

Gynecomastia

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Gynecomastia is defined as a benign enlargement of the male mammary glands due to an imbalance of free estrogen and androgen activity, resulting in palpable subareolar tissue.¹ This condition is frequently benign in origin but may have a serious underlying etiology. The overall prevalence of gynecomastia is estimated at 30% to 50%, with 3 peaks of occurrence during the life span:¹⁻³ the neonatal period (60%–90%), puberty (50%–60%), and older adulthood between the ages of 50 and 70 years (60%–70%).²⁻⁴ Physiologic gynecomastia related to a relative increase in the ratio of estrogen to androgen occurs during the neonatal period and puberty, while gynecomastia in older adulthood usually reflects aging-related physiologic changes involving declining androgen levels, accumulation of adipose tissue, and increasing aromatase activity. Gynecomastia that occurs outside of these peaks of prevalence may be a pathologic sign of an underlying process, thereby necessitating further work-up. In all cases of gynecomastia, however, a full history and physical examination is needed to ensure that a serious disease process is not missed. This article reviews the pathogenesis and causes of gynecomastia, with a focus on differentiating between physiologic and pathologic causes.

PATHOGENESIS

Gynecomastia results from conditions that cause an imbalance of estrogenic and androgenic effects on the breast, resulting in increased or unopposed estrogen action on breast tissue. Sources of estradiol include direct secretion from the testes, peripheral conversion of testosterone to estradiol, and conversion of estrone to estradiol.⁵ Estrogen production in males can occur from the peripheral conversion of androgens through the aromatase enzyme, which is concentrated in adipose tissue and the liver. Aromatase plays a role in the conversion of testosterone to estradiol as well as conversion of androstenedione to estrone (**Figure 1**).^{5,6} Other mechanisms known to contribute to the estrogen-androgen imbalance include exposure to exogenous estrogen, increased estrogen secretion, decreased se-

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- The peaks of prevalence for development of gynecomastia are the neonatal period, puberty, and older adulthood (age, 50–70 yr).
- Physiologic gynecomastia related to a relative increase in the estrogen to androgen ratio occurs during the neonatal period and puberty.
- Gynecomastia in older adulthood is related to hypogonadism, which results in lower testosterone levels, and increased accumulation of adipose tissue, which results in increased aromatase activity.
- Gynecomastia occurring outside the peaks of prevalence should be aggressively investigated for an underlying cause. Underlying causes include medications, cirrhosis, hypogonadism, testicular tumors, thyroid dysfunction, chronic kidney disease, and Klinefelter's syndrome.
- Gynecomastia is often self-limited, requiring no intervention.

cretion of testosterone by the testes, and an increased level of sex hormone-binding globulin, which binds testosterone more avidly than estrogen, resulting in decreased androgen activity.^{5,7-9}

HISTORY AND PHYSICAL EXAMINATION

Gynecomastia is often asymptomatic and may be an incidental finding on routine examination. In true gynecomastia, there is a firm, mobile, discoid mound of tissue evident beneath the nipple that can be palpated between the examiner's thumb and forefinger (**Figure 2**). In pseudogynecomastia (fatty breasts), commonly seen in obese men, the breasts are enlarged without firm

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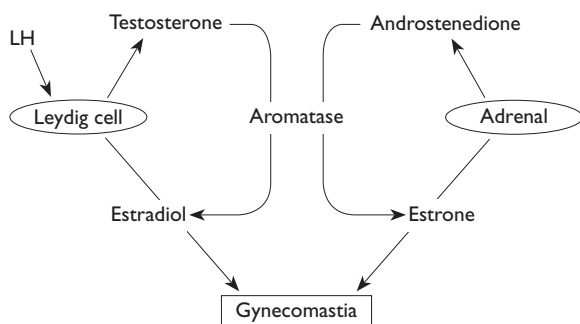


Figure 1. Pathogenesis of gynecomastia and the role of aromatase. LH = luteinizing hormone. (Adapted with permission from Lemack GE, Poppas DP, Vaughan ED. Urologic causes of gynecomastia: approach to diagnosis and management. *Urology* 1995; 45:314.)

palpable subareolar tissue. A careful history should document the onset and duration of gynecomastia. Transient gynecomastia commonly occurs in the neonatal period and during puberty.^{1,10} In both periods, the condition resolves spontaneously within 1 (neonates) to 2 years (puberty).

