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# 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
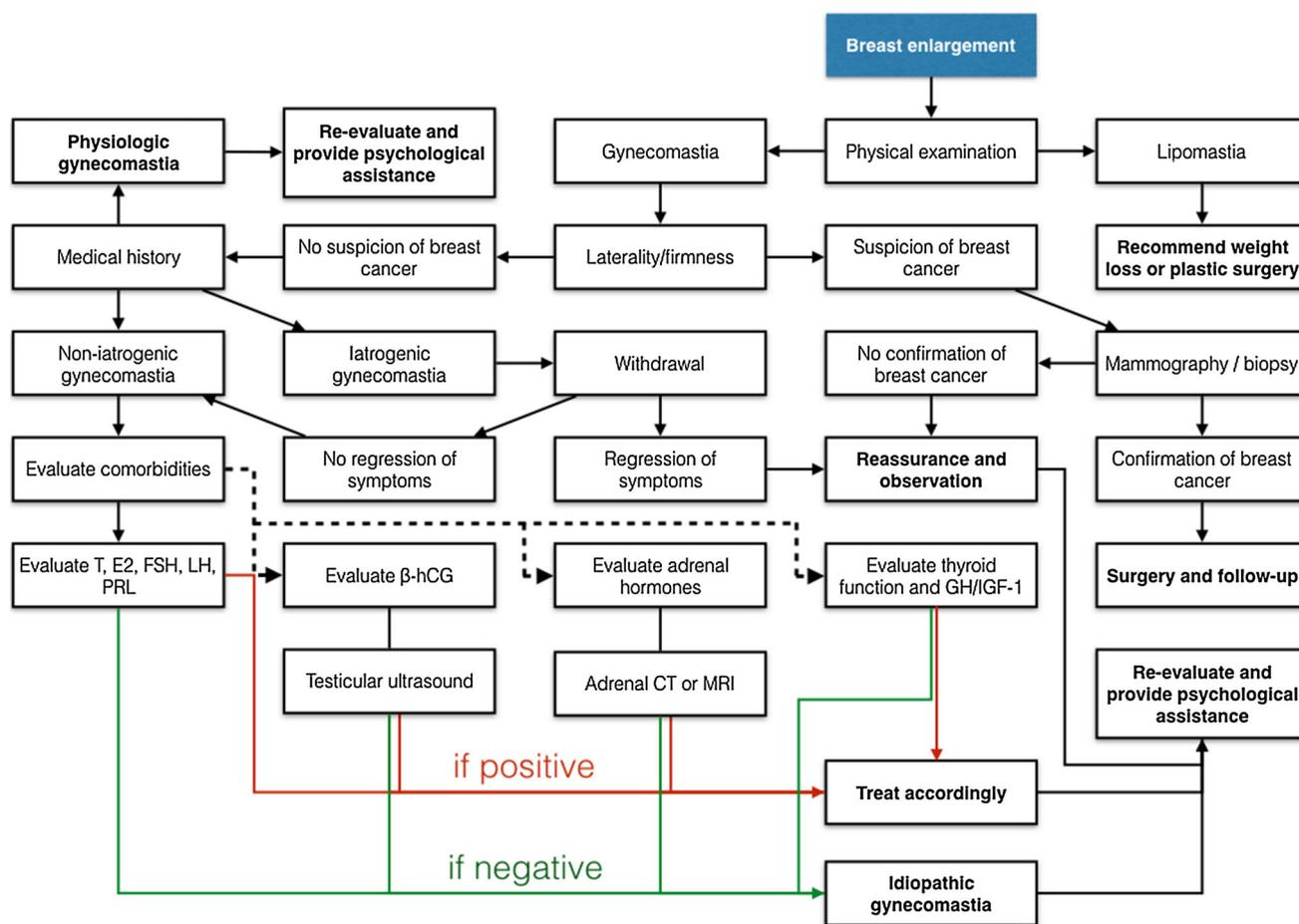
**Fig. 1** Flowchart for evaluation and treatment of gynecomastia

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**

# References

1. N. Cuhaci, S.B. Polat, B. Evranos, R. Ersoy, B. Cakir, Gynecomastia: clinical evaluation and management. Indian J Endocrinol Metab **18**(2), 150–158 (2014). doi:10.4103/2230-8210.129104

