

# Gynecomastia: Clinical evaluation and management

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### ABSTRACT

Gynecomastia is the benign enlargement of male breast glandular tissue and is the most common breast condition in males. At least 30% of males will be affected during their life. Since it causes anxiety, psychosocial discomfort and fear of breast cancer, early diagnostic evaluation is important and patients usually seek medical attention. Gynecomastia was reported to cause an imbalance between estrogen and androgen action or an increased estrogen to androgen ratio, due to increased estrogen production, decreased androgen production or both. Evaluation of gynecomastia must include a detailed medical history, clinical examination, specific blood tests, imaging and tissue sampling. Individual treatment requirements can range from simple reassurance to medical treatment or even surgery. The main aim of any intervention is to relieve the symptoms and exclude other etiologic factors.

**Key words:** Androgen, drug, estrogen, gynecomastia, surgery

## INTRODUCTION

Gynecomastia is defined clinically as generalized enlargement of male breast tissue, with the presence of a rubbery or firm mass extending concentrically and symmetrically from the nipple,<sup>[1-4]</sup> accompanied by histopathologically benign proliferation of glandular male breast tissue.<sup>[5-9]</sup> It usually occurs bilaterally and is the most common breast condition in males.<sup>[2-4]</sup> A related condition, pseudogynecomastia, manifests as fat deposition without glandular proliferation and occurs most frequently in obese men.<sup>[3,10]</sup> Because gynecomastia causes anxiety, psychosocial discomfort and a fear of breast cancer, patients seek medical attention and require diagnostic evaluation. Because of the increasing incidence of obesity, the number of patients with pseudogynecomastia is increasing. In addition, increased use of anabolic steroids

and environmental contamination with xenoestrogens or estrogen-like substances may stimulate glandular proliferation in male breast tissue.<sup>[10]</sup> In mild cases, simple reassurance coupled with advice on diet and exercise may be sufficient.<sup>[6]</sup> However, in more severe cases, medical and/or surgical intervention is required.<sup>[6]</sup> This review describes the pathophysiology, etiology and clinical evaluation of gynecomastia and may be helpful for selecting patients who will require treatment.

## PREVALENCE

The prevalence of gynecomastia was reported to be between 32-65%, due to use of different methods of assessment and the analysis of males of different ages and with different lifestyles, while autopsy data suggest a prevalence of 40%.<sup>[6]</sup> Generally, a trimodal age distribution is observed.<sup>[8]</sup> The first peak occurs in infancy or the neonatal period, with an occurrence of 60-90%. During pregnancy, the placenta converts DHEA (dehydroepiandrosterone) and DHEA-SO<sub>4</sub> (dehydroepiandrosterone-sulfate), derived from both mother and fetus, to estrone (E1) and estradiol (E2), respectively. E1 and E2 then enter the fetal circulation and later stimulate breast glandular proliferation, which results in transient neonatal gynecomastia. Normally, this condition regresses within 2-3 weeks of

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delivery.<sup>[2,5,8,11]</sup> The second peak occurs during puberty and has a prevalence of 4-69%. This wide variation is likely due to differences in what is considered to be normal sub-areolar glandular tissue, the diagnosing physician and most importantly variations in the age distribution of the patient populations.<sup>[6]</sup> Pubertal gynecomastia usually begins at age 10-12-years-old and peaks at ages 13-14. It usually regresses within 18m and is uncommon in males aged 17 and older.<sup>[8,11]</sup> The final peak occurs in older males (particularly in those aged 50-80-years-old), with a prevalence of 24-65%. Senile gynecomastia can generally be attributed to increased adiposity with aging, because adipose tissue is the major tissue in which androgens are converted to estrogens.<sup>[2]</sup> The higher estrogen production rates in older males are related to an age-related increase in cytochrome P19 (CYP19) activity in adipose tissue.<sup>[7]</sup> Additional contributing factors are decreased testosterone (T) and the use of medications that may alter androgen or estrogen concentrations or actions.<sup>[2]</sup>

## HISTOLOGY

Histological studies showed that glandular changes in breast tissue during gynecomastia are identical irrespective of the etiology, although the extent of glandular proliferation depends on the intensity and duration of stimulation. The early stages of gynecomastia are characterized by ductal epithelial hyperplasia (the proliferation and lengthening of the ducts), increases in stromal and periductal connective tissue, increased periductal inflammation, intensive periductal edema and stromal fibroblastic proliferation. These all usually occur in the first 6m after onset and are also correlated with pain or tenderness.<sup>[11]</sup> In the later stages (after 12m), there is marked stromal fibrosis, a slight increase in the number of ducts, but little to no epithelial proliferation and no inflammatory response. Consequently, pain or tenderness is uncommon in this stage.<sup>[11]</sup> Medical treatment can therefore be beneficial if implemented during the early proliferative phase, before the glandular structure has been replaced by stromal hyalinization and fibrosis.<sup>[10]</sup>