When examining adolescents, evaluation of secondary sexual characteristics is paramount, as delayed puberty may be a sign of Klinefelter's syndrome or Kallmann syndrome (*see* Hypergonadotropic Hypogonadism and Hypogonadotropic Hypogonadism).^{7,11} The physical examination should include measurement of testicle size, which can be done using an orchidometer, a string of 12 beads of increasing volume. Small testicle size (< 5 mL in volume) in an adolescent boy older than 13 years suggests hypogonadism from primary congenital causes such as those that occur in Klinefelter's syndrome.

Gynecomastia associated with galactorrhea suggests the presence of a prolactinoma.^{12,13} The most common presenting symptoms of prolactinomas in men are headaches and/or visual field defects.^{12,13}

Once gynecomastia has been confirmed on history and physical examination, the clinician must determine whether the cause is physiologic versus pathologic (**Table 1**). Physiologic gynecomastia is transient during the neonatal and adolescent periods, as mentioned above. Pathologic gynecomastia, as the name implies, results from a potentially serious underlying cause such as cirrhosis or testicular cancer.^{14–16} Gynecomastia is completely reversible when the underlying cause can be corrected (eg, drug-induced gynecomastia) but otherwise is irreversible (eg, chromosomal abnormalities).^{17,18}



Figure 2. Gynecomastia in a cachectic male patient with lung cancer.

PHYSIOLOGIC CAUSES

Neonatal Gynecomastia

Neonatal gynecomastia results from late fetal exposure to maternal-placental estrogens that stimulate breast tissue in the newborn. Neonatal gynecomastia can persist for several weeks after birth and usually resolves completely by the end of the first year. Galactorrhea can also occur in up to 5% of newborns. Neonate milk is referred to as “witch’s milk” in some folklore traditions, and this term continues to appear in the medical literature.^{19,20}

Puberty-Related Gynecomastia

Puberty-related gynecomastia results from a relative increase in estradiol due to stimulation of the testes by gonadotropins. In pubertal adolescents with normal genitalia, the presence of gynecomastia is a normal physiologic phenomenon. The possibility of testicular cancer should not be overlooked, however. The peak age of onset for puberty-related gynecomastia is between 13 and 14 years.^{1,4} Puberty-related gynecomastia usually resolves spontaneously within 2 years.^{1,4} Klinefelter's syndrome is a consideration in the adolescent with late-onset puberty associated with gynecomastia.

Aging-Related Gynecomastia

The gynecomastia of aging is partially related to increased aromatase activity, which increases conversion of androgens to estrogens.⁵ Aging is associated with accumulation of adipose tissue, one of the main sites of aromatase activity. It may be difficult to differentiate true gynecomastia from pseudogynecomastia (lipomastia) in an obese patient due to the accumulation of adipose tissue, although there are features that may help the clinician distinguish between the 2 conditions. In

Table 1. Causes of Gynecomastia

Maternal hormones during neonatal period
Puberty
Aging
Medications
Cirrhosis
Hypogonadism
Testicular tumors
Thyroid dysfunction
Chronic kidney disease
Klinefelter's syndrome

pseudogynecomastia as seen in obese men, the breast is composed of mostly fatty tissue (lipomastia), while in men aged 50 to 70 years, gynecomastia is associated with accumulation of adipose tissue as well as with hypogonadism and declining androgen levels.^{5,21}

PATHOLOGIC CAUSES

The pathologic causes of gynecomastia include systemic disorders, disorders that cause hypogonadism, and use of certain medications. Systemic disorders associated with gynecomastia include hepatic cirrhosis, chronic kidney disease, thyroid dysfunction, and malignancies, including testicular and lung cancer. The classic genetic cause of hypogonadism is Klinefelter's syndrome. Hypogonadism can be classified as hypergonadotropic or hypogonadotropic based on the patient's levels of luteinizing hormone (LH) and follicle-stimulating hormone. **Table 2** lists causes of hypogonadism based on this classification.

Systemic Diseases

Tumors. Tumors associated with gynecomastia secrete either estradiol or human chorionic gonadotropin (hCG). Leydig cell and Sertoli cell tumors secrete estradiol, while germ cell tumors secrete hCG, which stimulates Leydig cells to secrete estradiol. Ectopic production of hCG is also possible from extratesticular tumors (eg, lung).²² Gynecomastia can be the initial manifestation of a testicular tumor.^{16,23} In a retrospective review of 175 men referred to a breast surgeon due to breast enlargement or lumps, testicular tumors accounted for 2% to 3% of cases of gynecomastia.¹¹ Some patients with adrenal tumors develop gynecomastia, as adrenal tumors can secrete estradiol precursors, leading to elevated levels of estradiol.

