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REVIEW ARTICLE

Diagnostic And Surgical Approach To Gynecomastia: A Comprehensive Review

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ABSTRACT

Introduction: Gynecomastia is the benign proliferation of glandular tissue in the male breast. It is a known condition, which may be physiological or pathological.

Objective: To discuss the pathophysiology, etiology, clinical evaluation, investigation and management plans of gynecomastia.

Methods: The current literature was reviewed through PubMed, Scopus, and electronic databases to identify the best available evidence.

Conclusions: Gynecomastia is an enlarged male breast due to an increase in ductal tissue, stroma, or fat. It commonly occurs in adolescents, adults and old age. It appears in medical conditions like obesity, hypogonadism, liver, and kidney failure, and in certain drugs intake. Clinical evaluation must contain diagnostic confirmation, search for an etiological factor and classify gynecomastia into severity grades to guide the treatment. The optimal results are mainly achieved by surgery. Good preoperative preparation leads to good cosmetic results with high patient satisfaction and low complication rates.

KEYWORDS: Male breast. Gynecomastia, Endocrinal diseases, Drugs, Surgical treatment

INTRODUCTION

Gynecomastia is a physiological or pathological enlargement of male breast tissue, characterized by unilateral or bilateral enlargement of the male breast due to proliferation of glandular tissue. It is classified into true and pseudo-disease based on the predominance of glandular or fibroadipose tissue [1]. The underlying mechanisms are including the imbalance in the ratio of T/E, the increase in HCG receptors and LH receptors in male breast tissue [2]. Several classification systems of gynecomastia have been developed. The most popular are Simon's classification and Rohrich classification [3-5].

This condition is well known to plastic surgeons as it is reported to affect 32-65% of men. A significant proportion of these men desire surgical correction. The number of surgical treatments for gynecomastia and pseudogynecomastia has increased by more than 30% over the past 17 years. Breast reduction surgery has become one of the top five plastic surgery procedures in the past decade [6]. Numerous strategies for the surgical treatment of gynecomastia have been detailed to be viable with sensible restricted scar arrangement [7].

PREVELANCE

Gynecomastia is a common condition. Its prevalence was reported to be 32-65%. The primary peak happens within the neonatal period (60-90%), as a temporal neonatal gynecomastia. The placenta converts (DHEA) and (DHEA-SO4), coming from both mother and fetus, to estrone (E1) and estradiol (E2). E1 and E2 at that point enter the fetal circulation and afterward stimulate breast glandular multiplication. Regularly, this condition relapses inside 2-3 weeks of delivery. The 2nd peak happens during

adolescence and incorporates a predominance of 4-69% [8].

Pubertal gynecomastia more often starts at age 10-12 years old and peaks at ages 13-14. It more often relapses within 18 months. The final peak occurs in older males, with a predominance of 24-65% [9].

Senile gynecomastia is mostly due to expanded adiposity with aging, since fat tissue is the major tissue in which androgens are changed over to estrogens. Usually due to age related increase in cytochrome P19 (CYP19) action in fat tissue. Extra contributing factors are diminished testosterone (T) and the utilize of drugs which will modify androgen or estrogen concentrations or activities [10].

ANATOMY OF MALE BREAST

Until adolescence, breast in men and female are indistinguishable in origin and development. They originate from the fourth pair of lactiferous points. Advancement begins during the fourth week of pregnancy with the development of a basic milk streak. By the 9th week of gestation, a recognizable nipple bud has shaped from basal cells within the pectoral region. By the end of the 3rd month, squamous epithelium fills the nipple bud and ducts develop, which connect to the nipple at the skin's surface. These ended up canalized and shape lactiferous ducts. The development advances in women, though in men, the advance stops [11].

The nipple and areola in men are small in size. The nipples are found on the mid-clavicular lines; their heights are 2–5 mm. The nipple is found at the center of the breast and surrounded by the areola, a pigmented skin region with numerous sweat glands. The breast is bordered by the anterior and posterior superficial fascia of the thorax. The subcutaneous fat and fatty lobes are surrounded with connective tissue filaments [12, 13].

At adolescence, the breasts in boys stay rudimentary. Estrogens stimulate the multiplication of glandular tissue, whereas androgens counteract this effect. Most of boys have a 30 times increase in the level of testosterone and a 3 times increase within the level of estrogen at puberty [11].

During fast puberty, the proliferation of ducts and stroma leads to atrophy of ducts and involution of the breast. As a result, the breast of an adult man basically consists of fat tissue (subcutaneous fat) with insignificant subareolar remaining ducts and fibrous tissue [12].

Blood supply, lymphatic drainage of the breast:

The breast is profoundly vascular and supplied by branches of the internal thoracic, subclavian, axillary, and intercostal arteries that form a network of anastomoses, predominantly within the subareolar zone. The venous network goes with the relating arteries and arterioles. The lymphatic system is consisted of intramammary and adjoining lymph ducts and regional lymph nodes, the final presenting axillary, subclavian, supraclavicular, pectoral, and substernal groups. Intramammary lymph ducts shape a complex network with anastomoses and plexuses [14].

Nerve Supply of the breast:

Breast innervation is provided by the branches of thoracic, humeral, and intercostal nerves [15].

Zones of the chest wall:

The zoning system describes the units of fat distribution, allowing the surgeon to focus on the surrounding breasts and determine what potential treatments are needed in the axilla, lateral chest, lower chest, and the breasts themselves. This system can be used to guide surgical treatment. Patients with gynecological distribution of skin and adipose tissue in the breasts have a very feminine appearance, with significant breast tissue deformity and prolapse. In severe cases, the nipple lies below the inframammary fold (Fig.1) [16].

