Review Article

Indian Journal of Medical & Health Sciences
Volume 9 Number 2, July – December 2022
DOI: https://dx.doi.org/10.21088/ijmhs.2347.9981.9222.8

Gynecomastia: Review Article

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How to cite this article:
Marenika Manisekaran, Neljo Thomas, Ravi Kumar Chittoria/Gynecomastia: Review Article/Indian Journal of Medical & Health Sciences. 2022;9(2):81–87.

Abstract

Gynecomastia is a benign enlargement of the male breast that results from an overgrowth of the glandular portion of the breast, which is often bilateral but can occasionally be unilateral. Clinically, it can be identified by the presence of a rubbery or firm mass extending concentrically from the nipples. Pseudogynecomastia (lipomastia), which is characterised by fat accumulation without glandular development, should be distinguished from gynecomastia. Gynecomastia develops when the estrogen androgen ratio is altered in favour of oestrogen or when the breasts become more sensitive to a normal level of circulating oestrogen. The antagonistic effects of testosterone and oestrogen are what are causing the imbalance. (The typical ratio of testosterone to oestrogen during pregnancy is about 100:1, while the usual testosterone to oestrogen ratio in the blood is about 300:1). The goal of surgery is to reduce the size of breast and to improve cosmetic appearance.

Keywords: Gynecomastia; Drugs; Surgery.

INTRODUCTION

Gynecomastia is a benign enlargement of the male breast resulting from a proliferation of the glandular component of the breast (Fig. 1).

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Received on: 04.07.2022

Accepted on: 05.08.2022

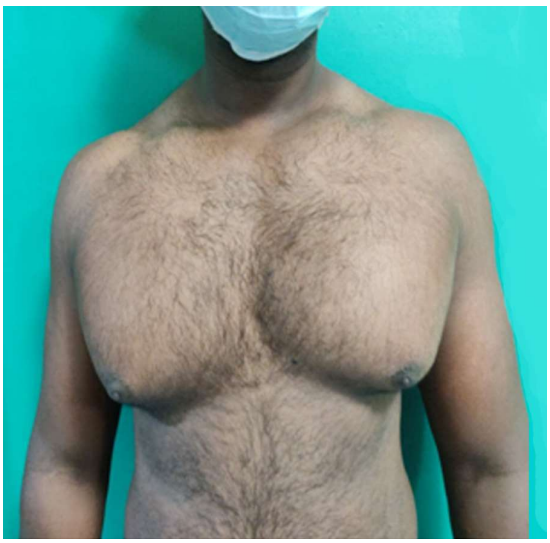

Fig. 1: Gynecomastia

Gynecomastia is defined clinically by the presence of a rubbery or firm mass extending concentrically from the nipples. Although the condition is usually bilateral, it can be unilateral. The condition known as pseudogynecomastia, or lipomastia, is characterized by fat deposition without glandular proliferation. Adolescent Male androgen production is primarily caused by the enzyme aromatase's peripheral conversion of androgens (testosterone and androstenedione) into estradiol and estrone (mainly in muscle, skin, and adipose tissue). Only 6–10 mg of estradiol and 2.5 mg of estrone are secreted daily by the testes. The remaining oestrogen in males is produced via the extra glandular aromatization of testosterone and androstenedione to estradiol and estrone, which only accounts for a small portion of the estrogens in circulation (15 percent of estradiol and 5 percent of estrone). Therefore, any cause of excess oestrogen, such as overproduction or peripheral androgen aromatization, might start the chain reaction that leads to breast growth. Increased production and/or action of oestrogen can happen in the testicles or around the periphery.[1,2]

ETIOLOGY

Gynecomastia develops when the estrogen-androgen ratio is altered in favour of oestrogen or when the breasts become more sensitive to a normal level of circulating oestrogen. The antagonistic effects of testosterone and oestrogen are what are causing the imbalance. (The typical ratio of testosterone to oestrogen during pregnancy is about 100:1, while the usual testosterone to oestrogen ratio in the blood is about 300:1.)

