Gynaecomastia—pathophysiology, diagnosis and treatment

Harmeet S. Narula and Harold E. Carlson

Abstract | Gynaecomastia (enlargement of the male breast tissue) is a common finding in the general population. Most cases of gynaecomastia are benign and of cosmetic, rather than clinical, importance. However, the condition might cause local pain and tenderness, could occasionally be the result of a serious underlying illness or a medication, or be inherited. Breast cancer in men is much less common than benign gynaecomastia, and the two conditions can usually be distinguished by a careful physical examination. Estrogens are known to stimulate the growth of breast tissue, whereas androgens inhibit it; most cases of gynaecomastia result from deficient androgen action or excessive estrogen action in the breast tissue. In some cases, such as pubertal gynaecomastia, the breast enlargement resolves spontaneously. In other situations, more active treatment might be required to correct an underlying condition (such as hyperthyroidism or a benign Leydig cell tumour of the testis) or medications that could cause breast enlargement (such as spironolactone) might need to be discontinued. For men with hypogonadism, administration of androgens might be helpful, as might antiestrogen therapy in men with endogenous overproduction of estrogens. Surgery to remove the enlarged breast tissue might be necessary when gynaecomastia does not resolve spontaneously or with medical therapy.

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Introduction

Gynaecomastia is very common.[1,2] Up to 70% of all boys develop pubertal gynaecomastia,[3–5] and up to two-thirds of all adult men might have palpable breast tissue on examination.[4–8] At autopsy, gynaecomastia is seen histologically in about half of all men.[9]

Physiologic gynaecomastia is seen during infancy, puberty and ageing. Gynaecomastia should be differentiated from lipomastia (also called fatty breasts or pseudogynaecomastia) by comparing the findings on palpation of the subareolar tissue to the adjacent subcutaneous adipose tissue in the anterior axillary fold or other sites on the chest wall.[1,2,10] The presence of subareolar ductular tissue and fibrosis in breasts affected by gynaecomastia results in a firmer consistency than that of adipose tissue, enabling gynaecomastia to be distinguished from lipomastia.[4]

Proliferation of the mammary ductules in a fibroconnective tissue stroma is seen histologically in gynaecomastia.[6,11–13] Extensive ductular hyperplasia and proliferation occur early on in the development of gynaecomastia, whilst the stroma is loose and oedematous. Medical treatment is most effective at this early stage as stromal fibrosis becomes the predominant feature during the later stages of the condition[13] and this feature is unlikely to respond to medical therapy.

Even though most cases of gynaecomastia are benign and do not increase the risk of breast cancer, patients and physicians might be concerned by the presence of a breast mass, breast discomfort or changes in body image. Additionally, gynaecomastia is occasionally associated with serious underlying systemic or endocrine disease. Over the past 20 years, endocrine and genetic studies have expanded our understanding of gynaecomastia and have resulted in new therapies being suggested. In this Review, we discuss the latest advances in the pathophysiology, evaluation and management of this condition.

Pathogenesis

Gynaecomastia seems to primarily result from an imbalance of androgenic and estrogenic influences on breast tissue. Estrogens stimulate the proliferation of breast tissue, whereas androgens inhibit it; normal male breast tissue has receptors for both types of hormones. Hence, breast enlargement in a male individual (that is, gynaecomastia) occurs with an absolute or relative deficiency of androgens, deficient androgen action or an increase in levels of estrogens or estrogenic action (Box 1).[14–18] In this context, an absolute deficiency of androgens refers to serum or tissue concentrations of androgens below the normal range found in healthy young adult men, whereas an absolute estrogen excess refers to serum or tissue concentrations of estrogen above the normal range found in the same population. A relative androgen deficiency or relative estrogen excess refers to the situation in which both androgen and estrogen levels are within the normal range, but the ratio of androgen to estrogen is abnormal. Unfortunately, because of normal fluctuations in serum

Medical Service, Veterans Affairs Medical Center, 6900 Pecos Road, North Las Vegas, NV 89086, USA (**H.S.N.**). Department of Medicine, Endocrinology Division, Stony Brook University School of Medicine, HSC T15-060, Stony Brook, NY 11794-8154, USA (**H.E.C.**).

Correspondence to: H.E.C. harold.carlson@stonybrookmedicine.edu

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Key points

- Gynaecomastia is a common condition and is usually benign
- Gynaecomastia typically results from an (absolute or relative) deficiency of androgen action or excessive estrogen action in the breast tissue
- Gynaecomastia often resolves by itself or upon removal of the underlying cause (such as medication)
- Treatment is indicated in men with symptoms (particularly pain and tenderness in the breast) and involves the use of androgens or antiestrogens
- Surgery can be offered to selected patients when the condition does not resolve spontaneously or respond to medical treatment

concentrations of these hormones as well as varying normal ranges in different laboratories, it is not possible to specify such ratios numerically.

In addition to decreased serum levels of androgens, absent or defective androgen receptors lead to deficient androgen action in breast tissue and might result in gynaecomastia. In the past 10 years, modulation of the activity of the androgen receptor as a result of the number of CAG (glutamine codon) repeats in the gene that encodes it has been recognized as an important factor in the pathogenesis of gynaecomastia.[19] In spinobulbar muscular atrophy (previously known as Kennedy disease), expanded CAG trinucleotide repeats in exon 1 of the gene that encodes the androgen receptor decrease transcriptional activity of the androgen receptor, which leads to partial androgen insensitivity and gynaecomastia.[19] In Klinefelter syndrome, expanded CAG repeats in the gene that encodes the androgen receptor might be associated with an increased risk of gynaecomastia, shorter penile length in boys and other phenotypic features of the syndrome.[20] In the general male population, the number of CAG repeats in the gene encoding the androgen receptor might be associated with increased or decreased activation of this receptor by circulating androgens, and might explain why some men develop gynaecomastia even though they have normal circulating levels of androgens.