Several morphological classifications have been reported, based on skin elasticity, the presence of an inframammary fold (IMF), mammary ptosis,<sup>[12]</sup> or following the recommendations of Cordova and Moschella.<sup>[13]</sup> Gynecomastia can be typically classified into four grades of increasing severity, from I to IV,<sup>[13]</sup> ranging from simple areolar protrusion, to breasts with a female appearance.<sup>[13]</sup> Cordova and Moschella proposed a morphological classification of gynecomastia based on the evaluation of the relationship between the nipple-areola complex and the inframammary fold, which makes it possible to establish an algorithm for the most suitable intervention.<sup>[13]</sup>

## PATHOPHYSIOLOGY

The major cause of gynecomastia is thought to be an altered imbalance between estrogen and androgen effects due to absolute increase in estrogen production, relative decrease in androgen production or a combination of both.<sup>[2,4,7,11]</sup> The pathophysiological mechanism of this is shown in Table 1.<sup>[2,8]</sup> Estrogen act as a growth hormone of the breast and therefore excess of estradiol in men leads to breast enlargement by inducing ductal epithelial hyperplasia, ductal elongation and branching, the proliferation of periductal fibroblasts and vascularity. The exposure to estrogen has similar histological results in males and females, except that luteal phase progesterone in females leads to aciner development, which does not occur in males.<sup>[14]</sup> Elevated serum estrogen levels in males can be derived from estrogen producing tumors (Leydig or Sertoli cell, human chorionic gonadotropin (hCG)-producing, or adrenocortical tumors), or more commonly from the extra-gonadal aromatization of androgens to estrogens.<sup>[5]</sup> Local tissue factors in the breast can also be important; for example, increased aromatase activity that can cause excessive local production of estrogen, decreased estrogen degradation and changes in the levels or activity of estrogen or androgen receptors.<sup>[11]</sup>

Although prolactin (PRL) receptors are present in male breast tissue, hyperprolactinemia may lead to gynecomastia through effects on the hypothalamus, causing central hypogonadism.<sup>[2,10,11]</sup> Activation of PRL also leads to decreased androgen and increased estrogen and progesterone receptors in breast cancer cells. If similar events occur in male breast tissue, it could lead to gynecomastia.<sup>[2]</sup> The role of PRL, progesterone and other growth factors (GFs) such as insulin like growth factor I (IGF-I) and epidermal growth factor (EGF), in the development of gynecomastia are unclear.<sup>[2]</sup>

**Table 1: Pathophysiological mechanisms leading to gynecomastia<sup>[2,8]</sup>**

|  |
|--|
| Increase in estrogens                                      |
| Direct secretion (from testes/adrenals/placenta)           |
| Extraglandular aromatisation of precursors                 |
| Decreased metabolism                                       |
| Exogenous administration                                   |
| Decrease in endogenous free androgens                      |
| Decreased secretion  |
| Increased metabolism                                       |
| Increased binding to sex hormone-binding globulin          |
| Altered serum androgen/estrogen ratio                      |
| Puberty, aging, refeeding gynecomastia, hepatic cirrhosis, |
| Hyperthyroidism, drugs, renal failure and dialysis         |
| Androgen receptor defects                                  |
| Enhanced sensitivity of breast tissue ?                    |

## ETIOLOGY

### Puberty

E2 levels rise more rapidly than T during early puberty, which leads to an elevated estrogen/androgen ratio.<sup>[4,7]</sup> In most pre-adolescent males, breast enlargement regresses concomitant with pubertal progression and the rise in T levels and so only small numbers of patients have persistent gynecomastia,<sup>[7]</sup> and the condition usually spontaneously regresses within two years of onset.<sup>[11]</sup> Interestingly, more than half of the patients with persistent pubertal gynecomastia have a family history of the condition.<sup>[10]</sup> Table 2 summarizes additional gynecomastia-related conditions.<sup>[8]</sup>

