analysis of clinical trials implementing aromatase inhibitors to treat male infertility. *Asian J Androl*. 2020;22(4):360-7.
17. Peivandi S, Jafarpour H, Abbaspour M, Ebadi A. Effect of letrozole on spermogram parameters and hormonal profile in infertile men: A clinical trial study. *Endocr Regul*. 2019;53(4):231-6.
18. Shuling L, Sie Kuei ML, Saffari SE, Jiayun Z, Yeun TT, Leng JPW, et al. Do men with normal testosterone-oestradiol ratios benefit from letrozole for the treatment of male infertility? *Reprod Biomed Online*. 2019;38(1):39-45.
19. Gregoriou O, Bakas P, Grigoriadis C, Creatsa M, Hassiakos D, Creatsas G. Changes in hormonal profile and seminal parameters with use of aromatase inhibitors in management of infertile men with low testosterone to estradiol ratios. *Fertil Steril*. 2012;98(1):48-51.
20. Shoshany O, Abhyankar N, Mufarreh N, Daniel G, Niederberger C. Outcomes of anastrozole in oligozoospermic hypoandrogenic subfertile men. *Fertil Steril*. 2017;107(3):589-94.
21. Schlegel PN. Aromatase inhibitors for male infertility. *Fertility and Sterility*. 2012;98(6):1359-62.
22. Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. *J Urol*. 2002;167(2 Pt 1):624-9.
23. Veldhuis JD, Sowers JR, Rogol AD, Klein FA, Miller N, Dufau ML. Pathophysiology of male hypogonadism associated with endogenous hyperestrogenism. Evidence for dual defects in the gonadal axis. *N Engl J Med*. 1985;312(21):1371-5.
24. T'Sjoen GG, Giagulli VA, Delva H, Crabbe P, De Bacquer D, Kaufman JM. Comparative assessment in young and elderly men of the gonadotropin response to aromatase inhibition. *J Clin Endocrinol Metab*. 2005;90(10):5717-22.
25. Raven G, de Jong FH, Kaufman JM, de Ronde W. In men, peripheral estradiol levels directly reflect the action of estrogens at the hypothalamo-pituitary level to inhibit gonadotropin secretion. *J Clin Endocrinol Metab*. 2006;91(9):3324-8.
26. Dias JP, Melvin D, Simonsick EM, Carlson O, Shardell MD, Ferrucci L, et al. Effects of aromatase inhibition vs. testosterone in older men with low testosterone: randomized-controlled trial. *Andrology*. 2016;4(1):33-40.
27. Gennari L, Nuti R, Bilezikian JP. Aromatase activity and bone homeostasis in men. *J Clin Endocrinol Metab*. 2004;89(12):5898-907.
28. Leder BZ, Finkelstein JS. Effect of aromatase inhibition on bone metabolism in elderly hypogonadal men. *Osteoporos Int*. 2005;16(12):1487-94.
29. Burnett-Bowie SA, McKay EA, Lee H, Leder BZ. Effects of aromatase inhibition on bone mineral density and bone turnover in older men with low testosterone levels. *J Clin Endocrinol Metab*. 2009;94(12):4785-92.
30. Yuxin L, Chen L, Xiaoxia L, Yue L, Junjie L, Youzhu L, et al. Research progress on the relationship between obesity-inflammation-aromatase axis and male infertility. *Oxidative Medicine and Cellular Longevity*. 2021;2021:1-7.
31. Colleluori G, Chen R, Turin CG, Vigeveno F, Qualls C, Johnson B, et al. Aromatase inhibitors plus weight loss improves the hormonal profile of obese hypogonadal men without causing major side effects. *Front Endocrinol (Lausanne)*. 2020;11:277.
32. Loves S, de Jong J, van Sorge A, Telting D, Tack CJ, Hermus A, et al. Somatic and psychological effects of low-dose aromatase inhibition in men with obesity-related hypogonadotropic hypotestosteronemia. *Eur J Endocrinol*. 2013;169(5):705-14.
33. Loves S, Ruinemans-Koerts J, de Boer H. Letrozole once a week normalizes serum testosterone in obesity-related male hypogonadism. *Eur J Endocrinol*. 2008;158(5):741-7.
34. de Boer H, Verschoor L, Ruinemans-Koerts J, Jansen M. Letrozole normalizes serum testosterone in severely obese men with hypogonadotropic hypogonadism. *Diabetes Obes Metab*. 2005;7(3):211-5.
35. Zumoff B, Miller LK, Strain GW. Reversal of the hypogonadotropic hypogonadism of obese men by administration of the aromatase inhibitor testolactone. *Metabolism*. 2003;52(9):1126-8.