Increased peripheral (nontesticular) aromatization of androgens to estrogens might contribute to gynaecomastia in ageing individuals and in patients with diseases such as hyperthyroidism, cirrhosis and the aromatase excess syndrome (Figure 1).[21–23] Peripheral aromatization of androgens, primarily in adipose tissue, is the main source of estrogens in men.[24] Adiposity increases with ageing and some evidence suggests that aromatase expression in adipose tissue might increase as men age.[25] Increased levels of inflammatory cytokines have also been hypothesized to increase aromatase expression in adipose tissue with ageing and in certain illnesses.[26–31] Polymorphic variants in aromatase that result in increased enzymatic activity have been reported to be associated with an increased prevalence of gynaecomastia.[32]

In addition to systemic hormone levels, local factors in breast tissue also probably have an important role in gynaecomastia. Increased local production of estrogens, decreased local production of androgens, decreased inactivation of estrogens or changes in the number and/or activity of androgen or estrogen receptors[19,33] in local breast tissue might all contribute to the development of gynaecomastia.

Other hormones might also be involved in the development of gynaecomastia; however, their importance has not yet been well defined. Receptors for prolactin, progesterone, insulin-like growth factor (IGF) 1, IGF-2 and luteinizing hormone (LH) and/or human chorionic gonadotropin (hCG) have been found in male breast tissue.[34–36] Female mice with knockout of either the prolactin receptor or the progesterone receptor have normal breast development at puberty, but do not lactate.[37,38] Progesterone has an important role in lobuloalveolar differentiation in normal female mouse breast tissue, but its role in the male breast is unclear.[37,39] Knockout of the growth hormone receptor or the IGF-1 receptor (IGF-1R) in female mice leads to a failure of ductular growth, which is similar to the effects produced by knocking out the estrogen receptors.[40,41] Estrogen increases the expression of IGF-1R in breast cancer cells and might therefore enhance the action of IGF-1 in normal breast tissue.[42] Progesterone and IGF-1 might act synergistically to stimulate breast ductular growth and development.[43]

In a study of boys with pubertal gynaecomastia, levels of leptin were raised.[44] In addition, the presence of certain polymorphisms in the gene that encodes the leptin receptor has been reported to predispose boys to the development of pubertal gynaecomastia.[33] Leptin might contribute to the development of gynaecomastia by increasing the expression of aromatase in adipose and/or breast tissue[45,46] (leading to increased levels of estrogens and an altered androgen to estrogen ratio). Alternatively, leptin might exert its effect by increasing the sensitivity of breast epithelial cells to estrogens via increased expression of estrogen receptors[47] or by direct stimulation of the breast epithelial cells.[44,48] In the MCF-7 cell line (breast cancer cells derived from a female patient), leptin activates estrogen receptor α in the absence of estrogen.[45] Nevertheless, boys with mutations in the genes that encode leptin or the leptin receptor have secondary hypogonadism and might therefore still develop gynaecomastia.[49–51]

Even though hyperprolactinaemia probably causes gynaecomastia primarily by suppression of gonadotropin-releasing hormone (GnRH) secretion, which results in hypogonadotropic hypogonadism, prolactin receptors are also expressed in breast tissue.[34] In cultured breast cancer cells, receptors for prolactin and sex steroids (especially the progesterone receptor) might be coexpressed and could crossregulate each other's expression;[35,52] acute treatment with prolactin increased the levels of progesterone receptor while decreasing the number of androgen receptors. A similar effect in men with hyperprolactinaemia could stimulate the growth of breast tissue by increasing the expression of progesterone receptor and decreasing the expression of androgen receptor.

In addition, breast tissue can produce and respond to numerous growth factors, including transforming growth factors (TGF-α and TGF-β), epidermal growth factor, platelet-derived growth factor, tumour necrosis

Box 1 | Pathogenesis of gynaecomastia

Absolute excess of estrogens

Administration of exogenous estrogens

- Intentional therapeutic use: therapeutic estrogens used in prostate cancer treatment
- Unintentional exposure to estrogens: occupational;[62,63] dietary (phytoestrogens): alcoholic beverages;[72] dietary supplements (dong quai,[74] supplements contaminated with estrogens[75]); transdermal absorption: antibalding lotions,[60] partner's vaginal lubricants[59]

Increased endogenous estrogen production

- Increased secretion of estrogens: from the testis (Leydig cell tumours,[83,84] Sertoli cell tumours,[78,81,82] stimulation of normal Leydig cells by human chorionic gonadotropin or luteinizing hormone); from the adrenal glands (feminizing adrenocortical tumours[89,90])
- Increased aromatization of androgens to estrogens: aromatase excess syndrome;[153] drugs (for example, androgens and ethanol):[100,101] alcoholic cirrhosis of the liver;[96] ageing; obesity; hyperthyroidism;[129] human chorionic gonadotropin-secreting tumours;[84] dietary supplements (contaminated with androgens)

Absolute deficiency of androgens (hypogonadism)

Primary hypogonadism

- Klinefelter syndrome
- Testicular trauma
- Cancer chemotherapeutic agents
- Testicular radiation
- Infections (for example, mumps orchitis, leprosy)
- Disorders in enzymes of testosterone biosynthesis: drugs (for example, ketoconazole, spironolactone, metronidazole); inherited defects in androgen biosynthesis

Secondary hypogonadism (pituitary and/or hypothalamic damage from disease, surgery or radiation)

Altered serum androgen to estrogen ratio

- Puberty
- Ageing
- Refeeding gynaecomastia
- Renal failure and dialysis
- Hepatic cirrhosis
- Hyperthyroidism
- Drugs (for example, ketoconazole)

Decreased androgen action

Drugs (for example, spironolactone, bicalutamide, cimetidine)

Androgen receptor defects

- Absent or defective androgen receptors (complete and partial androgen insensitivity syndromes)
- Expansion of CAG repeats in the androgen receptor gene (such as in spinobulbar muscular atrophy)[19]

factor, prostaglandins and IGF-1.[53,54] These factors might act in an autocrine or paracrine manner to contribute to the pathogenesis of gynaecomastia.