### Medications

Medications have been reported to cause up to 25% of cases of gynecomastia and they can be categorized by their hormone-like action.<sup>[6,10]</sup> Type 1 medications act like estrogens and include diethylstilbestrol (DES), oral contraceptives, phytoestrogens, digitalis and estrogen-containing cosmetics. Type 2 causes include gonadotropins, clomiphene and enhanced endogenous estrogen, type 3 include metronidazole, cimetidine, flutamide, cyproterone acetate and bicalutamide. Type 4 drugs act via unknown mechanisms and include isoniazid (INH), methyl dopa, captopril, tricyclic antidepressants (TCAD), diazepam, heroin and cannabis.<sup>[6,7]</sup> Spironolactone is a steroidal antimineralocorticoid and is one of the medications that have been most linked with gynecomastia. It increases the aromatization of T to E2, reduces T production in the testis, displaces T from Sex-hormone binding globuline (SHBG) and increases the metabolic clearance of T. It also binds to the androgen receptor, blocking the binding of T and DHT, or displacing

them from their receptors.<sup>[15]</sup> However, not all drugs in the same class cause gynecomastia: while the calcium channel blockers nifedipine and verapamil have the highest causative rate of gynecomastia, diltiazem has the lowest frequency. Conversely, cimetidine has the highest correlation of the H2 receptor antagonist family, while ranitidine has the lowest. Cimetidine reduces 2-hydroxylation of E2, which increases the concentrations of active E2.<sup>[4,15]</sup> Omeprazole has been reported to cause gynecomastia in case reports although in a review of all antiulcer drugs there was no evidence that the use of omeprazole was associated with increased risk of gynecomastia.<sup>[4]</sup> Drugs leading to gynecomastia is shown in table 3.

### Cirrhosis and liver disease

Gynecomastia in patients with cirrhosis or liver disease is caused by increased production of androstenedione (A) from adrenal glands, increased aromatization of A to E1, increased conversion of E1 to E2, decreased clearance of adrenal androgens from the liver and increased SHBG, which leads to a decrease in free T levels. Spironolactone is also used to treat cirrhotic patients, which can exacerbate the condition.<sup>[11,15]</sup> Alcohol use can also disrupt the hypothalamic–pituitary–testicular axis, causing a decrease in serum T levels.<sup>[11]</sup> Finally, tumors can lead to gynecomastia due to increased aromatase activity in the tumor itself.<sup>[4]</sup>

### Starvation

Malnourishment can cause gynecomastia due to decreased gonadotropin and T levels, coupled with normal production of estrogens (and their precursors) from the adrenal glands.<sup>[11]</sup> In the lead re-feeding gonadotropins are increased, leading to T secretion and E2 production, which mimics normal puberty. Patients who develop

**Table 2: Gynecomastia related conditions<sup>[8]</sup>**

|   |
|---|
| Physiological   |
| Neonatal  |
| Pubertal  |
| Involutional  |
| Pathological  |
| Cirrhosis/liver disease   |
| Starvation  |
| Male hypogonadism (primary or secondary)  |
| Testicular neoplasms (germ cell tumours, leydig cell tumours, sex-cord tumours) |
| Hyperthyroidism   |
| Renal failure and dialysis  |
| Feminizing adrenocortical tumours   |
| Ectopic hCG production  |
| True hermaphroditism  |
| Androgen insensitivity syndromes  |
| Aromatase excess syndrome   |
| Stressful life events   |
| Type 1 DM   |
| Kennedy's syndrome  |
| Drugs   |
| Idiopathic  |

**Table 3: Drugs that lead to gynecomastia<sup>[2]</sup>**

| Mechanism lead to gynecomastia | Drug   |
|--------------------------------|--|
| Increase serum estrogen        | Estrogens, including topical preparations<br>Aromatisable androgens<br>hCG   |
| Estrogen like activity         | Digitoxin, herbal products   |
| Decrease serum                 | GnRH agonist/antagonist  |
| Testosterone or DHT            | Leydig cell damage or inhibition<br>Ketoconazole, Metronidazole<br>Spironolactone, cancer chemotherapy<br>Finasteride or dutasteride |
| Androgen receptor blockers     | Flutamide, bicalutamide<br>Spironolactone  |
| Increase serum PRL             | Cimetidine, Marijuana<br>Antipsychotic agents<br>Metoclopramide, Verapamil   |
| Mechanism uncertain            | Isoniazid, Amiodarone, Antidepressants<br>Human GH, Proton pump inhibitors<br>Highly active retroviral therapy                       |

DHT: Dehydrotestosterone, PRL: Prolactin, hCG: Human chorionic gonadotropin, GH: Growth hormone

re-feeding gynecomastia are therefore often described to be undergoing a 'second puberty'.<sup>[11]</sup>

### Male hypogonadism

Primary hypogonadism can lead to decreased T production, compensatory LH increase, Leydig cell stimulation, the inhibition of 17, 20-lyase and 17-hydroxylase activities, elevated aromatization of T to E2 and finally an increase in the ratio of E2 to T.<sup>[11]</sup> Klinefelter's syndrome is associated with gynecomastia in approximately 80% of cases and is the only cause of the condition that additionally causes an increased risk of breast cancer (10-20 fold elevated risk).<sup>[7]</sup> In secondary hypogonadism, LH production is defective, which leads to decreased T and E2 production in the testis. The adrenal cortex continues to produce estrogen precursors that get aromatized in the extra-glandular tissues, resulting in an estrogen to androgen imbalance.<sup>[11]</sup> Although treatment with gonadotropins can lead to secondary hypogonadism, they do not directly cause gynecomastia.

