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MINI REVIEW

Gynecomastia and hormones

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Abstract Gynecomastia—the enlargement of male breast tissue in men—is a common finding, frequently observed in newborns, adolescents, and old men. Physiological gynecomastia, occurring in almost 25 % of cases, is benign and self-limited; on the other hand, several conditions and drugs may induce proliferation of male breast tissue. True gynecomastia is a common feature often related to estrogen excess and/or androgen deficiency as a consequence of different endocrine disorders. Biochemical evaluation should be performed once physiological or iatrogenic gynecomastia has been ruled out. Non-endocrine illnesses, including liver failure and chronic kidney disease, are another cause of gynecomastia which should be considered. Treating the underlying disease or discontinuing medications might resolve gynecomastia, although the psychosocial burden of this condition might require different and careful consideration.

Keywords Gynecomastia · Male breast enlargement · Testosterone · Estradiol · Hyperthyroidism · Hyperprolactinemia · Hypogonadism

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Introduction

Gynecomastia, commonly described as the enlargement of the male breast tissue, is clinically characterized by the presence of a mass extending concentrically from the nipple (e.g., bilateral or rarely unilateral). Gynecomastia is the most common breast alteration in males [1], occurring more frequently during infancy, puberty, and old age [1, 2]: prevalence rates, as suggested by Johnson et al. [3], are 60–90 % in newborns, 50–60 % in adolescents, and 70 % in men between 50 and 69 years.

Physical examination and careful medical history are invaluable tools in the assessment of a patient with breast enlargement. Palpation allows to rule out lipomastia, the accumulation of subareolar fat in the absence of a solid palpable disk of glandular tissue [4].

Histologically, true gynecomastia is mainly characterized by ductal epithelial hyperplasia and increase in stromal and periductal connective tissue [1], usually resulting from increased action of exogenous or endogenous estradiol (E2) and absolutely or relatively reduced effects of androgens (i.e., testosterone, T) [5] (Table 1). Referrals to breast clinic assessment are increasing [6] for preventive, aesthetic, and therapeutic reasons; however, in most cases, gynecomastia resolves spontaneously [5, 7]. Despite its frequent benignity, it is often cause for psychological distress [8]: fear of diseases (including breast cancer) and psychosocial discomfort are common complaints which should not be disregarded by the clinician [6, 8].

Physiological gynecomastia occurs in up to 25 % of patients [9]; likewise, no definite cause is identifiable in another 25 % of cases [9]. In the remaining half of the affected subjects, gynecomastia is either iatrogenic, or related to an underlying condition which should be identified and treated (Table 2).

Table 1 Mechanisms resulting in gynecomastia. Adapted from Cuhaci et al. [1]

Mechanisms leading to gynecomastia
Estrogen excess
Direct secretion
Reduced clearance
Increased aromatization
Exogenous administration
Androgen deficiency
Decreased secretion
Increased clearance
Increased binding to SHBG
Altered T-to-E2 ratio
Puberty, aging
Refeeding
Thyroid disorders
Liver and kidney disease

Table 2 Conditions associated with gynecomastia. Adapted from Cuhaci et al. [1]

Conditions associated with gynecomastia
Physiologic gynecomastia
Neonatal
Pubertal
Aging-related
Pathologic gynecomastia
Male hypogonadism
Primary hypogonadism
Secondary hypogonadism
Hyperprolactinemia
Estrogen excess
Tumors
Germ cell testicular tumors
Non-germ cell testicular tumors
Feminizing adrenal tumors
Thyroid disorders
Hyperthyroidism
Hypothyroidism
Obesity
Leptin excess
Excess GH/IGF-1
Starvation
Chronic kidney/liver disease
Iatrogenic gynecomastia
Use of performance-enhancing drugs
Anabolic androgenic steroids
Growth hormone
Use of antiandrogens
Exposure to exogenous estrogens
Exposure to phytoestrogens
Recreational drug use
Idiopathic

We aim to describe endocrine causes of gynecomastia, providing additional information in regard to non-endocrine causes.

Physiological gynecomastia

Neonatal gynecomastia

Transplacentar transfer of maternal estrogens leads to a transient and self-limited imbalance in E2-to-T ratio [10]. Spontaneous resolution of this phenomenon commonly occurs in a few weeks; further investigation is advised should symptoms persist for more than 1 year [11].