Finally, a note of caution should be added to this somewhat speculative discussion of the role of hormones and growth factors in the pathogenesis of gynaecomastia. Much of the data on the regulation of breast growth have come from studies of female breast tissue, particularly breast cancer (including breast cancer cell lines isolated from female patients). It is quite possible that sex differences exist in the way these processes operate, as well as differences between normal versus malignant breast cells and primary cell cultures versus immortalized cell lines. For example, expression of aromatase mRNA is increased by leptin and estradiol in cultured male human abdominal preadipocytes, but is decreased in preadipocytes obtained from women.[46] Similarly, cortisol inhibits aromatase activity in cultured abdominal subcutaneous stromal cells obtained from men, but stimulates aromatase activity in similar cells derived from women.[55]

Causes of gynaecomastia

Gynaecomastia can occur as a result of a relative or absolute excess of estrogens or a relative or absolute decrease in the levels of androgens or their action. An absolute excess of estrogens (that is, serum levels of estrogens above the normal range) might be attributable to administration of exogenous estrogens or to endogenous overproduction of estrogens in male individuals. Estrogens directly stimulate the proliferation of breast tissue. In addition, they suppress LH secretion, which causes hypogonadotropic hypogonadism with low serum levels of testosterone, thereby removing a major inhibitory influence on breast growth. Furthermore, estrogens increase serum levels of sex hormone-binding globulin (SHBG) by stimulating the production and glycosylation of SHBG, which leads to decreased levels of free testosterone that further amplify the androgen to estrogen imbalance and promote the development of gynaecomastia.

Exogenous administration of estrogens

Intentional (therapeutic) use of estrogens

Systemic estrogens are used therapeutically to initiate breast development in male-to-female transgender patients.[16,56] Male breast tissue is as sensitive to estrogens as breast tissue in women, and responds with breast enlargement to oral, transdermal or injectable estrogens.[56] Therapeutic estrogens are also used in men with prostate cancer and cause breast enlargement, breast pain (mastodynia) and tenderness.[57,58] Gynaecomastia in men with prostate cancer is discussed in detail later in this article.

Unintentional systemic exposure to estrogens

Unintentional systemic exposure to estrogens can occur transdermally, orally or possibly by inhalation. Gynaecomastia has been reported as a result of transdermal exposure to estrogens present in vaginal lubricants used during coitus,[59] and from skin creams and antibalding lotions[60] used by men.

Environmental exposure

Occupational gynaecomastia as a result of unintentional exposure to estrogens has been reported in barbers[60] and morticians[61] who were exposed to estrogens in hair lotions or embalming fluids and in factory workers involved in making oral contraceptives.[62] Even children of these factory workers have been reported to have enlarged breasts following exposure to estrogens via contact with their father's clothes.[63]

Exposure to endocrine disrupting chemicals in the environment has been hypothesized to be associated with premature thelarche in girls, and possibly early puberty in boys.[64–69] The role of endocrine disrupting chemicals in gynaecomastia is unclear, although one study has reported an association between gynaecomastia and lead exposure.[70]

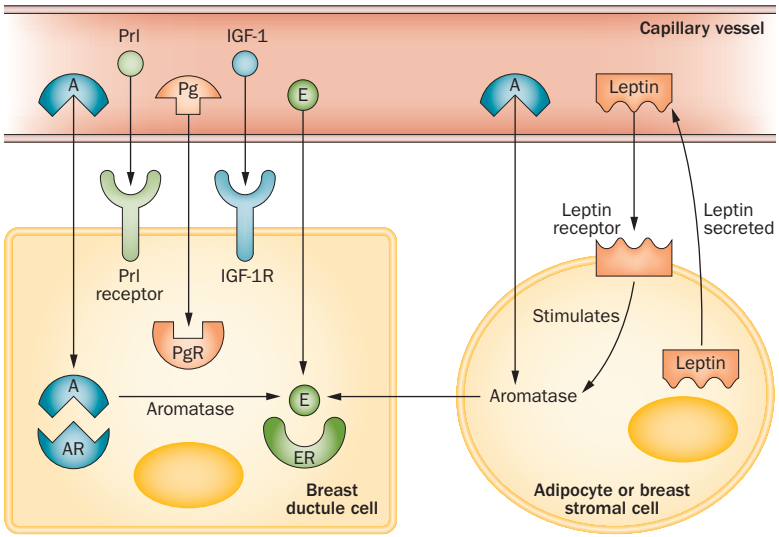

Figure 1 | The action of different hormones on breast tissue. Abbreviations: A, androgen; AR, androgen receptor; E, estrogen; ER, estrogen receptor; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; LR, leptin receptor; Pg, progesterone; PgR, progesterone receptor; Prl, prolactin.

Dietary ingestion of estrogens might occur as a result of endogenous estrogens in foods (such as plants containing phytoestrogens) or ingestion of meat or milk from estrogen-treated cows[66,71] and certain beers and wines.[72] Dietary estrogen intake is unlikely to be an important factor in most men with gynaecomastia unless large amounts of these foods are consumed.[73] Dietary supplements (such as dong quai[74] and others contaminated with estrogens[75]) have been reported to cause gynaecomastia. As a result of frequent under-reporting of the use of dietary supplements, physicians should always specifically ask the patient about their use in the evaluation of any man with new-onset gynaecomastia.[76,77]

Endogenous overproduction of estrogens

Excess testicular production of estrogens

Excessive testicular production of estrogens occurs in patients with Leydig cell tumours, Sertoli cell tumours or hCG-secreting tumours of the testes. These tumours cause rapid-onset gynaecomastia with breast pain and tenderness; serum levels of estrogen are clearly raised in these patients. Many of these tumours might be very small and not palpable. Testicular ultrasonography to rule out a testicular estrogen-secreting tumour is therefore imperative in any male patient with recent onset of symptomatic gynaecomastia with raised serum levels of estrogen.

Most Sertoli cell tumours do not generally have any endocrine effects, but some can secrete estrogens and thereby cause gynaecomastia. For example, large-cell calcifying Sertoli cell tumours occur in boys with Carney complex and secrete estrogen.[78–80] Sertoli cell tumours with excess aromatase activity and estrogen overproduction are also seen in patients with Peutz–Jeghers syndrome.[81,82]

Testicular Leydig cell tumours directly secrete estradiol.[83,84] These tumours are usually benign and are seen in young and middle-aged men, but can occur at any age. Most tumours are small and are often not palpable; testicular ultrasonography should be performed if these tumours are suspected in patients with gynaecomastia. Surgery (orchiectomy) will cure gynaecomastia in these patients.

hCG has considerable structural homology with LH, and directly stimulates LH or hCG receptors on normal Leydig cells in the testes to preferentially increase estradiol secretion.[85] In addition, many tumours that secrete hCG take up steroid precursors such as dehydroepiandrosterone sulphate from the circulation and aromatize them to active estrogens.[86] LH or hCG receptors have also been found in male breast tissue,[36] but their role in the pathogenesis of gynaecomastia is unclear.