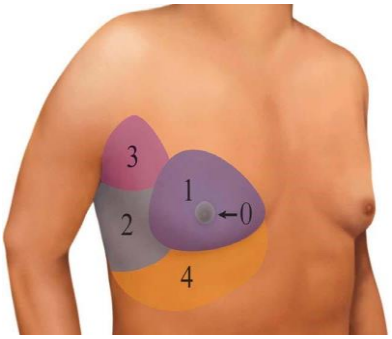

Fig. (1): *Zones of the male breast (Lemain et al., 2013).*

The development of pectoral muscles is closely linked to the shape of the chest and aesthetic standards. The perfect appearance of the chest is determined by the exposure of the surface anatomy, which reflects the arrangement and development of the pectoral muscles as well as the shape and contours of the surrounding tissues [17].

Five negative spaces (green and yellow) surrounding the pectoral muscle in a male patient. These areas should be concave to improve the concave appearance of the chest area (Fig. 2) [18].

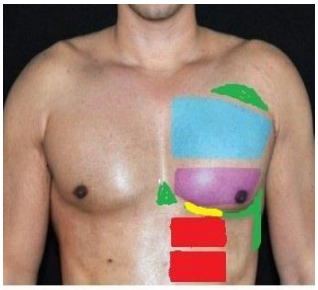

Fig. (2): *The five negative spaces surrounding the pectoralis muscle (Hoyos et al., 2021).*

Healthy men typically have a predominance of adipose tissue with few ducts and stroma. Adipose tissue plays an important role in the development of obesity and metabolic complications. Adipose tissue consists of adipocytes (the main cell type), adipocyte precursor cells, stromal vascular cells, immune cells, and neurons. In mammals, there are 2 types of adipose tissue: White adipose tissue mainly serves as energy storage tissue and brown adipose tissue mainly serves as thermogenic tissue [15, 19].

When the storage capacity of adipose tissue is exceeded or when adipose tissue does not function normally, fatty acids will increase in the circulation and triglycerides will accumulate in various organs. This ectopic fat deposition can severely affect the function of these organs and contribute to the pathogenesis of obesity-related conditions. In addition to its storage function, adipose tissue also has endocrine, paracrine and autocrine activities [20].

PATHOPHYSIOLOGY

Male breast tissue has protein receptors for estrogen and androgen. While estrogen stimulates the growth of milk ducts, androgens on the other hand, inhibit this process. Hormonal imbalance between these factors is the main characteristic of gynecomastia formation [21]. The imbalance may be due to increased free estrogen concentrations secreted by the testes or adrenal glands, extraglandular aromatization of estrogen precursors, decreased estrogen breakdown, exposure to chemicals that resemble estrogen or exogenous estrogen and using drugs that cause more displacement of estrogen than androgen from sex hormone binding globulin (SHBG) [22]. The testicle secretes approximately 95% of circulating testosterone, 15% of estradiol, and 5% of

estrone produced daily. In normal men, serum estrogen levels are very low. Most estrogen (80%) is produced by the peripheral conversion of two precursors, androstenedione and testosterone, to estrone and estradiol, respectively, under the influence of the enzyme aromatase, which plays a central role in male estrogen secretion. gender. Peripheral transformation occurs primarily in intramammary and subcutaneous fat, but is also seen in liver, skin, muscles, and kidneys. Aromatase activity increases with increasing age and BMI [23].

Continued environmental exposure to endocrine disrupting chemicals, air pollutants, radiation, organochlorine pesticides, plastics, plasticizers, fuels, and polycyclic aromatic hydrocarbons in consumer products substances are thought to develop gynecomastia, possibly due to epigenetic mechanisms [24].

It is proved that enlarged male mammary glands contain receptors for luteinizing hormone (LH) and human chorionic gonadotropin (hCG). Activation of these receptors may reduce androgenic effects by altering local metabolism. LH and hCG have also been reported to reduce the concentration of androgen receptors in the skin [25]. Progesterone appears to be necessary for the formation of true acini, acting synergistically with insulin growth factor-1 (IGF-1). In certain clinical conditions, such as hyperthyroidism and cirrhosis associated with gynecomastia, it is possible to detect increased serum progesterone concentrations. Another hormonal effect that stimulates male breast tissue is seen in hyperprolactinemia, as it causes central hypogonadism and changes the androgen/estrogen ratio. [26].

However, most men with gynecomastia do not have elevated serum prolactin levels, and it is clear that not all men with hyperprolactinemia develop gynecomastia [23].

Etiology of gynecomastia

Gynecomastia is a multifactorial disease and can be associated with many diseases. Table (1) summarizes various causes of gynecomastia. According to Braunstein (2021), almost two-thirds of patients have physiological, idiopathic or drug induced gynecomastia. The frequencies of the remaining causes were estimated as follows: Cirrhosis, 8%. Primary hypogonadism: 8%; testicular cancer, 3%. Secondary hypogonadism, 2%. Hyperthyroidism, 1.5%. Kidney disease, 1% [22].

- Neonatal gynecomastia

Palpable enlargement of the male breast in newborns is normal and occurs as a result of the action of prolactin, placental estrogen and progesterone on the newborn's breast parenchyma. At birth, these hormones decrease and breast enlargement usually resolves within a few weeks [8].

- Adolescent gynecomastia

It generally appears by age 13 or 14 and lasts 6–12 months, after which 95% of cases resolve spontaneously [28]. Enlarged glands may be asymmetric and tender. Hypertrophy is severe and can cause a feminine appearance in boys. Such occurrences may alter self-perceptions [12]. Relative increase of estrogen levels compared with androgens is implicated in the pathogenesis. Other factors may also interact and there is often a concomitant increase in serum IGF-1 concentrations. Family history may be found in more than half of the patients (Figure. 3) [8].