2. R.E. Johnson, M.H. Murad, Gynecomastia: pathophysiology, evaluation, and management. Mayo Clin. Proc. **84**(11), 1010–1015 (2009). doi:10.1016/S0025-6196(11)60671-X

3. R.E. Johnson, C.A. Kermott, M.H. Murad, Gynecomastia—evaluation and current treatment options. Ther. Clin. Risk Manag. **7**, 145–148 (2011). doi:10.2147/TCRM.S10181

4. R. Mathur, G.D. Braunstein, Gynecomastia: pathomechanisms and treatment strategies. Horm. Res. **48**(3), 95–102 (1997)

5. B. Ladizinski, K.C. Lee, F.N. Nutan, H.W. Higgins II, D.G. Federman, Gynecomastia: etiologies, clinical presentations, diagnosis, and management. South. Med. J. **107**(1), 44–49 (2014). doi:10.1097/SMJ.0000000000000033

6. M. Kipling, J.E. Ralph, K. Callanan, Psychological impact of male breast disorders: literature review and survey results. Breast Care (Basel) **9**(1), 29–33 (2014). doi:10.1159/000358751

7. H.S. Narula, H.E. Carlson, Gynaecomastia–pathophysiology, diagnosis and treatment. Nat Rev Endocrinol **10**(11), 684–698 (2014). doi:10.1038/nrendo.2014.139

8. L. Rew, C. Young, T. Harrison, R. Caridi, A systematic review of literature on psychosocial aspects of gynecomastia in adolescents

and young men. J. Adolesc. **43**, 206–212 (2015). doi:10.1016/j.adolescence.2015.06.007

9. G.D. Braunstein, Clinical practice. Gynecomastia. N. Engl. J. Med. **357**(12), 1229–1237 (2007). doi:10.1056/NEJMcp070677

10. E. Sloand, Pediatric and adolescent breast health. Lippincotts Prim. Care Pract. **2**(2), 170–175 (1998)

11. G. Dickson, Gynecomastia. Am. Fam. Physician **85**(7), 716–722 (2012)

12. G.D. Braunstein, Aromatase and gynecomastia. Endocr. Relat. Cancer **6**(2), 315–324 (1999)

13. R.S. Swerdloff, J. Ng, Gynecomastia: etiology, diagnosis, and treatment, in *Endotext*, ed. by L.J. De Groot, P. Beck-Peccoz, G. Chrousos, K. Dungan, A. Grossman, J.M. Hershman, C. Koch, R. McLachlan, M. New, R. Rebar, F. Singer, A. Vinik, M.O. Weickert (MDText.com, Inc, South Dartmouth, MA, 2000)

14. N. Rokutanda, T. Iwasaki, H. Odawara, R. Nagaoka, W. Miyazaki, A. Takeshita, Y. Koibuchi, J. Horiguchi, N. Shimokawa, Y. Iino, Y. Morishita, N. Koibuchi, Augmentation of estrogen receptor-mediated transcription by steroid and xenobiotic receptor. Endocrine **33**(3), 305–316 (2008). doi:10.1007/s12020-008-9091-9

15. S.A. Bembo, H.E. Carlson, Gynecomastia: its features, and when and how to treat it. Clevel. Clin. J. Med. **71**(6), 511–517 (2004)

16. R.N. Morcos, T. Kizy, Gynecomastia: when is treatment indicated? J. Fam. Pract. **61**(12), 719–725 (2012)

17. E. Nieschlag, Klinefelter syndrome: the commonest form of hypogonadism, but often overlooked or untreated. Dtsch. Arztebl. Int. **110**(20), 347–353 (2013). doi:10.3238/arztebl.2013.0347

18. F. Lanfranco, A. Kamischke, M. Zitzmann, E. Nieschlag, Klinefelter's syndrome. Lancet **364**(9430), 273–283 (2004). doi:10.1016/S0140-6736(04)16678-6

19. L.A. Brinton, Breast cancer risk among patients with Klinefelter syndrome. Acta Paediatr. **100**(6), 814–818 (2011). doi:10.1111/j.1651-2227.2010.02131.x