Unlike Leydig cell tumours, testicular hCG-secreting tumours are usually aggressive and malignant, and often present with rapidly progressive gynaecomastia.[87] In addition to testicular germ cell tumours, many other tumours might also secrete hCG. In male patients with new-onset gynaecomastia, rapidly progressive breast enlargement, pain or tenderness with raised serum levels of hCG, an aggressive workup to localize these malignant tumours should be performed. Testicular ultrasonography might help localize the tumour, but CT scans of the chest, abdomen and pelvis should be obtained to rule out metastatic disease. Patients with metastases should be referred to an expert oncologist for evaluation. A small number of boys with Klinefelter syndrome can develop extragonadal hCG-secreting germ cell tumours in the mediastinum, which causes rapidly progressive gynaecomastia.[88] Serum levels of hCG are a useful tumour marker in these patients.

Feminizing adrenocortical tumours

As with hCG-secreting germ cell tumours (and unlike the benign Leydig cell tumours), feminizing adrenocortical tumours are aggressive, malignant tumours that can cause gynaecomastia.[89,90] These cancers can secrete estrogens directly and often secrete massive amounts of weak adrenal androgens (such as dehydroepiandrosterone sulphate and androstenedione), which are then aromatized to estrogens in other tissues.[91]

These aggressive, poorly differentiated tumours are often large (half of patients present with a palpable abdominal mass), and are easily seen on abdominal CT scans. The peak incidence is in young and middle-aged men.[89,92] Prognosis is very poor, as most patients have extensive local invasion and/or distant metastases at the time of diagnosis. Surgery is the initial treatment; palliative therapy with mitotane or other chemotherapy or radiation therapy could be attempted by an expert oncologist. Successful treatment of the tumour might relieve the gynaecomastia. Alternatively, tamoxifen or raloxifene could be given to block the effects of estrogens on the breast, although there are no reports of this treatment to date.[89,92]

Increased peripheral aromatization

Familial aromatase excess syndrome leads to markedly increased production of estrogen in peripheral tissues as a result of increased aromatase expression.[93,94] Increased

aromatase expression is discussed in detail in the section on hereditary gynaecomastia later in the article.

Increases in peripheral aromatization of androgens to estrogens that leads to gynaecomastia could be the result of three factors: firstly, an increased amount of adipose tissue, the primary site of aromatization (as in obesity and ageing); secondly, increased aromatase expression in a tumour (as in a fibrolamellar hepatocellular carcinoma);[95] thirdly, increased availability of substrate for aromatization (such as in liver cirrhosis, with increased levels of androstenedione,[96] or adrenal feminizing tumours [increased production of weak androgens],[89,90] or androgen use or abuse [gynaecomastia in men receiving testosterone therapy, or in bodybuilders using testosterone]).

Gynaecomastia in anabolic steroid abuse

Androgens have long been used as performance-enhancing drugs by athletes and by bodybuilders to 'bulk up'. Aromatizable androgens such as testosterone or androstenedione are converted to estradiol or estrone and hence cause gynaecomastia (nonaromatizable androgens such as dihydrotestosterone and many synthetic androgens with a modified A ring do not usually cause gynaecomastia).[97,98] Interestingly, a nonaromatizable androgen, dihydrotestosterone, has been reported to stimulate the expression of aromatase mRNA (but not aromatase enzymatic activity) in preadipocytes isolated from male patients;[46] additional investigation of this issue is needed.

Androgen abuse should be suspected in men with gynaecomastia who are athletes, bodybuilders or weight lifters, who are well virilised and yet have small testes and low sperm counts, raised levels of hematocrit and low levels of SHBG.[76,98–101] Men who abuse anabolic steroids have a normal or raised urinary testosterone to epitestosterone ratio (>4:1, which is consistent with doping according to the World Anti-Doping Agency) and a low ^{13}C to ^{12}C ratio in urinary testosterone.[98] These tests are performed by the anti-doping agencies but are not available clinically.

Many dietary supplements can contain potent androgens that are not declared on the drug label. In an international study performed in 2001–2002, of the 634 nonhormonal nutritional supplements purchased in 13 countries, 15% were contaminated with anabolic steroids (generally prohormones).[77] It is worrisome that apparently harmless sounding products such as vitamin C, multivitamin and magnesium supplements were found to be contaminated with potent androgens such as stanozolol and metandienone. Increasingly, more 'designer' type steroids are being used in nutritional supplements. Some of these could theoretically be aromatized to estrogens, and might possibly cause gynaecomastia.

Absolute deficiency in serum androgens

Primary hypogonadism

Testicular damage from any cause (such as radiation, chemotherapy, infections, drugs, trauma or genetic defects) can impair androgen production and result in gynaecomastia. Testosterone therapy in men with primary hypogonadism of short duration usually leads to a decrease in breast tenderness and at least some shrinkage of the gynaecomastia.[102]

Low testosterone levels in patients with primary hypogonadism are associated with decreased androgen-mediated inhibition of breast growth.[15–18] The low serum levels of testosterone also lead to a compensatory rise in serum levels of LH, which stimulates the remaining Leydig cells in the testes to preferentially secrete estradiol. Peripheral conversion of adrenal androgens leads to an additional relative or absolute excess of estrogens. Increased estrogen levels lead to increased SHBG levels, which results in a further reduction in free testosterone levels (as testosterone is more tightly bound to SHBG than estradiol), and even greater decreases in the free androgen to free estrogen ratio.