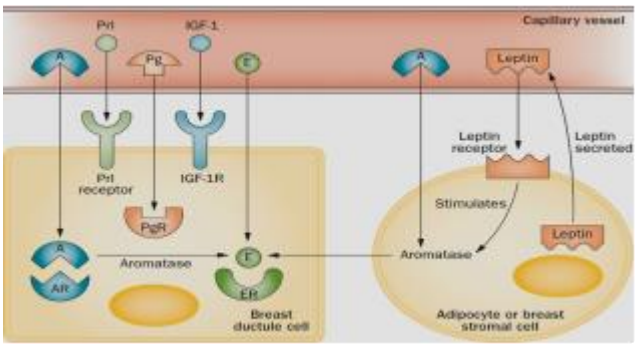

Fig. (3): *The action of different hormones on breast tissue (Kanakis et al., 2019).*

- Senile gynecomastia

It occurs in 32-65% of adult men, its prevalence correlates with body fat and does not require clinical evaluation unless it is symptomatic or of recent onset. Men over 65 years old usually have relative hypogonadism. Plasma testosterone levels begin to decrease at the age of 70. In addition, there is a concomitant increase in plasma sex hormone binding globulin (SHBG), leading to decrease in free or unbound testosterone concentrations. A concomitant increase in plasma LH may result in increase in the rate of conversion of androgens to estrogens in peripheral tissues. Moreover, increasing obesity creates favourable conditions for the activity of the peripheral aromatase enzyme and comorbidities at this age may contribute to or increase gynecomastia [29].

- Endocrine tumours

Benign testicular tumours (Sertoli or Leydig cell tumours) may secrete estradiol. Secondary inhibition of LH levels negatively interferes with testosterone production. High estrogen levels increase serum SHBG levels, which bind preferentially to testosterone, thereby reducing free testosterone levels [28]. Choriocarcinoma and other germ cell tumours produce hCG and stimulate testicular (Leydig) cells to secrete estradiol and further often cause gynecomastia. Other hCG-secreting tumours of ectopic origin can cause gynecomastia. Prolactin-producing pituitary adenomas (prolactinomas) can also cause gynecomastia [30]. Adrenocortical tumours are feminized tumours with direct secretion of estrogen and steroid precursors, such as androstenedione. Elevated serum estrogen also inhibits LH-mediated testosterone production [28].

- Endocrine dysfunction

Severe hyperthyroidism elevates serum SHBG. Since estradiol is less bound to SHBG than testosterone, the ratio of free estradiol to free testosterone increases, leading to gynecomastia in 10-40% of cases. Primary hypogonadism due to testicular trauma, chemotherapy, mumps, orchitis, and leprosy can cause gynecomastia by reducing serum testosterone levels [31]. Klinefelter syndrome is a chromosomal disorder associated with hypogonadism and infertility. Gynecomastia is observed in nearly 70% of those patients [29]. Pseudo hermaphroditism in men with Morris Syndrome is often associated with the appearance of female breasts due to the production of estrogen by the gonads. [22].

Other endocrine and metabolic causes include longstanding type I diabetes, metabolic syndrome, refeeding after severe starvation and significant weight loss, and functional hyperprolactinemia [32, 33].

- Non-endocrine disease

In cases of cirrhosis, the main sex hormone abnormalities are lowered serum testosterone levels and high estradiol levels. Men with

chronic kidney disease commonly have hypogonadism and abnormalities in the production of steroids in the testicles with subsequent gynecomastia. In HIV-infected men, gynecomastia occurs in 2 to 3% of cases, triggered by the antiviral therapy [35].

- Drug induction

Drug-induced gynecomastia deserves special attention because it may account for up to 25% of all new-onset cases in adults. Although the mechanisms by which a long list of drugs can cause gynecomastia are not completely clear, they derive from their estrogen-like actions, stimulating estrogen production in the testicles, inhibiting testosterone synthesis or androgen blockade [32, 36]. Spironolactone (a competitive aldosterone antagonist), is one of the commonest drugs associated with gynecomastia. It acts as antiandrogen by inhibiting testicular testosterone production, enhancing the aromatization of testosterone to estradiol, and binding to androgen receptors [37]. Androgen deprivation therapy for prostate cancer may induce gynecomastia as a side effect. The incidence depends on the type and duration of hormonal treatment, but can be as high as 40–70% [38].

Illicit and abuse drugs such as cocaine, heroin and amphetamines are often linked to gynecomastia. Cannabis is thought to interfere with estrogen receptors and act as a phytoestrogen [21]. Doping with anabolic steroids, gonadotropins and growth hormones is a common problem. In male athletes, these drugs may inhibit spermatogenesis and/or cause gynecomastia [40]. Table (2) shows that common pharmaceutical products can cause gynecomastia when used for a long time [8].

- Idiopathic gynecomastia

The high prevalence of idiopathic gynecomastia suggested that multiple environmental endocrine disruptors could be involved [21, 22].

CLINICAL EVALUATION

The primary goals of evaluating a patient with gynecomastia are to confirm the diagnosis and differentiate true gynecomastia from pseudodisease, rule out breast cancer, and detect possible causes through medical history, physical examination, and laboratory testing. All men with enlarged breasts should be examined to answer the following questions: (1), Time of onset? ; (2) Is enlargement associated with pain or tenderness? ; (3) Is this enlargement due to gland overgrowth or fat accumulation? ; (4) Does the patient have signs or symptoms of breast cancer? ; (5), is this disease related to testicular tumours? ; and (6), is the patient uncomfortable due to breast enlargment? A healthy man with long-term stable gynecomastia and a negative history and physical examination usually does not need further evaluation [40].

The presence of previously unreported breast pain or tenderness, or the presence of breast enlargement, rapid growth, or breast size > 5 cm, requires further evaluation to detect any systemic problems any potential [41].

Medical History

A detailed medical history should include onset and duration of gynecomastia, symptoms of pain or tenderness, weight loss or gain, changes in size, nipple discharge, contractures, virilization symptoms, and medical history. Medication (improvement after stopping medication strongly suggests that the medication is the cause), presence of systemic disease, fertility, sexual function, History of undescended testicles and mumps. Finally, a family history of gynecomastia should be considered, which may suggest androgen insensitivity syndrome, familial

aromatase excess, or Sertoli cell tumours [31].