20. M. Galdiero, R. Pivonello, L.F. Grasso, A. Cozzolino, A. Colao, Growth hormone, prolactin, and sexuality. J. Endocrinol. Investig. **35**(8), 782–794 (2012). doi:10.1007/BF03345805

21. M. Maggi, J. Buvat, G. Corona, A. Guay, L.O. Torres, Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA). J. Sex Med. **10**(3), 661–677 (2013). doi:10.1111/j.1743-6109.2012.02735.x

22. A. Sansone, F. Romanelli, D. Gianfrilli, A. Lenzi, Endocrine evaluation of erectile dysfunction. Endocrine **46**(3), 423–430 (2014). doi:10.1007/s12020-014-0254-6

23. M. Ferreira, M. Mesquita, M. Quaresma, S. Andre, Prolactin receptor expression in gynaecomastia and male breast carcinoma. Histopathology **53**(1), 56–61 (2008). doi:10.1111/j.1365-2559.2008.03059.x

24. H.C. Mertani, T. Garcia-Caballero, A. Lambert, F. Gerard, C. Palayer, J.M. Boutin, B.K. Vonderhaar, M.J. Waters, P.E. Lobie, G. Morel, Cellular expression of growth hormone and prolactin receptors in human breast disorders. Int. J. Cancer **79**(2), 202–211 (1998). doi:10.1002/(SICI)1097-0215(19980417)79:2<202:AID-IJC17>3.0.CO;2-B

25. R.C. Hovey, J.F. Trott, E. Ginsburg, A. Goldhar, M.M. Sasaki, S.J. Fountain, K. Sundararajan, B.K. Vonderhaar, Transcriptional and spatiotemporal regulation of prolactin receptor mRNA and cooperativity with progesterone receptor function during ductal branch growth in the mammary gland. Dev. Dyn. **222**(2), 192–205 (2001). doi:10.1002/dvdy.1179

26. M.L. Bravo, M.P. Pinto, I. Gonzalez, B. Oliva, S. Kato, M.A. Cuello, C.A. Lange, G.I. Owen, Progesterone regulation of tissue factor depends on MEK1/2 activation and requires the proline-rich site on progesterone receptor. Endocrine **48**(1), 309–320 (2015). doi:10.1007/s12020-014-0288-9

27. F. Chentli, I. Bekkaye, S. Azzoug, Feminizing adrenocortical tumors: literature review. Indian J. Endocrinol. Metab. **19**(3), 332–339 (2015). doi:10.4103/2230-8210.152764

28. S. Kayemba-Kays, G. Fromont-Hankard, G. Lettelier, S. Gabriel, G. Levard, Leydig cell tumour revealed by bilateral gynecomastia in a 15-year-old adolescent: a patient report. J. Pediatr. Endocrinol. Metab. **23**(11), 1195–1199 (2010)

29. H. Djaladat, C. Nichols, S. Daneshmand, Androgen-producing testicular germ cell tumors. J. Clin. Oncol. **29**(21), e634–e635 (2011). doi:10.1200/JCO.2011.35.1965

30. N. Kolitsas, S. Tsambalas, F. Dimitriadis, D. Baltogiannis, E. Vlachopoulou, S. Vappa, D. Giannakis, P. Tsounapi, A. Takenaka, N. Sofikitis, Gynecomastia as a first clinical sign of non-seminomatous germ cell tumor. Urol. Int. **87**(2), 248–250 (2011). doi:10.1159/000328387

31. S. Kaptanis, L. Parvanta, L. Beltran, Testicular seminoma presenting as unilateral gynecomastia. Breast J. **20**(4), 424–426 (2014). doi:10.1111/tbj.12287

32. S.M. Stevenson, W.T. Lowrance, Epidemiology and diagnosis of testis cancer. Urol. Clin. N. Am. **42**(3), 269–275 (2015). doi:10.1016/j.ucl.2015.04.001

33. B. Hayes-Lattin, C.R. Nichols, Testicular cancer: a prototypic tumor of young adults. Semin. Oncol. **36**(5), 432–438 (2009). doi:10.1053/j.seminoncol.2009.07.006

34. Y. Huang, J. Song, M. Xu, Q. Zan, Primary Leydig cell tumour of epididymis: a rare case report with review of literature. Andrologia **45**(6), 430–433 (2013). doi:10.1111/and.12049