Hepatic cirrhosis. Gynecomastia occurs in approximately 40% to 60% of patients with cirrhosis

Table 2. Male Hypogonadism Associated with Gynecomastia

Hypergonadotropic hypogonadism (increased LH)
Androgen insensitivity syndrome (increased testosterone and estradiol)
Klinefelter's syndrome (increased estradiol, decreased testosterone)
Hypogonadotropic hypogonadism (decreased LH)
Hypopituitarism (pituitary tumors such as prolactinoma with decreased GnRH)
Kallmann syndrome (congenital hypopituitarism)

GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

of the liver (**Figure 3**).^{14,24} A study of hormone levels in patients with hepatic cirrhosis found subnormal levels of dihydrotestosterone and elevated levels of estradiol.²⁵ In patients with cirrhosis, estrogen metabolism is impaired and hepatic production of sex hormone-binding globulin increases. These changes lead to decreased levels of free testosterone and a relative increase in estradiol as sex hormone-binding globulin has a higher affinity for androgens than estrogens.²⁶ Down-regulation of androgen receptors further contributes to the net decrease of androgen effect. Additionally, many patients with cirrhosis are treated with spironolactone, a drug associated with gynecomastia.²⁷

Thyroid dysfunction. Gynecomastia can occur in hyperthyroidism as a result of increased production of sex hormone-binding globulin, which leads to increased testosterone binding and decreased levels of unbound biologically active testosterone. In addition, there is increased peripheral conversion of androgens to estradiol by aromatase in patients with hyperthyroidism.²⁸ Gynecomastia presenting as the initial manifestation of hyperthyroidism is rare, but there are case reports of this occurrence.²⁹ The mechanism underlying the development of gynecomastia with hypothyroidism is less clear, but hypothyroidism is associated with lower concentrations of testosterone. The pituitary gland responds to the low testosterone level by increasing secretion of LH, which in turn results in increased estradiol production.³⁰ Gynecomastia can be the presenting sign of subclinical hypothyroidism.^{31,32} The gynecomastia associated with hypothyroidism resolves with thyroxine replacement therapy.³²

Chronic kidney disease and dialysis. The mechanism of gynecomastia in chronic kidney disease is complex and multifactorial. Early reports in patients started on hemodialysis suggest that refeeding of malnourished uremic patients plays a role in causing gynecomastia



Figure 3. Gynecomastia in a patient with hepatic cirrhosis. Note the spider angiomata on the chest.

via a mechanism thought to be similar to that of pubertal gynecomastia.³³ This process occurs about 1 to 2 months after initiation of hemodialysis. Later reports in patients on long-term hemodialysis also describe an association with calcium channel blockers used for hypertension control.³⁴

Hypergonadotropic Hypogonadism

Klinefelter's syndrome. Klinefelter's syndrome occurs in males who have at least 1 extra X chromosome.¹⁸ Characteristics of Klinefelter's syndrome include infertility, small testes, sparse hair in androgen-dependent areas, tall stature, and gynecomastia. The most common of these are infertility and small testes, which affect nearly 100% of patients.¹⁸ Testicular volume is usually less than 4 mL. Karyotyping is diagnostic, with 47,XXY being the most common karyotype. The condition results in a hypergonadotropic hypogonadism as a result of primary testicular failure. Patients with Klinefelter's syndrome have a eunuchoidal body habitus with long arm span and increased length of the lower body. Gynecomastia affects 50% to 75% of patients with Klinefelter's syndrome.¹⁸ There is an increased risk of breast cancer in patients with gynecomastia associated with Klinefelter's syndrome.^{1,18}

Androgen insensitivity syndrome. The androgen insensitivity syndromes are divided into complete and incomplete. Complete androgen insensitivity syndromes, not discussed in this article, result in a female phenotype in a genotypic male. Incomplete androgen insensitivity syndromes, such as Reifenstein's syndrome, are associated with hypospadias, gynecomastia, and cryptorchidism.³⁵ Persons with an incomplete androgen in-

sensitivity syndrome are often diagnosed during early childhood because of ambiguous genitalia.