Physical examination

It should include anthropometric measurements as height, weight, (BMI), upper and lower body measures, the side and degree of gynecomastia, and take photos before and after surgery. The presence of excess skin, breast redundancy, the level of the nipple-areola complex (NAC) are evaluated so that the degree of gynecomastia is determined [40]. Photos should be taken in anteroposterior, oblique, and lateral views, and compared after surgery with postoperative ones. Signs of virilization should be evaluated. Breast examination should include breast density, location of breast masses, if present, as well as any changes in the overlying skin, nipple discharge, axillary lymphadenopathy and distinguish between adipose tissue (pseudogynecomastia) and glandular tissue (true gynecomastia) [22].

The patient lies on his back with his hands behind his head. The doctor places his thumb and index finger on both breasts and slowly brings them closer together. In true cases of gynecomastia, the doctor will palpate a disc or hard tissue concentric with the nipple-areola complex. In patients with pseudo gynecomastia, the fingers will encounter no resistance until they reach the nipple. In contrast, breast carcinoma often presents as a hard, irregular unilateral mass located outside the areola, which may be accompanied by skin dimpling, nipple retraction, and axillary lymphadenopathy (Figure. 4) [8].

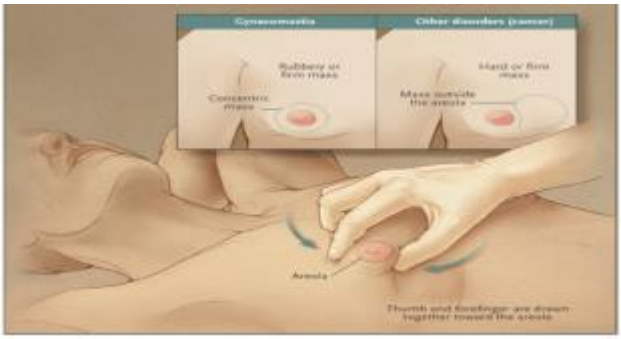

***Fig. (4)**: Technique and findings in breast palpation (Kanakis et al., 2019)*

Abdominal examination should be also done for abdominal masses and testicles. Signs of liver disease, kidney disease or hyperthyroidism can be identified. In adolescent patients if the physical and genital examination findings are normal, pubertal gynecomastia is suspected and evaluation should continue every 6 months [41].

Laboratory evaluation

It should be done in all cases of gynecomastia without an obvious cause. It should include liver, kidney and thyroid function tests, hormone tests (E2, total and free testosterone, A, LH, FSH), PRL, hCG, DHEA-SO4 or 17 ketosteroids, SHBG and αFP [29].

Image method

Mammography (MMG) is the main diagnostic imaging method used in cases of suspected cancer [21]. It accurately differentiates between malignant and benign male breast diseases and can distinguish true gynecomastia from a mass that requires tissue sampling to rule out malignancy, thereby reducing the need for biopsy [40]. The sensitivity and specificity of MMG for benign and malignant breast conditions is more than 90% [23].

Breast ultrasound is widely used in the diagnosis of gynecomastia. In cases of pseudogynecomastia, breast tissue is filled with radiolucent fat [41, 42]. Diffuse gynecomastia is characterized by increased breast volume and echogenicity, features similar to the ultrasound findings of dense female breasts, which should be evaluated along with medical history and findings. clinical manifestation [43].

Magnetic Resonance Imaging (MRI) may be useful in some cases of invasive tumours to evaluate possible chest wall damage, or in the context of cancer surveillance, to evaluate residual disease after surgery and response to chemotherapy [44].

Tissue biopsy

If it is not possible to differentiate between gynecomastia and breast cancer by clinical and imaging findings, a percutaneous biopsy should be performed [40]. However, the number of cells collected during a gynecomastia biopsy is often insufficient because gynecomastia is a predominantly fibrous lesion (Figure 5) [31].

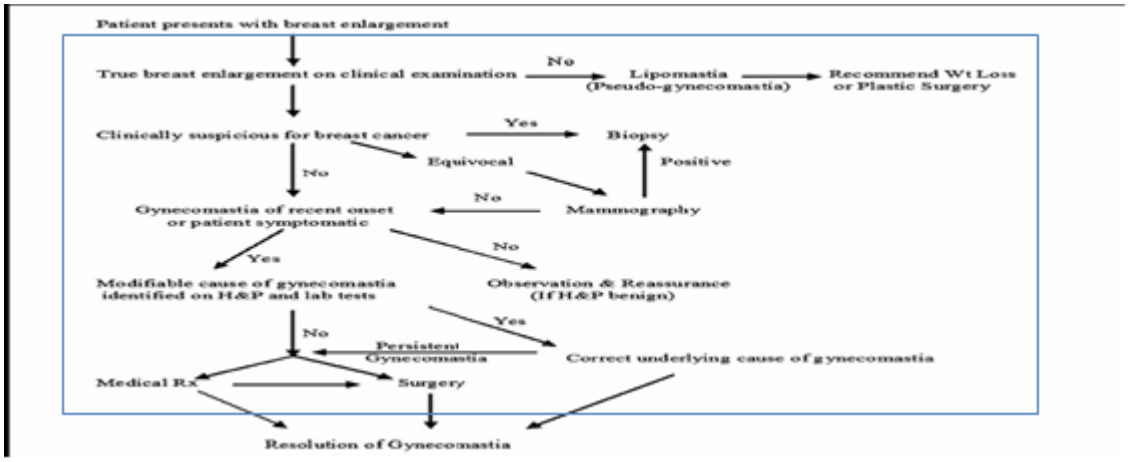

Fig. (5): *Algorithm for the evaluation and treatment of gynecomastia (Baumann, 2018).*

Classification of gynecomastia

Gynecomastia presents different clinical types, from simple protruding areola to female-shaped breasts. The main clinical features that characterize GM are breast swelling, increased areola diameter, the presence of abnormal breast folds, glandular ptosis, and excess skin. There are several morphological classifications of gynecomastia, as shown in table (3) [3, 4, 23, 45-47].