Klinefelter syndrome is the most common chromosomal anomaly in men that leads to primary hypogonadism, gynaecomastia and infertility.[103,104] This syndrome is also the only known cause of gynaecomastia that carries an increased risk of breast cancer; men with Klinefelter syndrome are at a 20-fold greater risk of developing breast cancer than men without the syndrome.[105] We suggest self-examination of the breast tissue should be performed regularly by men with Klinefelter syndrome; however, the role of screening mammograms is unclear. Clinically, men with Klinefelter syndrome have a eunuchoidal body habitus, small firm testes, severely decreased sperm counts and infertility. The phenotype in Klinefelter syndrome seems to be modified by the number of CAG repeats in the gene that encodes the androgen receptor: the longer the repeat (which reduces the activity of the androgen receptor), the more clinically significant are the gynaecomastia, taller stature, lower BMD and shorter penile length.[20,106]

Approximately 1% of boys with Klinefelter syndrome can develop malignant extragonadal hCG-secreting germ cell tumours in the mediastinum. These tumours cause rapidly progressive gynaecomastia (in contrast with the gradual onset, slowly progressive gynaecomastia typical of Klinefelter syndrome).[88]

Secondary hypogonadism

Damage to the hypothalamus or pituitary from any cause (such as radiation, chemotherapy, infections, drugs, trauma or genetic defects) can lead to impaired androgen production and gynaecomastia. As a result of the inhibitory effect of androgens on breast tissue,[15–18] testosterone therapy in men with secondary hypogonadism could lessen breast tenderness and decrease the size of the gynaecomastia.

Relative estrogen excess

Pubertal gynaecomastia

Gynaecomastia during puberty is extremely common: up to 70% of all boys might have breast enlargement during puberty, with the incidence peaking in early to mid-puberty.[3] Breast enlargement can be asymmetric and/or tender, provoking anxiety for the patient or the family.

The gynaecomastia resolves spontaneously in a year or two in most boys, but ~20% of men still have palpable breast tissue at age 20 years, which is probably the result of persistent pubertal gynaecomastia.[3,5,7,107] During early puberty, the testes might secrete more estradiol than they do after puberty, resulting in a relative estrogen excess.[108,109] The marked increase in IGF-1 levels during puberty could also contribute to the development of pubertal gynaecomastia.[110,111] As previously discussed, serum levels of leptin have also been found to be raised in boys with pubertal gynaecomastia,[44] and polymorphisms in the genes encoding the leptin receptor or estrogen receptor β might be associated with an increased incidence of breast enlargement during puberty.[33] Finally, use of anabolic steroids by many boys (to enhance athletic performance or for body building) might contribute to breast enlargement.[98,112]

Gynaecomastia of ageing

Gynaecomastia is very common in older men (>50 years of age), approaching a prevalence of ~70% in those who are hospitalized.[8] The age-related decline in serum levels of testosterone,[113] increasing adiposity (with resultant raised serum levels of leptin and increased aromatization of androgens to estrogens)[25] and rising serum levels of SHBG with a consequent decrease in free testosterone levels, all contribute to the relative estrogen excess in ageing men.

Older men might have multiple medical problems (including obesity, type 2 diabetes mellitus and sleep apnoea) and often take numerous medications, all of which can contribute to hypogonadism and the development of gynaecomastia.[8,100,101]

Refeeding gynaecomastia

Starvation and substantial weight loss cause secondary hypogonadism; return to a normal diet can lead to a 'second puberty' with a transient imbalance in the secretion of estrogen and androgen, which causes transient gynaecomastia.[114,115] This effect was first seen after World War II when many prisoners of war developed tender gynaecomastia after resuming a normal diet.[116] This type of gynaecomastia can also be seen in refugees[117] and impoverished groups (such as Haitian immigrants to the USA in the early 1980s)[118] and during therapeutic dieting.[116] Just as in puberty, 'refeeding' gynaecomastia is transient and resolves spontaneously in most men within 1–2 years of resuming a normal diet.[116–118] The role of leptin in refeeding gynaecomastia has not yet been explored.

Renal failure and dialysis

Gynaecomastia often develops in men with chronic kidney disease after they start dialysis.[119] Dialysis-associated gynaecomastia is probably attributable to 'refeeding' of the chronically ill and malnourished patients with renal failure when they are able to expand their diet and their appetite improves after initiating dialysis treatment. This effect is usually transient, and resolves spontaneously within 1–2 years of starting dialysis.[119]

Men with chronic kidney disease frequently have low levels of testosterone that are related to both decreased production and increased metabolism of testosterone.[120] In addition, raised serum levels of prolactin are often seen in patients with chronic kidney disease, as a result of decreased renal clearance and increased production of prolactin.[121–123] Metoclopramide and other medications frequently used in patients with chronic kidney disease might also raise prolactin levels.[121,123] As mentioned previously, hyperprolactinaemia can cause hypogonadism and androgen deficiency, and might alter androgen and progesterone receptors in the breast, thereby contributing to the development of gynaecomastia.

Cirrhosis

Men with alcoholic liver cirrhosis have increased serum levels of androstenedione (with resulting increased aromatization to estrone), raised levels of SHBG (with reduced free testosterone levels) and increased serum levels of progesterone, all of which might contribute to the development of gynaecomastia.[124,125] Additionally, alcohol has direct toxic effects on gonadal function;[126] hypogonadism and testicular atrophy are common in men with alcoholic liver cirrhosis.[126] However, the prevalence of gynaecomastia might not be different in men with liver disease compared with age-matched hospitalized control individuals according to one report;[96] this observation requires confirmation.

Hyperthyroidism

Up to 40% of men with hyperthyroidism might develop transient gynaecomastia that resolves with the restoration of euthyroidism.[127,128] In patients with hyperthyroidism, increased serum levels of SHBG and progesterone, as well as increased aromatization of androgens to estrogens, might contribute to gynaecomastia.[129–132]

Prostate cancer

As prostate cancer is an androgen-dependent neoplasm, androgen deprivation, androgen receptor blockade or estrogen administration are commonly used strategies to treat this disease, all of which might result in gynaecomastia.[133] The risk of gynaecomastia is higher in men treated with systemic estrogens (>70%) than in those treated with nonsteroidal antiandrogens such as flutamide or bicalutamide (up to 50%) or GnRH analogues (up to 25%); the risk is lowest in men who undergo bilateral orchiectomy (10%).[58]

HIV

Breast enlargement in men with HIV might be attributable to true gynaecomastia or to lipomastia (either as a result of generalized adiposity or of HIV-related lipodystrophy). Infections in the breast tissue, Kaposi sarcoma, Paget disease of the breast and lymphoma might also cause breast enlargement or pain in men with HIV.[134,135]