### Prolactin-secreting pituitary adenomas

These tumors have also been linked with a causative role in gynecomastia.<sup>[10]</sup>

### Hyperthyroidism

Gynecomastia is observed in 10-40% of males with Graves' Disease.<sup>[10]</sup> It is frequently caused by the direct stimulation of peripheral aromatase, because elevated LH levels contribute to increased E2 levels and T production from Leydig cells. In addition, SHBG is often increased, leading to increased concentrations of E2. In cases of hyperthyroidism, breast enlargement is usually resolved after restoration of the euthyroid state.<sup>[11]</sup>

### Renal failure and dialysis

Gynecomastia is observed in approximately 50% of hemodialysis patients, primarily due to Leydig cell dysfunction. Renal failure leads to hormonal abnormalities, in particular decreased T, increased E2 and LH levels and a modest increase in PRL.<sup>[11]</sup> Hormonal abnormalities can be reversed by renal transplantation but are not altered by dialysis.<sup>[11]</sup> Dialysis-associated gynecomastia may be pathogenetically comparable with re-feeding gynecomastia. Before dialysis, renal failure patients have restricted diets, can be malnourished and tend to lose weight. After dialysis, patients are free to resume a regular diet and often regain weight.<sup>[11]</sup> In renal transplantation patients, gynecomastia can also be a side effect of medications, such as cyclosporine.

### Ectopic hcg production

Healthy males have undetectable serum levels of hCG. However, large-cell lung carcinoma, gastric carcinoma,

renal cell carcinoma and rarely hepatoma can lead to the ectopic production of hCG, causing gynecomastia.<sup>[4,11]</sup> In pre-adolescent males with hCG-secreting hepatoblastoma, precocious puberty can also occur.

### True hermaphroditism

Patients with true hermaphroditism have both ovarian and testicular tissues. Excessive estrogen secreted from ovarian component may cause gynecomastia by inhibiting intra-testicular cytochrome P450 C17 activity, leading to decreased testosterone production.

### Aromatase excess syndrome

This is an OD and X-linked familial form of prepubertal gynecomastia.<sup>[7]</sup> Heterogeneous inversion or polymorphism of the p450 aromatase gene leads to increased aromatase activity in peripheral tissues, resulting in elevated estrogen levels.<sup>[7]</sup> Patients with aromatase excess syndrome are characterized by increased E2 levels, pre-pubertal gynecomastia, accelerated bone age in childhood and reduced final adult height due to premature epiphyseal fusion.<sup>[7]</sup>

### Stressful life events

Increased stress can stimulate the adrenal glands to secrete excess estrogen precursors.<sup>[11]</sup> Increased serum cortisol and E2 levels, combined with decreased serum T, have been reported in patients under extreme stress.<sup>[11]</sup>

### Type i diabetes mellitus

Males with long-standing type 1 diabetes mellitus may develop diabetic mastopathy, presenting with hard diffuse enlargements of one or both breasts.<sup>[16]</sup> In these cases, an inflammatory lesion characterized by lymphocytic infiltration of the mammary ducts and lobules is observed microscopically.<sup>[16]</sup>

### Kennedy's syndrome

This is characterized by X-linked spinal and bulbar muscular atrophy and gynecomastia and testicular atrophy are common.<sup>[4]</sup> Bodybuilders who abuse anabolic steroids to increase muscle mass may also develop gynecomastia.<sup>[4]</sup>

## EVALUATION

All males with breast enlargement should be examined with a view to answering the following questions<sup>[2]</sup>: (1), How recent was the onset?; (2), Is the enlargement associated with pain or tenderness?; (3), Is the enlargement due to glandular proliferation or fat deposition?; (4), Does the patient have signs or symptoms of breast cancer?; (5), Could the condition be associated with a testicular tumor?; and (6), Is the patient uncomfortable as a result of the breast

enlargement? A healthy male with long-stable gynecomastia and a negative history and physical examination generally does not require further evaluation.<sup>[2]</sup> The presence of previously unreported breast pain or tenderness, or the new onset of enlargement, rapid growth, or a breast size >5 cm, should prompt further evaluation to detect any underlying systemic problems.<sup>[2,7]</sup>