Management

Gynecomastia is often asymptomatic; however, it may be associated with pain and tenderness in the mammary gland [31]. Additionally, psychological disorders often occur due to altered body image and include depression, anxiety, low self-esteem, identity confusion, eating disorders, social phobia, and avoidance [27].

Before starting treatment, patients must be informed that these cases are usually mild and self-limited. Additionally, new-onset gynecomastia (<6 months) usually resolves spontaneously in adolescents and adults and therefore, in most patients, it requires only follow-up. During puberty gynecomastia; 85 to 90% of cases regress after 6 months to 2 years and treatment is rarely continued beyond 17 years [16].

In adult males, asymptomatic cases with long-term enlarged breasts do not need treatment other than reassurance. If gynecomastia persists for more than a year, complete regression is rare as dense fibrous tissue predominates. If it persists and is accompanied by pain, discomfort, and severe

psychological stress, medical and surgical options are available [8, 48].

Treatment is guided by the underlying cause and the goal of intervention (relief of discomfort, restoration of normal appearance, reassurance from cancer, or treatment of the underlying disease [49].

There are no specific recommendations regarding the exact timing of surgical management, but surgery is considered in adolescents who present with persistent gynecomastia after a follow-up period of at least 12 months, annoying chest pain or tenderness and/or significant psychosocial distress [16].

Drug-induced gynecomastia regrets after stopping this medication. Systemic illness-related gynecomastia will be relieved by treatment of these disorders. Gynecomastia associated with dialysis or refeeding is often self-limited and may require reassurance alone [41].

- **Medical treatment**

Duration of gynecomastia is the main factor influencing initial treatment. In the early stages, ductal hyperplasia and periductal inflammation are common and are also the most symptomatic and treatable stages. In cases lasting more than 12 months, fibrosis occurs while inflammation decreases. Therefore, if medical intervention is considered, it must be used only for the early stages of gynecomastia [31].

In general, medical treatment of gynecomastia aims to correct the estrogen-androgen imbalance and minimize the effects of excess estrogen through three possible mechanisms:

(a) Selective estrogen receptor modulators (SERMs), which block the effects of estrogen on the breast (e.g. clomiphene, tamoxifen, raloxifene); (b) Androgens (e.g., danazol), by directly increasing androgen levels and thereby rebalancing the androgen-estrogen ratio; and (c) aromatase inhibitors, which inhibit estrogen production by inhibiting testosterone aromatization and inhibiting estrogen production (e.g., anastrozole, testolactone) [8, 31].

- **Radiotherapy**

Several studies have shown that prophylactic breast irradiation is effective in preventing gynecomastia and mastodynia in prostate cancer patients receiving estrogen or antiandrogen therapy [31, 40].

- **Surgical treatment**

Because of limited experience and unknown long-term side effects, medical treatment trials should be limited to 6 months. Surgery should be considered in patients experiencing discomfort, psychological distress, or cosmetic problems, long-standing gynecomastia (>12m) and suspected malignancy [50].

In adolescents, Surgical interference is not recommended until the testis has reached adult size, because if surgery is performed before puberty is complete, breast tissue may be regrown [27].

The aim of the surgery is to achieve a normal appearance of the masculine thorax with the smallest possible scar. The surgical technique used depends on the degree of the gynecomastia, the distribution and proportion of the different breast components. 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 [50].

More extensive surgery, including skin resection, is required for patients with marked gynecomastia and those who develop excessive sagging of the breast tissue. Liposuction alone may be sufficient, if breast enlargement is purely due to excess fatty tissue without substantial glandular hypertrophy. Histological analysis of the removed tissues is recommended because unexpected findings such as spindle-cell hemangioendothelioma and papilloma occur in 3% of cases [51].

In grade I, the enlargement is caused solely by glandular proliferation without adipose accumulation. Surgical correction involves mammary adenectomy performed by a semicircular inferior periareolar incision so that, liposuction is not required. Grade II is characterized by excessive glandular tissue and local adiposity. In these cases, liposuction and surgical excision must be combined in the same operation. Mammary adenectomy without liposuction leads to unsatisfactory outcomes. In grade III, the operation begins with liposuction and is followed by glandular

excision with periareolar removal of the tissue. It is necessary to detach the excess skin to obtain a good chest appearance. The hallmarks of grade IV are severe ptosis and a large amount of redundant skin. One of the techniques for reduction mastoplasty is used to remove gland and skin and flatten the chest outline [21, 52].

An alternative modification to the simple liposuction is the power-assisted liposuction technique. It is performed to contour the breast tissue without exerting much physical. This technique works very effectively in combination with a tumescent and super tumescent approach. The aspirate volume from liposuction can range from 50 to over 1,000 mL. In contrast the excision of the fibroglandular tissue can range from a few grams to over 1,000 g. [51].

Ultrasound-assisted liposuction (UAL) is another modified method that may facilitate the removal of tougher sub-areola glandular tissue at the time of liposuction. Care is needed with this technique to avoid the potential complication of thermal injury to the overlying skin. Standard liposuction or UAL in combination with gland resection through a minimal caudal semicircular periareolar incision and conventional liposuction effectively corrects most grades of gynecomastia [21].

The use of mammotome which is a minimal invasive tool that appears safe and ensures reasonable cosmesis and patient satisfaction rates, although there are only limited reports of its use in gynecomastia and deficient long term follow up data. The potential risk of skin injury and hemorrhage may limit the use of mammotome [49].

Soliman et al., (2017) stated that in general, surgical treatment produces good cosmesis and is well tolerated. Nevertheless invasive techniques that require minimal surgical incision have recently emerged and may offer faster recovery and lower rates of local complications. Histologic analysis is recommended to rule out unexpected histologic findings [52].

- **Complications of Surgical treatment**

Rahmani et al. (2011) reported that the most frequent early complication following surgical correction of gynecomastia is hematoma. Seroma, overresection with saucer-type deformity, underresection, unappealing scarring and infections are also observed. Postoperative complications may also include 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. Patients and their parents or guardians should be well informed about possible risks, as some complications are managed surgically [53].