35. F. Deepinder, G.D. Braunstein, Drug-induced gynecomastia: an evidence-based review. Expert Opin. Drug Saf. **11**(5), 779–795 (2012). doi:10.1517/14740338.2012.712109

36. M.G. Forest, A. Lecoq, J.M. Saez, Kinetics of human chorionic gonadotropin-induced steroidogenic response of the human testis. II. Plasma 17 α-hydroxyprogesterone, δ4-androstenedione, estrone, and 17 β-estradiol: evidence for the action of human chorionic gonadotropin on intermediate enzymes implicated in steroid biosynthesis. J. Clin. Endocrinol. Metab. **49**(2), 284–291 (1979). doi:10.1210/jcem-49-2-284

37. S.A. Berson, S.S. Schreiber, Gynecomastia and hyperthyroidism. J. Clin. Endocrinol. Metab. **13**(9), 1126–1128 (1953). doi:10.1210/jcem-13-9-1126

38. K.L. Becker, J.L. Winnacker, M.J. Matthews, G.A. Higgins Jr, Gynecomastia and hyperthyroidism. An endocrine and histological investigation. J. Clin. Endocrinol. Metab. **28**(2), 277–285 (1968). doi:10.1210/jcem-28-2-277

39. H.K. Ho, K.C. Loh, Hyperthyroidism with gynaecomastia as the initial complaint: a case report. Ann. Acad. Med. Singapore **27**(4), 594–596 (1998)

40. W.B. Chan, V.T. Yeung, C.C. Chow, W.Y. So, C.S. Cockram, Gynaecomastia as a presenting feature of thyrotoxicosis. Postgrad. Med. J. **75**(882), 229–231 (1999)

41. E.A. Jannini, S. Ulisse, M. D'Armiento, Thyroid hormone and male gonadal function. Endocr. Rev. **16**(4), 443–459 (1995). doi:10.1210/edrv-16-4-443

42. A.W. Meikle, The interrelationships between thyroid dysfunction and hypogonadism in men and boys. Thyroid **14**(Suppl 1), S17–25 (2004). doi:10.1089/105072504323024552

43. G.E. Krassas, K. Poppe, D. Glinoer, Thyroid function and human reproductive health. Endocr. Rev. **31**(5), 702–755 (2010). doi:10.1210/er.2009-0041

44. M. Caprio, E. Fabbrini, A.M. Isidori, A. Aversa, A. Fabbri, Leptin in reproduction. Trends Endocrinol. Metab. **12**(2), 65–72 (2001)

45. M.J. Vazquez, A. Romero-Ruiz, M. Tena-Sempere, Roles of leptin in reproduction, pregnancy and polycystic ovary syndrome: consensus knowledge and recent developments. Metabolism **64**(1), 79–91 (2015). doi:10.1016/j.metabol.2014.10.013

46. A. Sansone, F. Romanelli, E.A. Jannini, A. Lenzi, Hormonal correlations of premature ejaculation. Endocrine **49**(2), 333–338 (2015). doi:10.1007/s12020-014-0520-7

47. I.S. Farooqi, S. O'Rahilly, 20 Years of leptin: human disorders of leptin action. J. Endocrinol. **223**(1), T63–T70 (2014). doi:10.1530/JOE-14-0480

48. B. Dundar, N. Dundar, T. Erci, E. Bober, A. Buyukgebiz, Leptin levels in boys with pubertal gynecomastia. J. Pediatr. Endocrinol. Metab. **18**(10), 929–934 (2005)

49. E. Eren, T. Edgunlu, H.A. Korkmaz, E.D. Cakir, K. Demir, E.S. Cetin, S.K. Celik, Genetic variants of estrogen beta and leptin receptors may cause gynecomastia in adolescent. Gene **541**(2), 101–106 (2014). doi:10.1016/j.gene.2014.03.013

50. S. Catalano, S. Marsico, C. Giordano, L. Mauro, P. Rizza, M.L. Panno, S. Ando, Leptin enhances, via AP-1, expression of aromatase in the MCF-7 cell line. J. Biol. Chem. **278**(31), 28668–28676 (2003). doi:10.1074/jbc.M301695200