Pubertal gynecomastia

A rapid increase in E2 occurring before a similar increase in T causes an elevated E2-to-T ratio and could be responsible for physiological gynecomastia at the start of puberty. The breast enlargement usually resolves spontaneously in <2 years, when the E2-to-T ratio is restored [11]. Psychological or sexual issues are among the chief complaints, although pain may frequent. Reassurance and follow-up are the treatment of choice; however, patients might require pharmacological or surgical treatment to ease their psychosocial burden.

Aging gynecomastia

Gynecomastia is a common symptom of many clinical conditions (e.g., diseases, drugs, etc.) occurring in the elderly; however, even in "healthy" aging a paraphysiological increase in aromatase activity is involved for many cases of asymptomatic gynecomastia [9, 12]. Increased aromatase activity may be secondary to increase in total body fat and SHBG, or to mild late-onset hypogonadism [13].

Pathologic gynecomastia

Androgen deficiency

In all circumstances of increased E2-to-T ratio, and therefore in almost all forms of male hypogonadism, the altered hormonal homeostasis contributes to the genesis of

gynecomastia [14]. In fact, the symptom gynecomastia might help identifying individuals with T deficiency. Primary male hypogonadism is characterized by decreased T production, increased LH production to stimulate Leydig cells, and elevated aromatization of T to E2; in secondary male hypogonadisms, low levels of T are subsequent to reduced LH secretion, despite normal production of adrenal estrogen precursors [15]. Therefore, in both conditions, serum E2-to-T ratio is increased. In hypogonadal men, T replacement therapy is usually able to reduce breast tenderness and size [1, 7, 16] as administration of exogenous androgens is able to restore the balance in sexual hormones ratio.

Klinefelter syndrome (KS) is the most common chromosomal anomaly associated with hypogonadism [17], although frequently overlooked [18]. KS can be suspected based on biochemical, developmental, and physical features, although confirmation of diagnosis requires karyotype testing. Prevalence of gynecomastia in men affected by KS is up to 70 % and, unfortunately, in this population the risk of developing breast cancer is significantly increased [19]; consequently, an adequate breast examination is of utmost importance in these patients. The observation of microorchidism during testicular examination should arouse suspicion; biochemical evaluation and karyotype testing should be recommended if KS is suspected.

Hyperprolactinemia

Hyperprolactinemia could be involved in the pathogenesis of gynecomastia as a cause of secondary hypogonadism [20–22]. However, prolactin receptors have been found in male breast tissue [23], and they might be co-expressed and cross-regulated with growth hormone [24] and progesterone receptors [25]. Activation of progesterone receptors is often linked to reduced expression of androgen receptors, hampering the androgen-mediated inhibition on breast tissue growth observed in condition of normal hormonal homeostasis. Consequently, besides male hypogonadism, hyperprolactinemia might induce gynecomastia through a completely different pathway: elevated levels of prolactin might stimulate breast tissue growth as a result of excessive progesterone receptor activation, and reduced availability of androgen receptors [26].

Absolute estrogen excess

In men, the small circulating quota of E2 and estrone results from extraglandular aromatization of T and androstenedione. Estrogens induce development of male and female breast tissue alike: therefore, any condition resulting in excess estrogen in males might cause gynecomastia. The most common causes of absolute estrogen excess include exogenous estrogen administration, reduced clearance, increased aromatization, and direct secretion from tumors [1, 7].

Estrogen-secreting tumors

Feminizing adrenal tumors are rare neoplasms, featuring gynecomastia as the most common clinical manifestation in adults [27] following increased adrenal production of estrogens. Weight loss, symptoms of Cushing's syndrome or mineralocorticoid excess, and the presence of an abdominal mass in the presence of gynecomastia suggest the presence of an adrenal tumor. Gynecomastia might also be the first clinical sign of a testicular cancer [28–31], the most common neoplasm in young adults [32, 33]. Germ cell tumors induce gynecomastia via a different pathway (discussed later), whereas non-germ cell tumors directly secrete estrogens or increase aromatization of T to E2 [34]. Testicular pain or enlargement should be evaluated during physical examination for all patients with gynecomastia [34].

Non-estrogen-secreting tumors

Besides feminizing adrenal tumors and non-germ cell testicular cancers, different neoplasms can induce gynecomastia via increased production of human chorionic gonadotropin (hCG), including germ cell testicular tumors (i.e., choriocarcinoma), large-cell lung carcinoma, gastric carcinoma, and renal cell carcinoma [1]. hCG increases aromatase activity in the Leydig cells, resulting in excess E2 and reduced T [35, 36].