Gynaecomastia in men with HIV is often multifactorial;[135,136] multiple comorbidities and confounding factors are frequently present. For example, many men with HIV have concomitant liver disease, and some use

Table 1 | Hereditary gynaecomastia

Disease	Gene	Mode of inheritance	Mechanism of gynaecomastia	Clinical features
Aromatase excess syndrome	*CYP19A1*	Autosomal dominant	Increased aromatase	Prepubertal or peripubertal gynaecomastia, central hypogonadism, advanced bone age (in boys) but short stature in adult male patients
Peutz–Jeghers syndrome	*STK11*, *LKB1*	Autosomal dominant	Increased aromatase	Prepubertal gynaecomastia, gastrointestinal hamartomatous polyps and mucocutaneous pigmentation
Carney complex	*PRKAR1A*	Autosomal dominant	Increased aromatase	Prepubertal or peripubertal gynaecomastia, LCCSCT, blue nevi, pigmented lentigines, myxomas, Cushing syndrome (PPNAD), thyroid nodules/cancer
Androgen insensitivity syndrome	*AR*	X-linked	Androgen receptor defect	Gynaecomastia, variable female phenotype, elevated serum testosterone levels
Spinobulbar muscular atrophy	Expanded CAG repeats in *AR*	X-linked	Androgen receptor defect	Gynaecomastia
Kallman syndrome	*KAL1*	X-linked	Secondary hypogonadism	Anosmia, hypogonadotropic hypogonadism
Congenital hypogonadotropic hypogonadism	*FGFR1*, *KISS1* (see text for others)	Autosomal dominant, autosomal recessive	Secondary hypogonadism	Normosmia, hypogonadotropic hypogonadism
CAH due to *CYP17A1* defect	*CYP17A1*	Autosomal recessive	Primary hypogonadism	Cortisol deficiency, hypertension, hypogonadism
CAH due to 3βHSD defect	*HSD3B2*	Autosomal recessive	Primary hypogonadism	Cortisol and aldosterone deficiency, hypogonadism
CAH due to P450 oxidoreductase deficiency	*POR*	Autosomal recessive	Primary hypogonadism	Cortisol deficiency, hypogonadism

Abbreviations: 3βHSD, 3-β hydroxysteroid dehydrogenase; CAH, congenital adrenal hyperplasia; LCCSCT, large-cell calcifying Sertoli cell tumours; PPNAD, primary pigmented nodular adrenocortical disease.

illicit drugs such as heroin and marijuana, which might cause gynaecomastia.[134–137] Nearly all of the medications used to treat HIV as part of highly active antiretroviral therapy have been associated with gynaecomastia, including nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors.[135] Some men with HIV, and many of those receiving highly active antiretroviral therapy, have secondary hypogonadism.[137] In addition, men with HIV might have obesity or sleep apnoea, and might be receiving opiates or ketoconazole, which could all contribute to gynaecomastia.[134,135] Finally, effective antiretroviral therapy is associated with increases in the levels of circulating cytokines,[138] which could stimulate aromatase[26,31] and thereby increase the circulating levels of estrogens and lead to gynaecomastia.

Hereditary gynaecomastia

Familial gynaecomastia can result from genetic defects that lead to any of the following three situations (Table 1): firstly, decreased androgen production attributable to primary hypogonadism (caused by defects in the steroid biosynthetic pathway involving 17-hydroxylase and 3-β-hydroxysteroid dehydrogenase) or secondary hypogonadism (seen in patients with Kallmann syndrome or idiopathic hypogonadotropic hypogonadism); secondly, deficient androgen action due to mutations in the androgen receptor gene that result in absent or defective androgen receptors (that is, complete and partial androgen insensitivity syndromes) or expanded CAG repeats in the gene that encodes the androgen receptor (resulting in spinobulbar muscular atrophy);[19] thirdly, increased production of endogenous estrogen attributable to increased aromatase activity, which can result from familial aromatase excess syndrome, Peutz–Jeghers syndrome and Carney complex.

Defects in steroid biosynthesis

Defects of critical enzymes in the testosterone biosynthetic pathway lead to decreased testosterone production and might cause gynaecomastia. For example, patients with a *CYP17A1* (which encodes steroid 17-hydroxylase/17,20-lyase) defect (OMIM #202110) have a total lack of testosterone production; hence, genotypic male patients have female external genitalia (pseudohermaphroditism) and are often raised as female individuals.[139] Patients with this defect are usually first recognised at puberty when they fail to menstruate (as they lack female internal genitalia). As the same enzyme is also present in the adrenal cortex and is required for the production of cortisol precursors (17-hydroxyprogesterone), the *CYP17A1* defect leads to cortisol deficiency, increased adrenocorticotropic hormone levels, and a form of congenital adrenal hyperplasia with increased deoxycorticosterone levels and resultant hypertension.[140] Hence, genotypic male patients (and female patients) often present with hypertension and failure to enter puberty. Of note, a different disorder, cytochrome P450 oxidoreductase deficiency (OMIM #613571), can also present as an isolated 17,20-lyase deficiency.[141]

Box 2 | Mechanisms of drug-induced gynaecomastia

Increased serum levels of estrogens or estrogen-like activity
- Exposure to exogenous estrogens (intentional or unintentional)
- Increased aromatization of androgens to estrogens (androgens, ethanol abuse)
- Estrogen agonist activity (digitoxin[186])

Decreased serum testosterone levels
- Hypogonadotropic hypogonadism (caused by gonadotropin-releasing hormone agonists/antagonists and possibly HAART therapy for HIV)
- Hypergonadotropic hypogonadism (possible causes: destruction or inhibition of Leydig cells by chemotherapeutic/cytotoxic agents (for example, alkylating agents, vincristine, methotrexate, nitrosoureas, cisplatin, imatinib) or inhibition of testosterone or DHT biosynthesis by ketoconazole, metronidazole, high doses of spironolactone or finasteride and dutasteride[187]

Androgen receptor blockade
- Flutamide, bicalutamide, enzalutamide
- Cimetidine
- Marijuana
- Spironolactone

Increased serum prolactin levels
- Antipsychotic agents
- Metoclopramide
- Possibly calcium channel blockers