- **Prognosis**

In conclusion, previous research studies found that adolescent gynecomastia has a favorable prognosis with spontaneous complete or partial resolution. Small percent have persistent gynecomastia after the end of pubertal development and some adolescents have concerns about the cosmetic correction. Therefore, the decision to perform surgery depends on the degree to which this condition has affected the quality of life and on their desire for cosmetic correction [31].

Table (1): ***Aetiology of Gynecomastia (Braunstein, (2021)***.

Causes	Examples
Physiological factors	Puberty or aging
Endocrine tumours	Testicular, adrenocortical or pituitary tumours, or ectopic hCG-secretion
Endocrine dysfunctions	Hypogonadism, hyperthyroidism, obesity or refeeding
Non-endocrine diseases	Cirrhosis, renal failure or HIV
Drug-induced factors	Medications, anabolic steroids or illicit drugs
Idiopathic factors	

Table (2): ***Common medications causing gynecomastia (Kanakis et al., 2019)***.

Type of agent	Medications
Antiandrogens	Bicalutamide, cyproterone, flutamide, finasteride, spironolactone
Antibiotics	Isoniazid, ketoconazole, metronidazole
Antihypertensives	Amlodipine, captopril, enalapril, nifedipine, reserpine, verapamil
Chemotherapeutic agents	Cyclophosphamide, methotrexate
Diuretic	Spironolactone
Gastrointestinal agents	Cimetidine, omeprazole, metoclopramide, ranitidine
Hormones	Androgens, anabolic steroids, estrogens, growth hormone
Psychiatric agents	Diazepam, haloperidol, phenothiazine, tricyclic antidepressants
Others	Amiodarone, antiretrovirals,

Table (3): Different Classification Systems of Gynecomastia:

Classification	Criteria and Description
Tanner's	Stage 1: Nipple prominence Stage 2: Mammillary button stage. The breast and the nipple-areola complex are slightly swollen and diameter of the areola increases Stage 3: Further swelling of the breast and areola without separation of their edges Stage 4: Areola and nipple become protrusive and form a secondary protrusion above the breast Stage 5: There is protrusion of the nipple only after retraction of the areola from the breast surface
Simon's	Grade 1: Small visible breast enlargement and no skin redundancy Grade 2a: Moderate breast enlargement without skin redundancy Grade 2b: Moderate breast enlargement with skin redundancy Grade 3: Marked breast enlargement with marked skin redundancy
Deutinger's and Freilinger's	Grade 1: Thoracic wall poor in the flesh with mammary tissue localized behind and around the nipple without skin excess Grade 2: Adipose thoracic wall with widespread alterations and breasts similar to feminine ones during puberty Grade 3: Widespread alterations with excess adipose tissue, skin redundancy and inframammary fold and ptosis
Cohen's	Group 1: Glandular gynecomastia Group 2: Glandular gynecomastia with ptosis Group 3: Adipose gynecomastia Group:4 Adipose gynecomastia with a slight glandular component
Rohrich's	Grade 1: Minimal hypertrophy, (less than 250g of tissue) without ptosis o 1a: Primarily glandular o 1b: Primarily fibrous Grade 2: moderate hypertrophy (250-500g of breast tissue) without ptosis o 2a: Primarily glandular o 2b: Primarily fibrous Grade 3: Severe hypertrophy (>500g of breast tissue with grade 1 ptosis glandular or fibrous Grade 4: Severe hypertrophy with grade 2 or 3 ptosis glandular or fibrous
Barros's	Grade I: Increased diameter and slight protrusion limited to the areola region Grade II: Moderate hypertrophy of the breast with the nipple-areola complex (NAC) above the inframammary fold (IMF) Grade III: Major hypertrophy of the breast with glandular ptosis and the NAC situated at the same height as or as much as 1 cm below the inframammary fold (IM) Grade IV: Major breast hypertrophy with skin redundancy, severe ptosis, and the NAC positioned ≥1 cm below the inframammary fold (IMF)

Classification	Criteria and Description
Cordova's and Moschella's	Grade I: Increase in diameter and protrusion limited to the areolar region Grade II: Hypertrophy of all the structural components of the breast and the nipple-areola complex (NAC) is above the inframammary fold (IMF) Grade III: Hypertrophy of all the structural components with nipple-areola complex (NAC) at the same height as or approximately 1 cm below the inframammaryfolds (IMF). In this group we can also include male tuberous breast Grade IV: Hypertrophy of all the structural components with nipple-areola complex (NAC) >1 cm below theinframammary fold (IMF)
Ratnam's	Type 1: Enlarged breasts with elastic skin and no fold Type 2: Enlarged breasts with elastic skin and an inframammory fold (IMF)Type 3: Ptotic breasts with inelastic skin
Webster's	Class 1: Periductal connective tissue hypertrophy without adipose tissue change Class 2: Increase in the amount of both connective and adipose tissue Class 3: Adipose tissue hypertrophy alone

CONCLUSION

Gynecomastia is a condition in which the male breast is enlarged due to an increase in ductal tissue, stroma, or fat. It is common, and occurs in adolescents, adults and in old age. Gynecomastia is associated with medical conditions such as extreme obesity, hypogonadism, liver, and kidney failure, in addition to the administration of certain drugs. Clinical evaluation must address diagnostic confirmation, search for an etiological factor and classify gynecomastia into severity grades to guide the treatment. The best results are generally achieved through surgery. Good preoperative planning leads to good cosmetic results with high patient satisfaction and low complication rates.

REFERENCES

1- **Taylor SA. Gynecomastia in children and adolescents (2020):** Post TW, ed. https://www.uptodate.com/contents/gynecomastia-in-children-and-adolescents.

2- **Nuzzi, L.C., Firriolo, J.M., Pike, C.M., et al. (2018):** The effect of surgical treatment for gynecomastia on quality of life in adolescents. J. Adolesc. Health, 63:759–765.