### History

A detailed history should include the onset and duration of breast enlargement, symptoms of pain or tenderness, weight loss or gain, change in size, nipple discharge, retraction, virilization symptoms, medication history (for example if gynecomastia is improved following discontinuation of a drug, it strongly suggests that the drug is responsible), the presence of systemic illness, fertility, sexual function, history of undescended testes and mumps. Finally, family history of gynecomastia should be assessed, which may suggest androgen insensitivity syndrome, familial aromatase excess, or Sertoli cell tumors.<sup>[2,5,11]</sup>

### Physical examination

Differentiating true gynecomastia from pseudogynecomastia and tumors is based on physical examination. The patient lies on his back with his hands behind his head and the physician places her/his thumb and forefinger on each side of the breast and slowly brings them together. In true cases of gynecomastia, the physician will feel a disc or firm tissue that is concentric with the nipple-areolar complex. In patients with pseudogynecomastia the fingers will not meet any resistance until they reach the nipple.<sup>[10]</sup> In contrast, breast carcinoma usually presents as a unilateral hard, irregular mass located outside the areola, which may be accompanied by skin dimpling, nipple retraction and axillary lymphadenopathy.<sup>[2,5,10]</sup> Physical examination should also include examination of the abdomen (an abdominal mass may be present) and testicles. Signs of liver, kidney disease, or hyperthyroidism can be determined by a physical examination. If the patient is adolescent and the results of physical and genital examinations are normal, pubertal gynecomastia is likely and evaluations should continue at 6-month intervals.

### Laboratory evaluation

In cases of true gynecomastia without a clear cause, laboratory tests should be pursued,<sup>[5]</sup> and must include, liver, kidney and thyroid function tests (to exclude the respective medical conditions), as well as hormonal tests (E2, total and free testosterone, A, LH, FSH, PRL, hCG, DHEA-SO4 or 17 ketosteroids, SHBG and  $\alpha$ FP).<sup>[2,3,6,9]</sup> In aging males, hypogonadism is commonly observed and measuring overnight T levels can be informative: if levels are low, T and LH levels should be measured. If testes are small, the patient's karyotype should be obtained to exclude

Klinefelter's Syndrome.<sup>[7]</sup> If all tests are negative, the patient should be diagnosed with idiopathic gynecomastia.<sup>[5]</sup>

### Imaging methods

Mammography (MMG) is the primary imaging method used when there is any suspicion of cancer.<sup>[10]</sup> It accurately distinguishes between malignant and benign male breast diseases and can differentiate true gynecomastia from a mass that requires tissue sampling to exclude malignancy, reducing the need for biopsies.<sup>[5]</sup> The sensitivity and specificity of MMG for benign and malignant breast conditions is greater than 90%, but its positive predictive value for malignancies is low (55%), because of the low prevalence of malignancy in patients presenting with gynecomastia.<sup>[5,10]</sup> In cases of pseudogynecomastia, breast tissue is filled with radiolucent adipose.<sup>[4,6]</sup> Breast ultrasonography (USG) is widely used in the diagnosis of gynecomastia cases and is more comfortable for male patients.<sup>[9]</sup> Scrotal USG and abdominal computerized tomography (CT) can also be used. However, when there is no history or physical examination suggestive of an underlying pathological cause, these tests are not recommended in clinical practice, since they are unlikely to be useful in the absence of suspicious pathology.<sup>[10]</sup> If necessary, pituitary magnetic resonance imaging is recommended.<sup>[11]</sup>

### Tissue biopsy

If differentiating between gynecomastia and breast cancer cannot be achieved using physical and imaging findings, a percutaneous biopsy should be taken.<sup>[10]</sup> However, the yield of cells taken in a gynecomastia biopsy is often insufficient, because gynecomastia is a predominantly fibrous lesion.<sup>[4]</sup>