Hypogonadotropic Hypogonadism

Kallmann syndrome. Classically, patients with hypogonadotropic hypogonadism and anosmia have been diagnosed with Kallmann syndrome.³⁶ In this syndrome, anosmia is due to the absence of olfactory bulbs. Kallmann syndrome is the result of gonadotropin-releasing hormone (GnRH) deficiency. The diagnosis of Kallmann syndrome is typically delayed until adolescence when patients fail to begin puberty and do not develop secondary sexual characteristics.³⁶ The inheritance pattern for Kallmann syndrome is variable, with X-linked recessive, autosomal dominant, and autosomal recessive patterns.

Pituitary tumors. Prolactinomas are the most common functional pituitary tumors.¹³ A retrospective review of 19 patients (10 aged ≤ 30 yr, 9 aged ≥ 60 yr) who presented with prolactin-secreting pituitary tumors suggested that the clinical presentation depends on the age of the patient, with patients younger than 30 years more likely to present with gynecomastia as well as other typical features of prolactinomas, including visual field defects, headache, and impotence.¹² Headaches and visual field defects are the most common initial symptoms, however, in both younger and older patients. Patients aged older than 60 years are more likely to go undiagnosed as there are other more common causes of hypogonadism in this age-group.¹² Elderly patients are also more likely to present with a nonfunctioning pituitary adenoma.³⁷ Large nonfunctioning pituitary adenomas can compress the pituitary stalk, interrupting the flow of dopamine from the hypothalamus that normally inhibits the release of prolactin from the pituitary gland. As a result, nonfunctioning pituitary adenomas can cause a mild increase in prolactin levels (≤ 100 ng/mL), while prolactinomas cause a marked elevation in prolactin levels (> 200 ng/mL). Normal prolactin levels in men are less than 15 ng/mL. The hypogonadism associated with prolactinomas is the result of suppression of the hypothalamic-pituitary-gonadal axis. Very high prolactin levels cause a secondary hypogonadism with decreased secretion of GnRH.

Medication-Induced Gynecomastia

Approximately 4% to 10% of cases of gynecomastia are due to medications.^{38,39} Medications that cause gynecomastia do so by different mechanisms, including inadvertent exposure to exogenous estrogens, direct action of estrogen-like substances, inhibition of androgen synthesis, and blocking of the androgen

receptor (Table 3). There is a paucity of evidence regarding drug-induced gynecomastia. Most publications are case reports that describe only the temporal relationships between the drug and onset of gynecomastia, and the high prevalence of gynecomastia as a normal finding further confounds the evidence.^{1,17}

HIV-related gynecomastia. Male patients treated with highly active antiretroviral therapy (HAART) for HIV infection may develop gynecomastia.⁴⁰ In a prospective study of 1304 men with HIV infection receiving HAART, 2.3% presented with gynecomastia.⁴¹ In nearly 75% of these patients, the gynecomastia completely resolved after a median duration of 9 months. In a report of 4 cases of HIV-associated gynecomastia, the time to onset of gynecomastia was 3 to 7 months after initiation of HAART.⁴²

Hypertension. The development of gynecomastia during treatment of hypertension has been noted.²¹ The most commonly implicated class of antihypertensive agents are the calcium channel blockers.¹⁷ The mechanism by which calcium channel blockers induce gynecomastia is unclear with the exception of verapamil, which has been reported to cause hyperprolactinemia.⁴³

Congestive heart failure. Digoxin and spironolactone are commonly used in the treatment of heart failure and both are associated with gynecomastia.^{17,44} The structural similarities of digoxin and estrogen-like substances are commonly cited as the likely mechanism.¹³ Spironolactone induces the development of gynecomastia by causing the displacement of androgen from its receptor.⁴⁵ Additionally, spironolactone blocks the biosynthesis of testosterone from cholesterol.⁴⁶

Gastroesophageal reflux disease. Gynecomastia associated with treatment of gastroesophageal reflux disease has been reported with cimetidine and metoclopramide.^{47,48} Cimetidine acts as an androgen receptor antagonist,⁴⁹ while metoclopramide has been demonstrated to raise levels of prolactin.⁵⁰