Estrogens cause the periductal fibroblasts to proliferate, ductal elongation and branching, ductal epithelial hyperplasia, and increased vascularity. After exposure to oestrogen, the histologic image in the breast tissue of men and women is identical.

Male androgen production is primarily caused by the enzyme aromatase's peripheral conversion of androgens (testosterone and androstenedione) into estradiol and estrone (mainly in muscle, skin, and adipose tissue). Only 6–10 mg of estradiol and 2.5 mg of estrone are secreted daily by the testes. The remaining oestrogen in males is produced via the extraglandular aromatization of testosterone and androstenedione to estradiol and estrone, which only accounts for a small portion of the estrogens in circulation (15 percent of estradiol and 5 percent of estrone). Therefore, any cause of excess oestrogen, such as over production or peripheral androgen aromatization, might start the chain reaction that leads to breast growth.[3]

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Increased estrogen production and/or action can occur at the testicular level or at the periphery and is characterized as follows:

From the testes: Can be caused by testicular tumours or by ectopic hCG production, as has been documented with cancers of the lung, kidney, GI tract, and extragonadal germ cell tumours.

From peripheral conversion: May result from an increase in substrate or an increase in aromatase activity, as in chronic liver illness, starvation, hyperthyroidism, adrenal tumours, and hereditary gynecomastia.

Both physiologic and pathologic causes of gynecomastia exist. Newborn babies, adolescent boys in their pubescent years, and the elderly can all develop physiological gynecomastia.

With median ratios of 22, 12, and 18, respectively, *Reinehr* et al. found that pubertal males with gynecomastia have a considerably higher estradiol/testosterone ratio than do those with pseudogynecomastia and healthy controls without breast growth. Boys with gynecomastia also had much less testosterone in their bodies than the other two groups.

Adult gynecomastia frequently has multiple causes. Gynecomastia in adult males is often caused by increased testosterone aromatization to estradiol and a progressive decline in testosterone synthesis in ageing testes. In comparison to younger men, older men are also more prone to use gynecomastia-related drugs.

Rarely, central hypogonadism brought on by hyperprolactinemia's effects on the hypothalamus may result in gynecomastia.[4] In breast cancer cells, prolactin has also been shown to increase oestrogen and progesterone receptors while decreasing androgen receptors, which can result in male gynecomastia. Despite the fact that prolactin itself does not directly induce gynecomastia, it does enhance milk production in breast tissue that has been prepped by oestrogen and progesterone.

Pathologic gynecomastia can be brought on by drug usage, an increase in oestrogen production and/or action, a decrease in testosterone production and/or action coupled with increased oestrogen and increased aromatization, or a combination of

these factors. Gynecomastia can, however, also be idiopathic.

The following examples show a pathologic increase in oestrogen or decrease in androgen:

Reduced androgen action and decreased output

Increased sex hormone binding globulin (SHBG) binds testosterone more strongly than oestrogen, promoting increased peripheral oestrogen activity.

Increased androgenic precursors [dehydroepi androsterone (DHEA) and androstenedione] • Increased SHBG - binds testosterone > oestrogen favouring higher peripheral oestrogen action • Estrogen receptor agonism.[5]

Increased estrogen action

- Increased aromatization of androgens to estrogens
- Increased androgenic precursors [dehydroepi androsterone (DHEA) and androstenedione]
- Increased SHBG – binds testosterone > estrogen favoring greater peripheral estrogen action
- Estrogen receptor agonism

Different conditions that cause primary or secondary hypogonadism might cause gynecomastia. Infection, infiltrative diseases, testicular trauma, age, an enzymatic impairment in testosterone production, Klinefelter syndrome, and other congenital abnormalities can all contribute to primary hypogonadism. A decrease in serum testosterone concentration and an increase in leuteinizing hormone (LH) release are the results of the accompanying reduction in testosterone production. A higher ratio of estradiol to testosterone is secreted as a result of the excess LH's improved stimulation of the Leydig cells, suppression of the 17,20-lyase and 17-hydroxylase activities, and increased aromatization of testosterone.