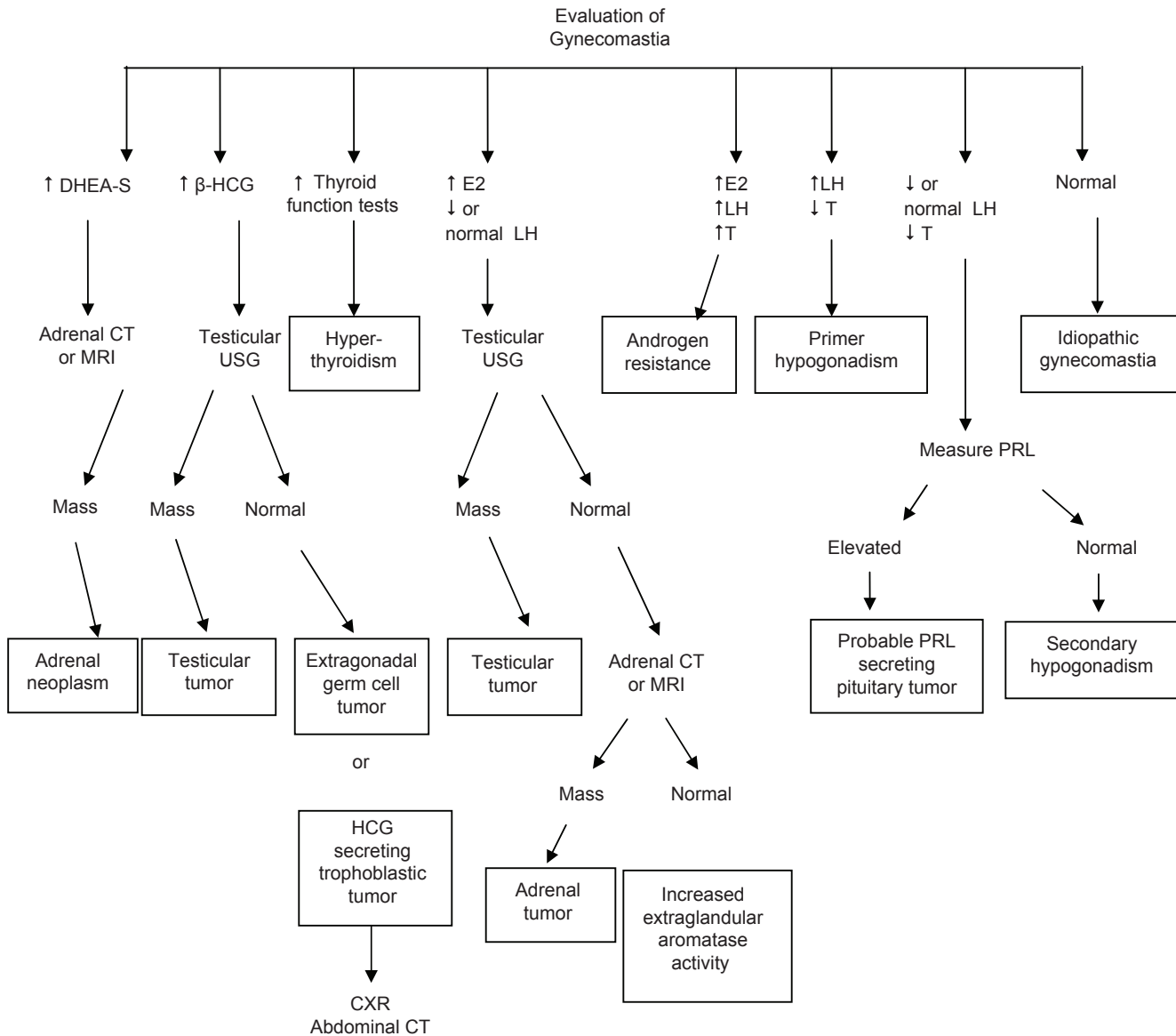
It is recommended that physicians follow the algorithm for gynecomastia in patients under the age of 50 years, unless one of the atypical criteria shown in Figure 1 is met.<sup>[2]</sup>

### Differential diagnosis

In patients presenting with palpable breast tissue, gynecomastia, pseudogynecomastia, breast carcinoma and benign lesions (including dermoid cysts, lipomas, sebaceous cysts, lymphoplasmocytic inflammation, ductal ectasia, hematomas and fat necrosis) should all be considered.<sup>[5]</sup> Pseudogynecomastia and true gynecomastia can be differentiated by physical examination, as described above. Malign and benign conditions can be distinguished using MMG or tissue sampling.

## TREATMENT

Before beginning treatment, the patient must be informed that these cases are usually benign and self-limiting and that over time fibrotic tissue replaces the symptomatic



**Figure 1:** Hormonal evaluation of gynecomastia

proliferation of glandular tissue, meaning that the pain and tenderness will resolve. In addition, new-onset gynecomastia (<6 months) often spontaneously regresses in both adolescent and adults and so in most patients only follow-up is necessary.<sup>[5]</sup> In pubertal males; 85-90% of cases regress between 6m and 2 years and continuation after the age of 17 is rare.<sup>[2,5]</sup> In adults, asymptomatic males with long-standing breast enlargement do not require treatment and instead reassurance is sufficient. However, if gynecomastia persists for more than 1 year, instances of complete regression are low, due to the predominance of dense fibrous tissue.<sup>[2,7]</sup> If gynecomastia persists and is associated with severe pain, tenderness and with psychological distress, medical and surgical options are available.<sup>[5]</sup> Treatment is guided by the underlying cause

and the aim of the intervention (relief of discomfort, restoration of normal appearance, reassurance regarding cancer, or the treatment of an underlying disease).<sup>[2]</sup> If gynecomastia is drug induced, symptoms may regress when the causative medication is stopped or changed.<sup>[5,6,11]</sup> Systemic illness-related gynecomastia regresses with the treatment of these disorders (for example the treatment of hyperthyroidism, or surgical removal of testicular, adrenal, or other causative tumors may lead to regression).<sup>[11]</sup> In hypogonadal patients, treatment with T may lead to regression by producing androgens, although in some patients T may get aromatized to E2, resulting in further breast enlargement.<sup>[2,11]</sup> Dialysis or re-feeding related gynecomastia is usually self-limited and reassurance may be sufficient.<sup>[2]</sup>