Possible refeeding gynaecomastia
- Isoniazid
- Digoxin
- Effective HAART therapy for HIV infection

Unknown
- HAART
- Human growth hormone
- Amiodarone
- Calcium channel blockers (for example, nifedipine, verapamil, diltiazem)
- Amphetamines
- Diazepam
- Antidepressants (tricyclics and selective serotonin reuptake inhibitors)

Abbreviations: DHT, dihydrotestosterone; HAART, highly active antiretroviral therapy.
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In patients with a defect in 3-β-hydroxysteroid dehydrogenase (OMIM #613890),[142] synthesis of all steroid hormones is impaired. As a result of an inability to generate testosterone, male patients present with varying degrees of undervirilization and genital development and might develop gynaecomastia. As cortisol and aldosterone cannot be synthesized, most patients present early in life with symptoms of cortisol and aldosterone deficiency. Diagnosis can be established on the basis of an adrenocorticotropic hormone stimulation test by measurement of levels of the Δ5 steroid 17-hydroxypregnenolone[143] in serum.

Hypogonadotropic hypogonadism

Congenital hypogonadotropic hypogonadism (OMIM #147950)[144] is often sporadic but can be familial, with various patterns of inheritance (X-linked, autosomal dominant or autosomal recessive).[145] Patients with associated anosmia or hyposmia are considered to have Kallmann syndrome. In the past 20 years, several genes have been described that are associated with hypogonadotropic hypogonadism, including *KAL1* (the classic X-linked form of Kallmann syndrome), *FGFR1* (which encodes fibroblast growth factor receptor 1 and is also called *KAL2*), *KISS1* (which encodes kisspeptin), *KISS1R* (which encodes the kisspeptin receptor), *GnRH1* (which encodes the GnRH1 receptor), *PROK2* (which encodes prokineticin 2 and is also called *KAL4*), and *PROKR2* (which encodes prokineticin 2 receptor and is also called *KAL3*).[146–148] Other inherited causes of secondary hypogonadism in men include mutations in the genes that encode leptin or the leptin receptor, mutations in the β subunit of LH or follicle-stimulating hormone (FSH), and Prader–Willi syndrome.[50,51,149] The presence of testosterone deficiency in all of these syndromes might lead to gynaecomastia.[150]

Boys and men with hypogonadotropic hypogonadism can be treated with testosterone to promote virilization, or with hCG (or LH) and human menopausal gonadotropin (or FSH) or pulsatile GnRH through a mini-pump (not FDA approved) for induction of spermatogenesis.[145]

Androgen insensitivity syndromes

Defective androgen receptors lead to androgen insensitivity syndrome,[151] which is an X-linked disorder. In patients with complete androgen insensitivity syndrome (also known as testicular feminization syndrome), absent or nonfunctional androgen receptors lead to a complete lack of androgen action and an external female phenotype despite raised serum levels of testosterone. Patients have a total lack of pubic and axillary hair, and have breast development (that is, gynaecomastia) as a result of conversion of testosterone to estrogens in peripheral tissues. In patients with partial androgen insensitivity syndrome, less severe defects in the androgen receptor lead to variable androgen action with a variable clinical phenotype (variable degree of virilization, might present as a patient with ambiguous genitalia at birth, or a hirsute female individual with clitoromegaly, or an undervirilized male individual with variable gynaecomastia).

In patients with spinobulbar muscular atrophy, expanded CAG trinucleotide repeats in exon 1 of the gene that encodes the androgen receptor result in decreased transcriptional activity of the androgen receptor, which leads to partial androgen insensitivity and gynaecomastia.[19]

Aromatase excess syndrome (OMIM #139300) is a rare autosomal dominant disorder that is the result of overexpression of the aromatase gene (*CYP19A1*, located on chromosome 15q21.2). This syndrome is characterized by prepubertal or peripubertal gynaecomastia, central hypogonadism, advanced bone age (in boys), but short stature in male adults due to premature closure of long bone epiphyses.[23,152] Female patients are usually asymptomatic, although macromastia and short stature have occasionally been reported.[94,153] Aromatase excess syndrome is caused by duplications involving *CYP19A1*, and also by rearrangements with neighbouring genes that place promoters of other genes (expressed in multiple other tissues) in front of the coding region of *CYP19A1*, which leads to constitutive expression of this chimeric gene in multiple organs.[93] However, these mechanisms do not explain all cases of aromatase excess syndrome, and other, currently unknown, defects remain to be elucidated.

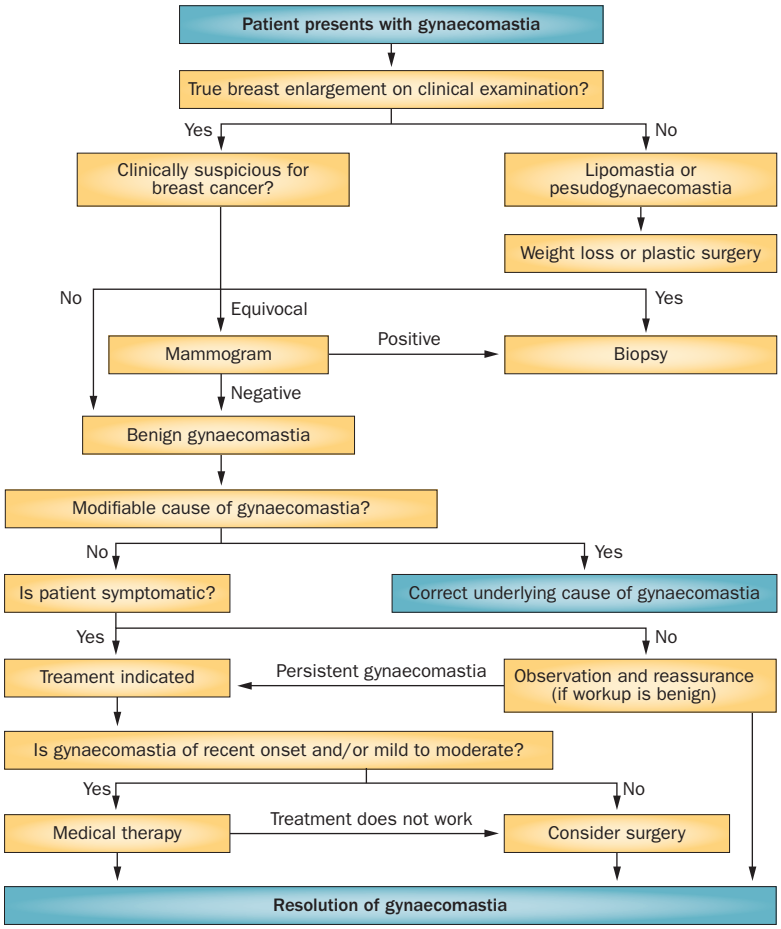

Figure 2 | Suggested algorithm for the evaluation and treatment of gynaecomastia. Permission obtained from Elsevier Inc. © Narula, H. S. & Carlson, H. E. *Endocrinol. Metab. Clin. North Am.* **36**, 497–519 (2007).