Secondary hypogonadism due to a hypothalamic or pituitary abnormality may also be associated with gynecomastia. In these patients, the production of LH is deficient, resulting in a low testosterone production rate and low estradiol production from the testes. However, the adrenal cortex continues to produce estrogen precursors that are aromatized in extraglandular tissue; the result is an estrogen/androgen imbalance.

The following are some of the conditions associated with gynecomastia:

- Klinefelter syndrome
- Congenital anorchia
- Testicular trauma
- Viral orchitis

Kallmann syndrome: A form of hypogonadotropic hypogonadism, Kallmann syndrome is usually associated with varying degrees of abnormality in olfactory perception; this results from the defective migration of gonadotropin releasing hormone secreting cells (which co-migrate with the cells of the olfactory epithelium) during embryogenesis.

Pituitary tumors or abnormalities such as the ones that lead to either hypersecretion or hyposecretion of LH.

Malignancies that increase the serum level of hCG (eg, large cell lung cancer, gastric carcinoma, renal cell carcinoma, hepatoma).

Renal failure: Men with end-stage renal disease may have reduced testosterone and elevated gonadotropin values. This apparent primary testicular failure may then lead to increased breast development.

Hyperthyroidism: Gynecomastia seen with hyperthyroidism is due to increased aromatase activity and increased levels of SHBG. SHBG binds androgens more avidly than estrogen, allowing for higher free levels to act on peripheral tissues such as the breast.

Malnutrition: Gynecomastia seen with malnutrition and starvation is probably due to reduced gonadotropin and testosterone levels relative to estrogen and may worsen with refeeding, owing to a rise in estradiol production that outpaces the increases in gonadotropin and testosterone.

Environmental pollutants: The most likely mechanism is through estrogen receptor binding and activation.

Androgen insensitivity syndrome

Familial prepubertal gynecomastia is a rare autosomal dominant hereditary condition that causes an excess oestrogen state as a result of enhanced aromatase activity. The P450 aromatase gene's heterozygous inversion or polymorphisms appear to be the cause of this illness. An 8 year old boy's phenotypic profile was defined as fast development, bone maturation, severe feminization, and gynecomastia due to a high rate of plasma androstenedione conversion to estrone.

Different medicines that cause gynecomastia can

be divided into categories (although drugs in the same class do not all cause gynecomastia to the same extent).

It's important to note that the pathophysiologic process for some medications, like estrogens or antiandrogens, is very obvious. Others, like spironolactone, have more complicated mechanisms.

The following list of antiandrogens and androgen production inhibitors:

Flutamide, bicalutamide, and nilutamide; Cyproterone acetate;

- ***Dutasteride vs finasteride:*** According to a research by *Hagberg* et al., dutasteride carries a higher risk of gynecomastia than does finasteride.

Tea tree oil, Spironolactone, and Ketoconazole

Cancer/chemotherapeutic drugs are as follows:

- Alkylating agents
- Methotrexate
- Vinca alkaloids
- Imatinib

Cardiac and antihypertensive medications are as follows:

- Calcium channel blockers (verapamil, nifedipine, diltiazem)
- ACE Inhibitors (captopril, enalapril)
- Digoxin
- Alpha-blockers
- Amiodarone
- Methyldopa
- Reserpine
- Nitrates

Hormones are as follows:

- Androgens
- Anabolic steroids
- Estrogens
- Growth hormones
- Chorionic gonadotropin

Psychoactive drugs are as follows:

- Haloperidol
- Diazepam
- Tricyclic antidepressants
- Haloperidol
- Phenothiazines

Drugs for infectious diseases are as follows:

- Antiretroviral therapy for HIV/AIDS (eg, indinavir)
- Isoniazid
- Ethionamide
- Griseofulvin
- Minocycline
- Metronidazole
- Ketoconazole

Drugs of abuse are as follows:

- Amphetamines
- Heroin
- Methadone
- Alcohol
- Marijuana

Others are as follows:

- Theophylline
- Omeprazole
- Auranofin
- Diethylpropion
- Domperidone
- Penicillamine
- Sulindac
- Heparin
- Methotrexate

The following drugs can also be categorised based on the data that links them to gynecomastia:

Estrogenlike or oestrogen receptor binders, verapamil with a relative risk (RR) of 9.7, spironolactone with an RR of 9.3, cimetidine with an RR of 7.2, finasteride, and ketoconazole are all considered to be probable.