51. S. Catalano, L. Mauro, S. Marsico, C. Giordano, P. Rizza, V. Rago, D. Montanaro, M. Maggiolini, M.L. Panno, S. Ando, Leptin induces, via ERK1/ERK2 signal, functional activation of estrogen receptor alpha in MCF-7 cells. J. Biol. Chem. **279**(19), 19908–19915 (2004). doi:10.1074/jbc.M313191200

52. M.N. Dieudonne, A. Sammari, E. Dos Santos, M.C. Leneveu, Y. Giudicelli, R. Pecquery, Sex steroids and leptin regulate 11 β-hydroxysteroid dehydrogenase I and P450 aromatase expressions in human preadipocytes: sex specificities. J. Steroid Biochem. Mol. Biol. **99**(4–5), 189–196 (2006). doi:10.1016/j.jsbmb.2006.01.007

53. B. Lapauw, G. T'Sjoen, A. Mahmoud, J.M. Kaufman, J.B. Ruige, Short-term aromatase inhibition: effects on glucose metabolism and serum leptin levels in young and elderly men. Eur. J. Endocrinol. **160**(3), 397–402 (2009). doi:10.1530/EJE-08-0881

54. C.N. Habib, A.M. Al-Abd, M.F. Tolba, A.E. Khalifa, A. Khedr, H.A. Mosli, A.B. Abdel-Naim, Leptin influences estrogen metabolism and accelerates prostate cell proliferation. Life Sci. **121**(C), 10–15 (2015). doi:10.1016/j.lfs.2014.11.007

55. S.T. Ng, J. Zhou, O.O. Adesanya, J. Wang, D. LeRoith, C.A. Bondy, Growth hormone treatment induces mammary gland hyperplasia in aging primates. Nat. Med. **3**(10), 1141–1144 (1997)

56. M.G. Mieritz, K. Sorensen, L. Aksglaede, A. Mouritsen, C.P. Hagen, L. Hilsted, A.M. Andersson, A. Juul, Elevated serum IGF-I, but unaltered sex steroid levels, in healthy boys with pubertal gynaecomastia. Clin. Endocrinol. (Oxf.) **80**(5), 691–698 (2014). doi:10.1111/cen.12323

57. L.J. De Groot, P. Beck-Peccoz, G. Chrousos, K. Dungan, A. Grossman, J.M. Hershman, C. Koch, R. McLachlan, M. New, R. Rebar, F. Singer, A. Vinik, M.O. Weickert, R.S. Swerdloff, J. Ng, *Gynecomastia: etiology, diagnosis, and treatment*, vol. 53 (MDText.com, Inc, South Dartmouth, MA, 2000)

58. M.G. Mieritz, L.L. Raket, C.P. Hagen, J.E. Nielsen, M.L. Talman, J.H. Petersen, S.H. Sommer, K.M. Main, N. Jorgensen, A. Juul, A longitudinal study of growth, sex steroids, and IGF-1 in boys with physiological gynecomastia. J. Clin. Endocrinol. Metab. **100**(10), 3752–3759 (2015). doi:10.1210/jc.2015-2836

59. F.M. Souza, P.F. Collett-Solberg, Adverse effects of growth hormone replacement therapy in children. Arq. Bras. Endocrinol. Metab. **55**(8), 559–565 (2011)

60. H. Liu, D.M. Bravata, I. Olkin, S. Nayak, B. Roberts, A.M. Garber, A.R. Hoffman, Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann. Intern. Med. **146**(2), 104–115 (2007)

61. S.V. Acharya, R.A. Gopal, T.R. Bandgar, P.S. Menon, N.S. Shah, Prepubertal gynecomastia a rare complication of growth hormone therapy. Indian J. Pediatr. **77**(4), 443–444 (2010). doi:10.1007/s12098-010-0012-6

62. D.B. Young, 6′6″ United States marine seeks treatment for gynecomastia only to learn it is all in his head. Mil. Med. **180**(12), e1290–e1292 (2015). doi:10.7205/MILMED-D-15-00248

63. M. Derkacz, I. Chmiel-Perzynska, A. Nowakowski, Gynecomastia—a difficult diagnostic problem. Endokrynol. Pol. **62**(2), 190–202 (2011)