3- **Rohrich, R. J., Ha, R.Y., Kenkel, J. M. and Adams, W. P. (2003)**: Classification and management of gynecomastia: defining the role of ultrasound-assisted liposuction Plast. Reconstr. Surg., 111: 909-923.

4- **Simon, B. E.,** Hoffman, S., Kahn, S. (**1973):** Classification and surgical correction of gynecomastia. Plast. Reconstr. Surg.,51:48–52.

5- **Waltho, D., Hatchell, A., and Thoma, A. (2017):** Gynecomastia classification for surgical management: a systematic review and novel classification system. Plast. Reconstr. Surg.,638e–648e.

6-**Mett, T. R., Pfeiler, P., Rosalia, P., Alperen, L., Bingöl, S., Krezdorn, N., and Vogt, P. M. (2020):** Surgical treatment of gynaecomastia: a standard of care in plastic surgery. Eur. J. Plast. Surg., 43:389–398.

7-**Mohanty, A. (2022)**: Applying the Passot Technique in the surgical treatment of severe gynecomastia: A case report and literature review. Chinese J. Plast. Reconstruct. Surg., 4(1): 13-16.

8- **Kanakis, G. A., Bang, A. K., Nordkap L., Calogero, A. E., Bártfai, G., Corona, G., et al., (2019):** Clinical practice guidelines—gynecomastia evaluation and management. Androl.,7:778–793. doi: 10.1111/ andr.12636.

9- **Akgül, S. Kanbur, N. and Derman, O. (2014):** Pubertal gynecomastia: what about the remaining 10%? J. Pediatr. Endocrinol. Metab., 27: 1027–1028.

10- **Mieritz, M. G., Christiansen, P., Jensen, M. B., Joensen, U. N., Nordkap, L., Olesen, I. A., Bang, A. K., Juul, A. and Jørgensen N. (2017):** Gynaecomastia in 786 adult men: clinical and biochemical findings. Eur. J. Endocrinol., 176:

555–566.

11- **Cieśla, S. Wichtowski, M. Poźniak-Balicka, R. Murawa, D. (2020):** The surgical anatomy of the mammary gland (part 1.) General structure, embryogenesis, histology, the nipple-areolar complex, the fascia of the glandular tissue and the chest wall. NOWOTWORY J. Oncol.,70 (5), 211–219. DOI: 10.5603/NJO.2020.0042

12- **Hassiotou, F. and Geddes, D. (2013):** Anatomy of the human mammary gland: Current status of knowledge. Clin. Anat., 26(1): 29–48. doi: 10.1002/ca.22165, indexed in Pubmed: 22997014.

13-**Cooper, A.P. (2018):** Anatomy of the Breast. London, UK: Longman, Orme, Green, Browne, and Longmans, 1840. https://jdc. jefferson. edu/cooper/60/(6.09.2018).

14-**Netter, F. H. (2014):** Atlas of Human Anatomy. 6th; Gold 25th Anniversary Edition. Elsevier.

15- **Blau, M., Hazani, R. and Hekmat, D. (2016):** Anatomy of the Gynecomastia Tissue and Its Clinical Significance. Wolters Kluwer Health, Inc. on behalf of The American Society of Plastic Surgeons. 1-7 DOI: 10.1097/GOX .0000000 000000844

16- **Lemain, V., Simmons, Cayci, C. and Petty, P. (2013):** Gynecomastia in adolescent males. Semin Plast Surg., 27(01):056–61.
doi: 10.1055/s-0033-1347166

17-**Agarwal, Wall, V. T., Mehta, D. P., Sagar, T., and Walzer, N. K., et al., (2017):** Creation of an aesthetic male nipple areolar complex in female to male transgender chest reconstruction. Aesth. Plast. Surg., 41: 1305-1310.

18- **Hoyos, A. E., Perez, M. E., and Milla´n D. R. (2021):** Gynecomastia treatment through open resection and pectoral high-definition liposculpture. Plast. Recons. Surg., (147):1072–1083.

19- **Gómez-Hernández, Beneit, N., Díaz-Castroverde, S., and Esccribano, Ó. (2016**): Differntial role of adipopse tissues in obesity and related metabolic and vascular complications. Int. J. Endocrinol.Doi.org/10.1155/2016/1216 783.

20- **Snel, M., Jonker, J. T., Schoones, H. Lamb, A. Smit, A. E.,Meinders, A. E. and Jazet, I. M. (2012):** Ectopic fat and insulin resistance: pathophysiology and effect of diet and lifestyle interventions. Int. J. Endocrinol., Doi:10. 1155 /2012/983814

21- **Barros, A. C. and Sampaio, M. C. (2012):** Gynecomastia: Physiopathology, evaluation and treatment. Sao Paulo Med. J.,130:187-197.

22- **Braunstein, G. D., and Anawalt, B. D. (2021):** Clinical features, diagnosis, and evaluation of gynecomastia in adults. https://www. uptodate.com/contents/ clinical-features-diagnosis-and-evaluation of-gynec- omastia- in-adults.

23- **Billa, G. A., Kanakis, D. Goulis, G. et al. (2021).** Imaging in gynecomastia Evangelia Androl.,9:1444–1456.

24- **Mieritz, M. G., Rakêt, L. L., Hagen, C.P. et al. (2015):** Alongitudinal study of growth, sex steroids, and IGF-1 in boys with physiological gynecomastia. J Clin Endocrinol. Metab.,100: 3752-3759.

25- **Swerdloff, R. S. and Ng, C. M. (2019)**: Gynecomastia: etiology, diagnosis, and treatment. Endotext. Available at: https://www.ncbi.nlm.nih.gov/books/NB K279105/

26- **Sansone, A., Romanelli, F., Sansone, M., Lenzi, A., deLuigi, L. (2017):** Gynecomastia and hormones. Endocrine.,55:37-44.