Thyroid disorders

Gynecomastia during thyrotoxicosis has been reported for more than 60 years [37–40], and has occasionally been described as the first symptom of hyperthyroidism [39, 40]. Effects of thyroid hormones on the hypothalamic–pituitary–gonadal axis have been described in literature [41]: hypothyroid men have reduced T secretion [42] and often develop hyperprolactinemia, whereas hyperthyroidism is associated with increased E2, SHBG, and T concentrations [43]. Elevated SHBG leads to low free T concentrations associated to increased E2 concentrations: therefore, this leads to a status of hormonal imbalance, resulting in gynecomastia among other symptoms. In both hypothyroidism and hyperthyroidism, gynecomastia is commonly resolved after euthyroid state restoration.

Obesity

Aromatization of T to E2 occurs in the adipose tissue and, as previously discussed, is the main source of E2 in men. The role of aromatase in the pathogenesis of gynecomastia has been extensively studied [4, 12]. In obese people, both increased expression and activity of aromatase can be involved in development of gynecomastia. It is also worth remembering that aging does increase aromatase activity [9, 12], resulting in a further increased prevalence of gynecomastia in aging, obese men.

Leptin

Research on leptin has steadily increased in the last decades: although traditionally associated with energy expenditure and satiety, leptin seems to be involved in many pathophysiological processes. The effect of leptin on the hypothalamic–pituitary–gonadal axis has been clearly identified [44–46]: patients with defective leptin signaling are affected by delayed puberty and some degree of infertility, and investigation on treatment with recombinant leptin has shown promising results [47]. Recent studies have shown that both increase in total leptin levels [48] and polymorphisms in its receptor [49] can be involved in the pathogenesis of gynecomastia: accelerated estrogen metabolism and increased expression of aromatase have been identified as possible gynecomastia-inducing factors [50–54].

Growth hormone and IGF-1 excess

Enlargement of mammary glands following exogenous growth hormone administration has been observed almost two decades ago in primates [55]: in humans, a role of the GH-IGF-1 axis on the pathogenesis of gynecomastia has been speculated [56], and the synergistic role of estrogens, which induce expression of IGF-1 receptors on breast tissue, seems to prove that [57]. As a further proof, a recent study aiming to perform hormonal evaluation in pubertal gynecomastia has shown a significant positive association between breast enlargement and IGF-1 levels in pubertal boys [58].

Gynecomastia is common in patients treated with growth hormone [59–61], and cases of acromegaly manifesting with gynecomastia as its first symptom are reported [62].

Other conditions

Gynecomastia has been observed after resumption of a normal diet following long periods of malnourishment [63]. During starvation, decreased levels of T and gonadotropins are observed despite normal concentrations of E2: the resulting impairment in the E2-to-T ratio is, as already reported, the main factor involved in the pathogenesis of gynecomastia.

Gynecomastia is a common symptom of chronic liver disease, since T levels are frequently low [64]; in advanced liver disease, increased SHBG levels reduce the bioavailable quota of T, contributing to the pathogenesis of gynecomastia.

Testicular damage from chronic kidney disease results in impaired T secretion [65] which can present as gynecomastia. Dialysis does not affect gynecomastia, which occasionally regresses idiopathically [63].

Pharmacological gynecomastia

There is solid evidence that many drugs are able to induce gynecomastia via a plethora of mechanisms (Table 3): estrogen-like actions, increased endogenous estrogen secretion or effects, increased aromatization of androgens to E2, reduced T secretion, reduced sensitivity of androgens receptors, and so forth. Antipsychotics, corticosteroids, spironolactone, antiretrovirals, statins, proton pump inhibitors, and opioids are just a few of the many contributors to the development of gynecomastia [66, 67].

Drug abuse in sports

Medication use and abuse (i.e., doping) are the most common cause of gynecomastia in adults [11]. Anabolic androgenic steroids (AAS) are perhaps the most used performance-enhancing drugs [68–70]. Although prohibited by the World Anti-Doping Agency (WADA), AAS are very often abused by athletes and non-athletes, as they can supposedly provide a boost to performance and/or to muscle development. Gynecomastia and acne are common side effects of AAS abuse, mainly resulting from increased E2 concentration following peripheral AAS aromatization [71]. Negative feedback in the regulation of the hypothalamic–pituitary–gonadal axis resulting from the continuous administration of AAS might also cause gynecomastia, erectile dysfunction, and infertility due to hypogonadism. Gynecomastia can also be the result of conjoined abuse of AAS and growth hormone [72, 73]. hCG is another commonly abused drug, able to induce gynecomastia on its own.