64. M. Sinclair, M. Grossmann, P.J. Gow, P.W. Angus, Testosterone in men with advanced liver disease: abnormalities and implications. J. Gastroenterol. Hepatol. **30**(2), 244–251 (2015). doi:10.1111/jgh.12695

65. P. Iglesias, J.J. Carrero, J.J. Diez, Gonadal dysfunction in men with chronic kidney disease: clinical features, prognostic implications and therapeutic options. J. Nephrol. **25**(1), 31–42 (2012). doi:10.5301/JN.2011.8481

66. W. Krause, Drug-inducing gynaecomastia—a critical review. Andrologia **44**(Suppl 1), 621–626 (2012). doi:10.1111/j.1439-0272.2011.01240.x

67. J.D. Bowman, H. Kim, J.J. Bustamante, Drug-induced gynecomastia. Pharmacotherapy **32**(12), 1123–1140 (2012). doi:10.1002/phar.1138

68. L. Di Luigi, F. Romanelli, A. Lenzi, Androgenic–anabolic steroids abuse in males. J. Endocrinol. Investig. **28**(3 Suppl), 81–84 (2005)

69. L. Di Luigi, F. Romanelli, P. Sgro, A. Lenzi, Andrological aspects of physical exercise and sport medicine. Endocrine **42**(2), 278–284 (2012). doi:10.1007/s12020-012-9655-6

70. E. Nieschlag, E. Vorona, Mechanisms in endocrinology: medical consequences of doping with anabolic androgenic steroids: effects on reproductive functions. Eur. J. Endocrinol. **173**(2), R47–R58 (2015). doi:10.1530/EJE-15-0080

71. S. Basaria, Androgen abuse in athletes: detection and consequences. J. Clin. Endocrinol. Metab. **95**(4), 1533–1543 (2010). doi:10.1210/jc.2009-1579

72. A. Momaya, M. Fawal, R. Estes, Performance-enhancing substances in sports: a review of the literature. Sports Med. **45**(4), 517–531 (2015). doi:10.1007/s40279-015-0308-9

73. V. Birzniece, Doping in sport: effects, harm and misconceptions. Intern. Med. J. **45**(3), 239–248 (2015). doi:10.1111/imj.12629

74. A. Eckman, A. Dobs, Drug-induced gynecomastia. Expert Opin. Drug Saf. **7**(6), 691–702 (2008). doi:10.1517/14740330802442382

75. J. Martinez, J.E. Lewi, An unusual case of gynecomastia associated with soy product consumption. Endocr. Pract. **14**(4), 415–418 (2008). doi:10.4158/EP.14.4.415

76. M. Messina, Soybean isoflavone exposure does not have feminizing effects on men: a critical examination of the clinical evidence. Fertil. Steril. **93**(7), 2095–2104 (2010). doi:10.1016/j.fertnstert.2010.03.002

77. A. Vivacqua, A.G. Recchia, G. Fasanella, S. Gabriele, A. Carpino, V. Rago, M.L. Di Gioia, A. Leggio, D. Bonofiglio, A. Liguori, M. Maggiolini, The food contaminants bisphenol A and 4-nonylphenol act as agonists for estrogen receptor alpha in MCF7 breast cancer cells. Endocrine **22**(3), 275–284 (2003). doi:10.1385/ENDO:22:3:275

78. D.V. Henley, N. Lipson, K.S. Korach, C.A. Bloch, Prepubertal gynecomastia linked to lavender and tea tree oils. N. Engl. J. Med. **356**(5), 479–485 (2007). doi:10.1056/NEJMoa064725

79. L.R. Chadwick, D. Nikolic, J.E. Burdette, C.R. Overk, J.L. Bolton, R.B. van Breemen, R. Frohlich, H.H. Fong, N.R. Farnsworth, G.F. Pauli, Estrogens and congeners from spent hops (*Humulus lupulus*). J. Nat. Prod. **67**(12), 2024–2032 (2004). doi:10.1021/np049783i

80. R.D. Goldman, Drug-induced gynecomastia in children and adolescents. Can. Fam. Phys. **56**(4), 344–345 (2010)

81. M.A. Sauer, S.M. Rifka, R.L. Hawks, G.B. Cutler Jr, D.L. Loriaux, Marijuana: interaction with the estrogen receptor. J. Pharmacol. Exp. Ther. **224**(2), 404–407 (1983)