27- **Rew, L., Young, C., Harrison, T., Caridi, R. (2015):** A systematic review of literature on psychosocial aspects of gynecomastia in adolescents and young men. J. Adolesc., 43:206–212. doi:10.1016/j.adolescence.2015.06.007

28- **Stone, K., and Wheeler, A. A. (2015):** Review of Anatomy, Physiology, and Benign Pathology of the Nipple. Ann. Surg. Oncol.,22(10): 3236–3240. doi: 10.1245/s10434-015-4760-4, indexed in Pubmed: 26242366.

29- **Narula, H. S., Carlson, H. E. (2014)**: Gynaecomastia-pathophysiology, diagnosis and treatment. Nat Rev Endocrinol., 10:684-698.

30- **Gastounioti, A., Hsieh, M. K., Cohen, E., et al. (2018):** Incorporating Breast Anatomy in Computational Phenotyping of Mammographic Parenchymal Patterns for Breast Cancer Risk Estimation. Sci. Rep.,8(1): 17489, doi: 10.1038/s41598-018-35929-9, indexed in Pubmed: 30504841.

31-**Baumann, K. (2018)**: Gynecomastia -conservative and surgical management. Breast Care (Basel). 13:419–424.
doi: 10.1159/000494276

32- **Krause, W. (2012):** Drug-inducing gynaecomastia-a critical review. Androl., 44(Suppl.1):621-626.

33- **Grigg, J., Worsley, R., Thew, C., Gurvich, C., Thomas, N. and Kulkarni, J. (2017):** Antipsychotic-induced hyperprolactinemia: synthesis of world-wide guidelines and integrated recommendations for assessment, management and future research. Psychopharmacol., 234, 3279–3297.

34-**Gudin, J. A., Laitman, A. and Nalamachu, S. (2015):** Opioid related endocrinopathy: Table 1. Pain Med.,16(suppl 1), S9–S15.

35- **Iglesias, P., Carrero, J. J., and Dez J. J. (2012):** Gonadal dysfunction in men with chronic kidney disease: clinical features, prognostic implications and therapeutic options. J. Nephrol., 25: 31–42.

36- **Nuttall, F. Q., Warrier, R. S. and Mary Gannon, M. C. (2015):** Gynecomastia and drugs: a critical evaluation of the literature. Eur. J. Clin. Pharmacol., 71:569–578 DOI 10.1007/s00228-015-1835-x

37- **Goldman RD. (2010):** Drug-induced gynecomastia in children and adolescents. Can. Fam. Physician. 56(4):344-345.

38- **Alesini, D., Iacovelli, R., Palazzo, A., Altavilla, A., Risi, E., Urbano, F., Manai, C., Passaro, A., Magri, V. and Cortesi, E. (2013):** Multimodality treatment of gynecomastia in patients receiving antiandrogen therapy for prostate cancer in the era of abiraterone acetate and new antiandrogen molecules. Oncol., 84, 92–99.

39- **Basaria, S. (2010):** Androgen abuse in athletes: detection and consequences. J. Clin. Endocrinol. Metab.,95:1533-1543.

40-**Cuhaci, N., Polat, S. B., Evranos, B., Ersoy, R. and Cakir, B. (2014):** Gynecomastia: Clinical evaluation and Management. Indian J. Endocrinol. Metab.,18(2): 150-152.

41-**Carlson, H. E. (2011)**: Approach to the patient with gynecomastia. J. Clin. Endocrinol. Metab., 96:15-21.

42- **Chau, A., Jafarian, N. and Rosa, M. (2016):** Male breast: clinical and imaging evaluations of benign and malignant entities with histologic correlation. Am. J. Med.,129:776-791.

43- **Muñoz, C. R., Alvarez, B. M., Rivin, C. E., Córdoba, E. and Villejuif, F. (2013):** Pictorial review: the imaging findings of male breast lesions. In: Proceedings from the European Congress of Radiology. C-1875.

44- Shin, K., Martaindale, S. and Whitman, G. J. (2019): Male breast magnetic resonance imaging: when is it helpful? Our experience over the last decade. Curr. Probl. Diagn. Radiol.,48:196-203.

45- Ratnam, B. V. (2009): A new classification and treatment protocol for gynecomastia. Aesthet Surg J. 29(1):26-31.

46- Cordova, A. and Moschella, F. (2008): Algorithm for clinical evaluation and surgical treatment of gynaecomastia. J Plast Reconstr Aesthet Surg.;61(1):41-49.

47- Hammond, D. C. (2009): Surgical correction of gynecomastia. Plast Reconstr Surg.,124(1 Suppl):61e-68e.

48- Fagerlund, A., Lewin, R., Rufolo, G., Elander, A., Santanelli, di Pompeo, F. and Selvaggi, G. (2015): Gynecomastia: a systematic review. J Plast Surg Hand Surg. 49:311–8. doi:10.3109/2000656X.2015.10533 98.

49- Ordaz, D. L. and Thompson, J. K. (2015): Gynecomastia and psychological functioning: a review of the literature. Body Image. 15:141–8. doi: 10.1016/j.bodyim. 2015.08.004

50- Ghanem, M. Ahweidi, A.S. and AMR, A. H. (2020): A New Modified Postero-Inferior Technique in Management of Grade III Gynecomastia. J. Plast. Reconstr. Surg.,44(4): 545-553.

51- Ladizinski, B. Lee, K. C., Nutan, F. N. U., Higgins, H. W. and Federman, D. G. (2014): Gynecomastia: Etiologies, clinical presentations, diagnosis, and management. South Med. J., 107(1): 44-49.

52- Soliman, A. T., Sanctis, D. V. and Yassin. M. (2017): Management of adolescent gynecomastia: an update. Acta. Biomed., 88,2:204-213. doi:10.23750/abm.v88i2.6665

53- Rahmani, S., Turton, P., Shaaban, A. and Dall, B. (2011): Owerview of gynecomastiain the modern era and the Leeds Gynaecomastia Investigation algorithm. Breast J.,17:246-255.

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