Antiandrogens

Antiandrogens, binding to the androgen receptors, inhibit the action of T and dihydrotestosterone on breast glandular tissue and hamper the negative feedback of the

Table 3 Medications associated with gynecomastia. Adapted from Bowman et al. [69]

Category	Specific drugs
Antiandrogens	Bicalutamide, flutamide, nilutamide, finasteride, dutasteride
Antibiotics	Ketoconazole
Antihypertensives	Spironolactone, calcium channel blockers
Antipsychotics	Haloperidol, olanzapine, paliperidone, risperidone, ziprasidone
Antiretrovirals	Protease inhibitors
Chemotherapeutic agents	Methotrexate, cyclophosphamide, carmustine, etoposide, cytarabine, melphalan, bleomycin, cisplatin, vincristine, actinomycin D, procarbazine
Environmental exposure	Phytoestrogens
Exogenous hormones	Estrogen, androgen abuse, prednisone
Gastrointestinal agents	H2-receptor blockers, proton pump inhibitors
GnRH agonists	Leuprorelin, buserelin, nafarelin, histrelin, goserelin, deslorelin
Miscellaneous agents	Amiodarone, amphetamines, aripiprazole, atorvastatin, auranofin, benserazide, captopril, cetirizine, clonidine, cyproterone acetate, dasatinib, diazepam, diethylstilbestrol, digoxin, domperidone, entecavir, ethanol, etretinate, fenofibrate, fluoxetine, gabapentin, heroin, imatinib, isoniazid, lisinopril, loratadine, marijuana, methadone, metronidazole, misoprostol, Mytosterone, paroxetine, penicillamine, phthalates, pravastatin, pregabalin, ranitidine, rosuvastatin, sulindac, sulpiride, sunitinib, theophylline, thiacetazone, venlafaxine

hypothalamic–pituitary–gonadal axis. Therefore, antiandrogens lead to an increase in T levels; aromatization of T to E2 increases the E2-to-T ratio which, as already described, promotes the development of gynecomastia.

Similarly, GnRH analogues have reportedly [35] been associated with gynecomastia, although with a smaller incidence.

Exogenous estrogen

Accidental exposure to estrogen has been observed in subjects using topical creams for baldness, or in those eating foods from estrogen-treated animals [74].

Phytoestrogens

Phytoestrogens are estrogens not produced by the endocrine system, but obtained through dietary intake or taken as medications and interacting with the estrogen receptor. Soy products and digoxin are both commonly used phytoestrogens, which have been linked to gynecomastia in mice: it seems likely that their similarity with endogenous estrogens exerts some effects of excess E2, although there is still uncertainty in regard to the degree of feminization in humans [75, 76]. Phytoestrogens are ubiquitous [77]: lavender and tea tree oil [78] are used for cosmetics and in some foods; hops [79] are used as flavoring and stability agent in beer; phthalates and herbicides have gained media exposure as endocrine disruptors in recent years, and are still used in most countries for industrial and agricultural needs.

Recreational drug use

Recreational drug use has been occasionally associated with increased risk of gynecomastia [35, 66, 74, 80]. Although exact mechanisms are still unclear, the presence of plant estrogens has been considered as a possible trigger for marijuana-related gynecomastia [81]. Furthermore, opioids reduce T, FSH, and LH; this effect is likely to be caused by inhibitory effects on both the hypothalamic–pituitary–gonadal axis and the testicular production of T [35].

Conclusions

Gynecomastia is a common, usually benign symptom, which might be perceived as a serious health issue by some patients. Clinicians should not underestimate gynecomastia: even physiological gynecomastia, transient and benign by definition, might have serious psychological consequences which deserve careful consideration. We propose a standardized diagnostic approach (Fig. 1) for a thorough evaluation of gynecomastia, aiming at reducing waste of time and resources while at the same time providing the necessary care. Detailed medical history, including medication intake and dietary habits, and thorough physical examination can identify physiological or iatrogenic