36. Nordman IC, Dalley DN. Breast cancer in men: should aromatase inhibitors become first-line hormonal treatment? *Breast J*. 2008;14(6):562-9.
37. Maugeri-Sacca M, Barba M, Vici P, Pizzuti L, Sergi D, De Maria R, et al. Aromatase inhibitors for metastatic male breast cancer: molecular, endocrine, and clinical considerations. *Breast Cancer Res Treat*. 2014;147(2):227-35.
38. Zagouri F, Sergentanis TN, Azim Jr HA, Chrysikos D, Dimopoulos MA, Psaltopoulou T. Aromatase inhibitors in male breast cancer: a pooled analysis. *Breast Cancer Res Treat*. 2015;151(1):141-7.
39. Kuba S, Ishida M, Oikawa M, Nakamura Y, Yamanouchi K, Tokunaga E, et al. Aromatase inhibitors with or without luteinizing hormone-releasing hormone agonist for metastatic male breast cancer: report of four cases and review of the literature. *Breast Cancer*. 2016;23(6):945-9.
40. Di Lauro L, Vici P, Del Medico P, Laudadio L, Tomao S, Giannarelli D, et al. Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer. *Breast Cancer Res Treat*. 2013;141(1):119-23.
41. Arriola E, Hui E, Dowsett M, Smith IE. Aromatase inhibitors and male breast cancer. *Clin Transl Oncol*. 2007;9(3):192-4.
42. Chen F, Qiu L. Biological and clinical implications of aromatase inhibitors in early male breast cancer patients. *Zhonghua Yi Xue Za Zhi*. 2014;94(4):273-5.
43. Hero M, Norjavaara E, Dunkel L. Inhibition of estrogen biosynthesis with a potent aromatase inhibitor increases predicted adult height in boys with idiopathic short stature: a randomized controlled trial. *J Clin Endocrinol Metab*. 2005;90(12):6396-402.
44. Mauras N, Gonzalez de Pijem L, Hsiang HY, Desrosiers P, Rapaport R, Schwartz ID, et al. Anastrozole increases predicted adult height of short adolescent males treated with growth hormone: a randomized, placebo-controlled, multicenter trial for one to three years. *J Clin Endocrinol Metab*. 2008;93(3):823-31.
45. Neely EK, Kumar RB, Payne SL, Ranadive SA, Suchet DI. Letrozole vs anastrozole for height augmentation in short pubertal males: first year data. *J Clin Endocrinol Metab*. 2014;99(11):4086-93.
46. Salehpour S, Alipour P, Razzaghy-Azar M, Ardeshirpour L, Shamshiri A, Monfared MF, et al. A double-blind, placebo-controlled comparison of letrozole to oxandrolone effects upon growth and puberty of children with constitutional delay of puberty and idiopathic short stature. *Horm Res Paediatr*. 2010;74(6):428-35.
47. Dunkel L. Update on the role of aromatase inhibitors in growth disorders. *Horm Res*. 2009;71(Suppl 1):57-63.
48. Miller BS, Ross J, Ostrow V. Height outcomes in children with growth hormone deficiency and idiopathic short stature treated concomitantly with growth hormone and aromatase inhibitor therapy: data from the ANSWER program. *Int J Pediatr Endocrinol*. 2020;2020:19.
49. Riepe FG, Baus I, Wiest S, Krone N, Sippell WG, Partsch CJ. Treatment of pubertal gynecomastia with the specific aromatase inhibitor anastrozole. *Horm Res*. 2004;62(3):113-8.
50. Mauras N, Bishop K, Merinbaum D, Emeribe U, Agbo F, Lowe E. Pharmacokinetics and pharmacodynamics of anastrozole in pubertal boys with recent-onset gynecomastia. *J Clin Endocrinol Metab*. 2009;94(8):2975-8.
51. Grandone A, del Giudice EM, Cirillo G, Santarpia M, Coppola F, Perrone L. Prepubertal gynecomastia in two monozygotic twins with Peutz-Jeghers syndrome: two years' treatment with anastrozole and genetic study. *Horm Res Paediatr*. 2011;75(5):374-9.
52. Rhoden EL, Morgentaler A. Treatment of testosterone-induced gynecomastia with the aromatase inhibitor, anastrozole. *Int J Impot Res*. 2004;16(1):95-7.
53. Kara C, Kutlu AO, Tosun MS, Apaydin S, Senel F. Sertoli cell tumor causing prepubertal gynecomastia in a boy with peutz-jeghers syndrome: the outcome of 1-year treatment with the aromatase inhibitor testolactone. *Horm Res*. 2005;63(5):252-6.