The duration of gynecomastia is a major factor affecting the initial approach to treatment. In the early stages, ductal hyperplasia and periductal inflammation are common and this is also the most symptomatic and treatable stage. In cases of over 12m' duration, fibrosis occurs, while inflammation subsides. If medical intervention is planned, it should therefore be used in the early stages of gynecomastia.<sup>[2,5]</sup> Below, the treatment options are discussed in more detail.

### Observation

Because gynecomastia usually regresses spontaneously, if the appropriate work-up does not reveal any considerable underlying pathology, reassurance and periodic follow-up are recommended at 6-month intervals.<sup>[5]</sup> In some cases, treatment may be needed, for example if severe breast enlargement, pain, or tenderness interferes with the patient's normal daily activities.

### Medical treatment

Although no medical treatments cause the complete regression of gynecomastia, they may provide partial regression, or symptomatic relief. Several agents regulate the hormonal imbalance that is thought to cause the gynecomastia. However, most clinical trials evaluating their efficacy and effectiveness are small and uncontrolled.<sup>[5]</sup> The major medical intervention options are androgens, anti-estrogens and aromatase inhibitors.

**Androgen Therapy**—In males with hypogonadism, testosterone replacement usually improves gynecomastia, but there are no supportive data for the use of androgens in eugonadal males. In these patients, testosterone replacement may worsen the gynecomastia because of the aromatization of T to E2. Indeed, trials revealed that testosterone is not effective compared with placebo. Dehydrotestosterone (DHT) is a non-aromatizable androgen that has been approved for the treatment of gynecomastia in some countries and was found to be effective in uncontrolled studies.<sup>[17,18]</sup> Danazole is a weak androgen that inhibits the secretion of LH and FSH from the pituitary.<sup>[11]</sup> The first reported controlled trial investigating the efficacy of danazole in adult idiopathic gynecomastia was published in 1979 and showed that 200mg/day danazole could effectively control the symptoms,<sup>[19]</sup> although no effect was found in cases of pubertal gynecomastia.<sup>[4]</sup> In a randomized, double blind study, danazole significantly reduced breast tenderness and size.<sup>[11]</sup> In an additional report, danazole was found to be less effective than tamoxifen (Tmx) and the relapse rate was higher.<sup>[20]</sup> Although both Tmx and danazole have been used to treat gynecomastia, the effect of 20-mg/day Tmx gave 78% resolution, which was better 400-mg/day danazol,

which had only a 40% resolution rate.<sup>[20]</sup> Side effects of danazol include edema, acne, nausea, muscle cramps and weight gain.<sup>[4]</sup>

**Anti-estrogens**—In recent years, anti-estrogens have been increasingly used to decrease the stimulatory effects of estrogen on the male breast.<sup>[2]</sup> Although clinical data are limited, more studies have determined the efficacy of anti-estrogens compared with other gynecomastia therapies.<sup>[2]</sup> Importantly, there is also a growing body of evidence supporting the utility of this class of drugs in gynecomastia, particularly Tmx.<sup>[21-24]</sup> Tmx is an estrogen antagonist,<sup>[6]</sup> and is a well-tolerated, reliable and non-toxic agent.<sup>[25]</sup> Because it rapidly reduces pain, it should be considered a first-line treatment for symptomatic cases of acute gynecomastia, or those that fail to resolve spontaneously.<sup>[6]</sup> However, it is less effective in instances of chronic gynecomastia.<sup>[6]</sup> Studies revealed that the effective dose range of Tmx in gynecomastia is 10-20mg/day for 2-4m.<sup>[6]</sup> In one study, Alagaratnam *et al.* treated sixty-one Chinese males with gynecomastia for a median of 2m. After 36m of follow-up, 84% of patients were in complete remission.<sup>[26]</sup> The effective dose of raloxifen (Rlx, an alternative anti-estrogen) was found to be 60 mg/day. Lawrence *et al.* treated 38 persistent pubertal gynecomastia patients with Tmx or Rlx and demonstrated a mean reduction in breast nodule to a diameter of 2.1 cm, with no serious adverse events.<sup>[24]</sup> Finally, 50 mg/day clomiphene citrate has been used to treat gynecomastia, but it had limited and variable effects.<sup>[6,11]</sup> While anti-estrogens do not result in complete regression, they may be effective in patients with painful gynecomastia.