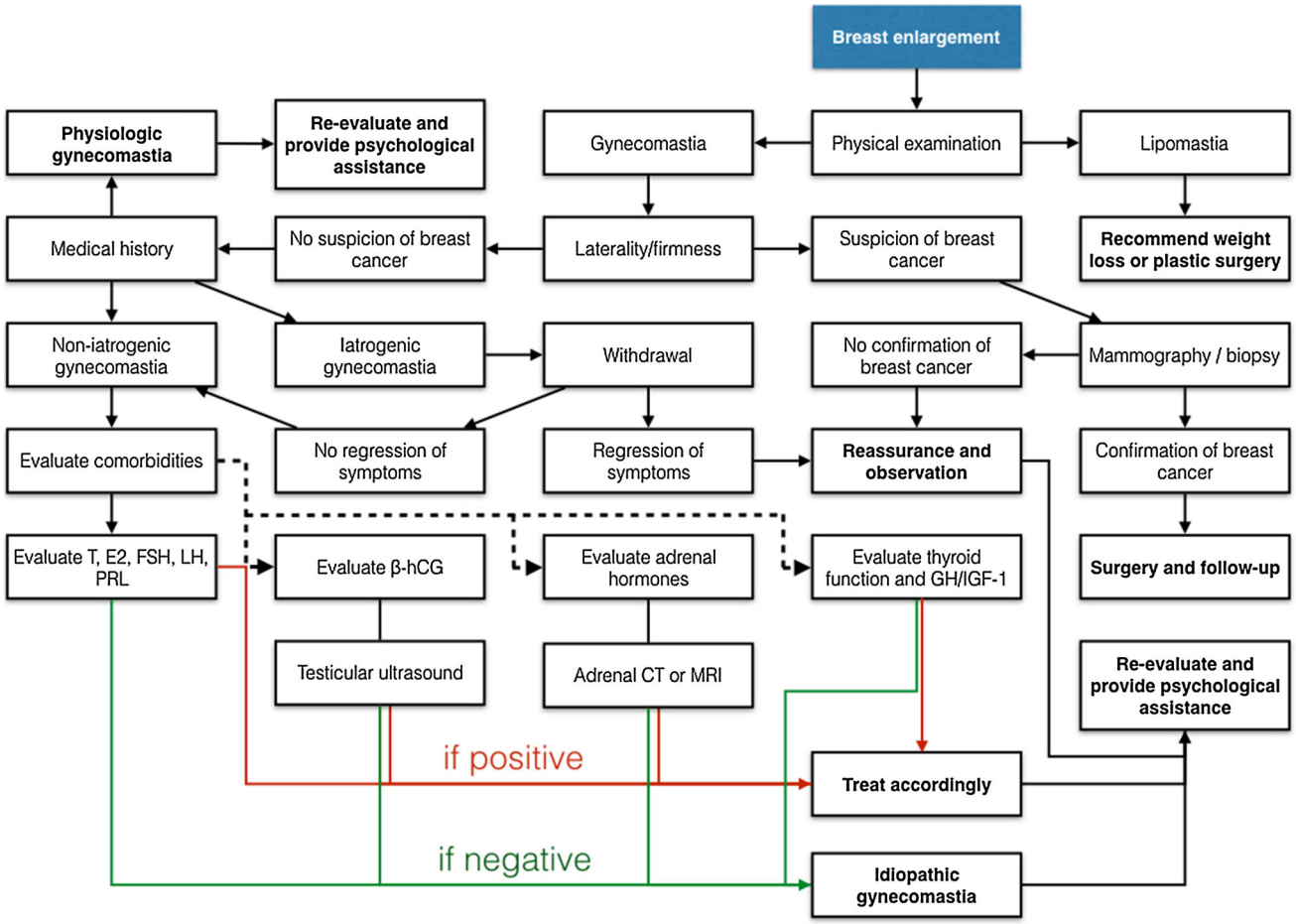

Fig. 1 Flowchart for evaluation and treatment of gynecomastia

gynecomastia; however, although rarely, gynecomastia might be the first symptom of an underlying serious disease. When initial findings from medical history and physical examination rule out iatrogenic and physiological gynecomastia, we suggest investigating T, E2, FSH, LH, prolactin, and β-hCG as a first approach to a biochemical diagnosis. Specific following evaluation, including thyroid and adrenal hormones, SHBG, karyotype testing, and GH and IGF-1 assessment, should be guided by clinical signs and symptoms.

Treatment should be tailored on the basis of clinical and biochemical findings. If no cause of gynecomastia has been found despite a thorough evaluation, diagnosis of idiopathic gynecomastia should be made: reassurance and follow-up are the mainstay of treatment although surgical or pharmacological treatment might be required for aesthetic or psychological reasons.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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