Prostate disease. Gynecomastia is a potential adverse effect in men receiving antiandrogen therapy for prostate cancer. It is difficult to determine the actual incidence of gynecomastia in patients undergoing antiandrogen treatment for prostate cancer due to the high background rate of gynecomastia in the older male population.⁵¹ Hormonal antiandrogen therapy for prostate cancer includes luteinizing hormone-releasing hormone (LHRH) agonists (goserelin, leuprolide, buserelin), estrogens (diethylstilbestrol), nonsteroidal antiandrogens (bicalutamide, flutamide), and steroidal antiandrogens (cyproterone).³⁸ The incidence of gynecomastia associated with types of antiandrogen therapy varies by report but is lowest for orchiectomy at 10%, with nonsteroidal

Table 3. Drugs Associated with Gynecomastia

Androgen receptor antagonists
Cimetidine
Spironolactone
Flutamide
Bicalutamide
Inhibitors of testosterone synthesis and metabolism
Spironolactone (also has androgen receptor antagonism)
Ketoconazole
Finasteride and dutasteride (5 α -reductase inhibitors)
Drugs with estrogen-like activity
Digitalis
Marijuana
Estrogen vaginal cream (exposure during intercourse)
Unknown mechanism
Theophylline
Highly active antiretroviral therapy
Calcium channel blocker

antiandrogen therapy at 30% to 50% and LHRH agonist therapy at 25%.^{3,51} Treatment of benign prostatic hypertrophy with finasteride has been associated with gynecomastia.⁵² Finasteride and dutasteride are inhibitors of 5 α -reductase, the enzyme responsible for metabolizing testosterone to dihydrotestosterone.

APPROACH TO EVALUATION

Laboratory evaluation is not needed in most cases of gynecomastia.¹ Instead, a careful history and physical examination should be emphasized with reversible causes sought first, such as drug-induced gynecomastia. When no underlying cause can be elucidated from the history and physical examination, initial laboratory evaluation should include hepatic, renal, and thyroid function panels. If these studies are normal, measurement of levels of testosterone, hCG, estradiol, and LH may be helpful (Table 4).¹

There is no consensus regarding the use of mammography in evaluating the male breast.⁵³ Male breast cancer accounts for only 1% of all cases of breast cancer.^{53,54} Male breast cancer occurs at an average age of 60 years.⁵² Gynecomastia does not increase the risk of breast cancer except in patients with Klinefelter's syndrome.^{1,14} In addition to a discrete palpable breast mass, other findings associated with male breast cancer include nipple or skin retraction, axillary adenopathy, and bloody nipple discharge.⁵⁴ One could argue that mammography should be restricted to men older than

Table 4. Laboratory Evaluation of Gynecomastia with Predominant Abnormal Findings

	Testosterone	Estradiol	hCG	LH	TSH	Prolactin
Testicular germ cell tumor*		↑	↑			
Leydig or Sertoli cell tumor *		↑		↑		
hCG-secreting neoplasm [†]		↑	↑			
Hyperthyroidism	↓				↓	
Hyperprolactinemia [‡]	↓					↑
Primary hypogonadism	↓			↑		
Secondary hypogonadism	↓			↓		
Adrenal neoplasm [§]		↑				
Increased aromatase activity		↑				
Cirrhosis of the liver [¶]	↓	↑				

Note: Gynecomastia is the result of an increased ratio of estrogen (estradiol) to androgen (testosterone). It can be an absolute increase in estradiol or a relative increase due to a lower testosterone level.

hCG = human chorionic gonadotropin; LH = luteinizing hormone; TSH = thyroid-stimulating hormone.

*Testicular ultrasound is warranted.

[†]Computed tomography scan of the chest and abdomen is helpful (lung, liver, kidney).

[‡]Magnetic resonance imaging of the brain should be performed to evaluate the pituitary gland.

[§]Computed tomography scan of the abdomen is helpful.

[¶]Liver ultrasound is used to confirm the diagnosis.

age 50 years, but 1% of male breast cancer occurs below the age of 30 years and 6% occurs below the age of 40 years.⁵⁵ Rather than using age as the sole criteria for determining the need for mammography, the clinician should consider the presence of associated findings, most importantly the skin changes associated with male breast cancer.⁵⁶

CONCLUSION

The causes of gynecomastia are divided into physiologic and pathologic. Transient physiologic gynecomastia is common in the neonatal period and during puberty, while aging-related gynecomastia is commonly seen in patients aged 50 to 70 years. Gynecomastia that occurs outside of the peaks of prevalence may be a sign of an underlying process, and physicians should be aware of the pathologic and physiologic causes and be able to distinguish between them. In most cases, the cause of gynecomastia can be determined by a thorough history and physical examination. **HP**

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