**Aromatase Inhibitors**—these powerful agents block estrogen synthesis and as such decrease the estrogen to androgen ratio. Anastrozole is a potent, highly selective aromatase inhibitor that decreases the estrogen concentration in males.<sup>[6]</sup> Anastrozole treatment is well tolerated and is more effective in patients with pubertal gynecomastia.<sup>[27]</sup> It was also successfully used to reduce the estrogen excess and breast enlargement in a patient with familial aromatase excess,<sup>[28]</sup> a patient with Sertoli cell tumor,<sup>[29]</sup> and two hypogonadal males with gynecomastia that had been induced by testosterone therapy.<sup>[30]</sup> Testolactone is an aromatase inhibitor was tested in a small, uncontrolled trial of pubertal gynecomastia; results were positive.<sup>[7,11]</sup> Overall, the use of aromatase inhibitors is supported by incomplete evidence and the potential benefits and adverse effects should be considered before commencing treatment.

### Surgery

Surgery should be considered as the last resort in patients with considerable discomfort, psychological stress,

cosmetic problems, long-standing gynecomastia (>12m) and suspected malignancy.<sup>[7,11]</sup> It is not recommended in adolescents until the testis has reached adult size, because if surgery is performed before puberty is complete, breast tissue may be regrow.<sup>[2,7]</sup> The aim of the surgery is to achieve a normal appearance of the masculine thorax with the smallest possible scar.<sup>[6]</sup> The surgical technique used depends on the degree of the gynecomastia and the distribution and proportion of the different breast components (fat, parenchyma and looseness of the skin envelope).<sup>[6]</sup> The most commonly used technique is subcutaneous mastectomy, that involves direct resection of the glandular tissue using a peri-areolar or trans-areolar approach, with or without liposuction.<sup>[5,11]</sup> More extensive surgery, including skin resection, is required for patients with marked gynecomastia and those who develop excessive sagging of the breast tissue (with weight loss).<sup>[5]</sup> Liposuction alone may be sufficient, if breast enlargement is purely due to excess fatty tissue without substantial glandular hypertrophy.<sup>[5]</sup> Histological analysis of the gynecomastia tissue is recommended because unexpected findings such as spindle-cell hemangioendothelioma and papilloma occur in 3% of cases.<sup>[5]</sup> Complications of the surgery may include contour irregularity, hematoma/seroma, numbness of the nipple and areolar areas, the shedding of tissue due to loss of blood supply, breast asymmetry, nipple necrosis or flattening and hypertrophic or broad scars.<sup>[6]</sup> It is important to note that results are cosmetically unsatisfactory in 50% of patients.<sup>[11]</sup>

## GYNECOMASTIA IN PROSTATE CANCER

Gynecomastia is common in patients with prostate cancer that receive androgen deprivation therapy. The prevalence in males treated with anti-androgen monotherapy is 75%, because drugs are used at high doses (for example 150mg/day bicalutamide), whereas the prevalence is only 15% in males receiving anti-androgen and GnRH analog combination therapy, where the bicalutamide dose is 50 mg/day.<sup>[31,32]</sup> In these patients, the effectiveness of medical treatment and irradiation (RT) is limited when gynecomastia occurs. The aim of the treatment is therefore to prevent breast development with anti-estrogens or RT.

In one study of the use of Tmx, 69% of prostate cancer patients in the high-dose bicalutamide (150 mg/day) group had gynecomastia, but this was reduced to only 9% in the group receiving both bicalutamide and Tmx (10-20 mg/day).<sup>[30,31,32]</sup> Tmx must be continued throughout the anti-androgen therapy, since its effects do not persist after it has been discontinued.<sup>[33]</sup> Anastrozole also reduced anti-androgen related gynecomastia, but was less effective than Tmx. In one study of 88 patients with

prostate cancer, gynecomastia was found at a rate of 73% in the bicalutamide group, 51% in the bicalutamide and anastrozole (1 mg/day) group and 10% in bicalutamide and Tmx (20 mg/day) group after 48 weeks of therapy.<sup>[34]</sup>

In several studies, prophylactic RT was found to be effective in preventing gynecomastia and mastodynia in patients with prostate cancer.<sup>[2,11]</sup> However, although the high radiation doses may improve pain, they are less effective in reducing the volume of the tissue. Nevertheless, concomitant therapy with Tmx may be more effective than prophylactic RT alone in patients receiving a high dose (150 mg/day) of bicalutamide alone after radical prostatectomy.<sup>[2]</sup> However, it must be noted that Tmx can modulate the effects of anti-androgen therapy.

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