Digoxin (RR of 2.7), nifedipine (RR of 2.9),

cytotoxic substances, and marijuana are all possible.

Nitrates, alfa-blockers, and diazepam are undetermined (reported but may be coincidental) medications.

Greater blood levels of lead increased the study subjects' likelihood of developing gynecomastia, whereas higher serum levels of hexachlorobenzene decreased the risk, according to a study by Den Hond et al. on the impact of pollutants on sexual maturation. The study included 1679 teenagers between the ages of 14 and 15. Gynecomastia is believed to be caused by the binding of oestrogen receptors.

Uncertain (reported but could be coincidental) - Nitrates, alfa-blockers, and diazepam.

Not certain (reported but could be coincidental) - Alfa-blockers, nitrates, and diazepam.

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According to estimates, the following etiologies may be present in men seeking medical care for gynecomastia:

- 25 percent of men have persistent pubertal gynecomastia
- Drug use (10–25%)
- No discernible abnormality: 25%
- Cirrhosis or undernutrition: 8%
- Primary hypogonadism: 8%
- 3 percent of men have testicular cancers
- 2% of people have secondary hypogonadism.
- About 1.5% of people have hyperthyroidism.
- 1% of people have chronic renal insufficiency.

EPIDEMIOLOGY

The most frequent reason for a male breast examination is gynecomastia. In addition to middle aged to older male adults, the illness is prevalent in childhood and adolescence. According to one estimate, the high levels of oestrogen during pregnancy cause temporary gynecomastia in 60–90% of newborns.

Puberty is when the next peak of occurrence occurs, with a prevalence of 4-69 percent. In several studies, males who develop gynecomastia have a brief rise in estradiol levels at the start of puberty. Usually, pubertal gynecomastia develops in boys between the ages of 10 and 12 years. In men older than 17 years, persistence is uncommon, and it typically regresses within 18 months. Between 24 and 65 percent of elderly men experience the third peak.[3,5]

SYMPTOMS AND SIGNS

The following questions should be covered in a complete history:

- The condition's age of start and duration.
- Any recent changes in nipple size, together with any discomfort or discharge from them.
- A history of testicular injuries, the measles, alcoholism, or drug abuse.
- Gynecomastia in the family history.
- A history of infertility, hypogonadism, or sexual dysfunction.

PHYSICAL EXAMINATION

Following should be included in the physical examination:

- A thorough examination of the breasts, paying close attention to their size and consistency.
- Distinguish between genuine gynecomastia and false gynecomastia.
- Evaluation of the glandular tissue.
- Examining the testicles to check for nodules or asymmetry as well as size and consistency.
- Observation of any feminization indicators.
- Examining the patient for any signs of chronic renal, thyroid, or liver.

DIAGNOSIS

Patients that have physiologic gynecomastia don't need any more testing. Similar to asymptomatic gynecomastia, pubertal gynecomastia doesn't need any additional testing and has to be checked again in six months. In the following circumstances, additional analysis is required:

- A breast size of at least 5 cm (macromastia).
- A lump that is sensitive, recently developed, advancing, or long-lasting.
- Malignancy indicators (eg, hard or fixed lymph nodes or positive lymph node findings).

The following list of laboratory examinations could be taken into account:

- Panel for serum chemistry.
- Levels of dehydroepiandrosterone sulphate, luteinizing hormone (LH), estradiol, and free or total testosterone.
- Free thyroxine and thyroid stimulating hormone (TSH) levels.

The following imaging tests are a few that could be beneficial:

- *Mammography:* Recommended if one or more breast cancer symptoms are noticeable during a clinical examination, followed by a breast biopsy or fine needle aspiration, when necessary.
- If the serum estradiol level is high and the findings of the clinical examination suggest the possibility of a testicular tumour, testicular ultrasonography is advised.
- Breast ultrasonography, not withstanding the modest positive predictive value of imaging in men.
- On CT scans, gynecomastia is frequently detected.
- Management.

The following are general management considerations:

- Physiologic gynecomastia typically do not need any therapy.
- In the majority of individuals, pubertal gynecomastia resolves spontaneously within a few weeks to three years, albeit breasts greater than 4 cm in circumference may not fully retreat.
- Reducing breast enlargement is frequently made easier by recognising and treating an underlying fundamental condition.
- Medical or surgical treatment may be considered for people with idiopathic gynecomastia or with remaining gynecomastia following treatment of the original aetiology.

Early on in the course of the ailment should be tried any medical therapy.

The following pharmaceuticals are used to treat gynecomastia:

- Clomiphen
- Tamoxifen
- Danazol (less frequently used)

Following are some surgical techniques that could be taken into consideration:

Reduction mammoplasty: In cases of macromastia, persistent gynecomastia, or ineffective medical treatment, this procedure may be considered.

More comprehensive plastic surgery: It might be an option in cases of severe gynecomastia or excessive breast tissue sagging as a result of weight reduction.

Without skin removal, endoscopic subcutaneous mastectomy

The following surgical problems are possible:

Tissue sloughing brought on by a weakened blood supply:

- An asymmetrical contour
- Formation of haemorrhages or seromas
- Nipple-areolar area numbness that never goes away

Gynecomastia that develops as a result of an underlying, treatable reason (such as gynecomastia put on by drugs) typically responds to therapy or elimination of the underlying cause. The chance of developing breast cancer is ten to twenty times higher in men with Klinefelter syndrome.

According to research, gynecomastia can have a psychological impact on a person's mood by causing sadness, anxiety, disordered eating, body dissatisfaction, and low self-esteem.

Gynecomastia may affect a man's ability to have sex. The International Index of Erectile Function (IIEF) was used to assess erectile function, orgasmic function, and intercourse satisfaction. The study, which involved 47 patients and 30 healthy controls, found that the scores for these variables were significantly lower in patients with gynecomastia than in the control group. However, compared to controls, gynecomastia patients had a considerably higher mean IIEF desire score. The study also discovered that the hormone profiles of the gynecomastia patients were comparable to those of the controls, with the exception of FSH and free T3, which were significantly lower than those of the controls (serum free triiodothyronine (T3), free thyroxine (T4), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), prolactin, estradiol, total testosterone, except for FSH and free T3, which were significantly lower,

the levels of free testosterone, luteinizing hormone, and dehydroepiandrosterone sulphate (DHEA-SO_4) in the gynecomastia patients were comparable to those in the controls.

PROGNOSIS

Gynecomastia does not result in any long-term problems aside from the potential risk of breast cancer. Pubertal gynecomastia goes away between a few months to many years in about 90% of instances. However, macromastia seldom disappears completely and frequently calls for surgery.

REFERENCES

1. Carlson HE. Approach to the patient with gynecomastia. J Clin Endocrinol Metab. 2011;96:15–21.
2. Binder G, Iliev DI, Dufke A, Wabitsch M, Schweizer R, Ranke MB, et al. Dominant transmission of prepubertal gynecomastia due to serum estrone excess: Hormonal, biochemical and genetic analysis in a large kindred. J Clin Endocrinol Metab. 2005;90:484–92.
3. Johnson RE, Kermott CA, Murad MH. Gynecomastia-evaluation and current treatment options. Ther Clin Risk Manag. 2011;7:145–8.
4. Gikas P, Mokbel K. Management of gynaecomastia: an update. Int J Clin Pract.2007;61:1209–15.
5. Binder G, Iliev DI, Dufke A, Wabitsch M, Schweizer R, Ranke MB, et al. Dominant transmission of prepubertal gynecomastia due to serum estrone excess: Hormonal, biochemical and genetic analysis in a large kindred. J Clin Endocrinol Metab. 2005;90:484–92.