Peutz–Jeghers syndrome is an autosomal dominant disorder characterized by intestinal hamartomatous polyps and mucocutaneous pigmentation. Prepubertal boys with Peutz–Jeghers syndrome present with advanced bone age and gynaecomastia, which are associated with Sertoli cell lesions.[81,82] Inactivating mutations in *STK11* are seen in patients with Peutz–Jeghers syndrome. *STK11* encodes serine/threonine-protein kinase STK11 (also known as liver kinase B1), a tumour suppressor that interacts with p53 protein and AMPK to inhibit aromatase expression via a multi-step pathway. In Peutz–Jeghers syndrome, loss of heterozygosity of *STK11* leads to increased aromatase expression in the Sertoli cells of the testes and in breast tissue, resulting in increased aromatization of androgens to estrogens and, consequently, gynaecomastia.[154] The Sertoli cell lesions are mostly benign, and treatment with aromatase inhibitors is beneficial for the gynaecomastia.[81,155]

Carney complex is an autosomal dominant disorder characterized by abnormalities in skin pigmentation (such as blue nevi and pigmented lentigines), endocrine tumours or overactivity of endocrine organs and non-endocrine tumours (for example, atrial, breast and skin myxomas and schwannomas).[79,80] Large-cell calcifying Sertoli cell tumours are seen in all adult men with Carney complex and might be present in a third of all boys who present with Carney complex (in the first decade of life).[79,80] These tumours are often multicentric and bilateral; except for one reported case of malignancy, these tumours are benign.[79,80] Increased aromatase expression in these tumours frequently causes gynaecomastia in prepubertal or pubertal boys.[79,80] Large-cell calcifying Sertoli cell tumours can obstruct seminiferous tubules, resulting in oligospermia and infertility.[78–80] Other endocrine tumours seen in Carney complex include Cushing syndrome due to primary pigmented nodular adrenal disease (with an increase in urinary cortisol secretion on dexamethasone administration during a Liddle test), acromegaly (due to a growth-hormone-secreting pituitary tumour), and nodules and cancer of the thyroid gland.

Point mutations or deletions of the tumour suppressor gene *PRKAR1A* can be detected in up to 70% of patients with Carney complex.[156] As in Peutz–Jeghers syndrome, treatment with aromatase inhibitors might decrease estrogen production and shrink the enlarged breasts of patients with Carney complex.[155]

Drug-induced gynaecomastia

Prescription and recreational drugs could be an important, potentially reversible cause of new-onset gynaecomastia.[4,157] Hence, a detailed history of all prescription and recreational drugs should be obtained from all patients with gynaecomastia. While some drugs (for example, estrogens and antiandrogens such as spironolactone) are well known to cause gynaecomastia, the evidence linking other drugs to gynaecomastia is anecdotal and might be merely coincidental.[100,101] Box 2 outlines the possible mechanism(s) of drug-induced gynaecomastia.

Breast cancer in men

Breast cancer is uncommon in men. With the notable exception of Klinefelter syndrome, gynaecomastia does not increase the risk of breast cancer.[158] Men with an inherited *BRCA2* mutation have a 100-fold increased risk of developing breast cancer.[159–161] Men with *CHEK2* and *PTEN* mutations also have an increased risk of breast cancer,[159,162] although not as elevated as with *BRCA2* mutations. Men with a family history of breast cancer in female relatives have a 2.5-fold increased risk of breast cancer.[158]

A rapidly growing breast mass that is hard, eccentrically located, asymmetric, with ulceration, retraction or deformity of the nipple, or fixed to the skin or underlying structures is worrisome for malignancy and should be promptly biopsied to diagnose (or exclude) cancer.[158,163] Men with breast cancer seem to have a similar prognosis to women with the same stage of the disease at the time of diagnosis.[159] Similarly to women with breast cancer, treatment can include surgery, radiation or chemotherapy.

Gynaecomastia is far more common in men than breast cancer; a man's lifetime risk of developing breast cancer is 0.1%, whereas around 70% of men experience gynaecomastia at some stage during their lives.[5,8] Breast biopsy should not be routinely performed in all men with breast enlargement;[165,166] it should only be performed if worrisome clinical features, as outlined above (Figure 2), are present.

Box 3 | Diagnostic evaluation of gynaecomastia

History
- Related to breast enlargement: duration of breast enlargement; presence of breast pain or tenderness; worrisome symptoms of breast cancer (bleeding, ulceration)
- Systemic illness: recent abnormal weight loss or weight gain; liver disease; chronic renal failure or dialysis; symptoms of hyperthyroidism; changes in libido, sexual functioning, or other symptoms of hypogonadism; medication use; recreational drug use (for example, marijuana, heroin); occupational, dietary or accidental exposure to estrogen

Physical examination
- Degree of virilization: voice, facial and body hair, muscular development
- Breast examination: true gynaecomastia versus pseudogynaecomastia; signs suspicious for breast cancer; breast tenderness
- Examination of genitalia: testicular size; testicular masses; phallus size and development; pubic hair development
- Stigmata of chronic liver or kidney disease
- Examination of thyroid and signs of hyperthyroidism

Laboratory evaluation
- Kidney function tests (blood urea nitrogen and creatinine)
- Liver function tests
- Thyroid function tests (thyroid-stimulating hormone with or without free thyroxine)
- Serum levels of testosterone (total and bioavailable), LH, FSH, prolactin
- Serum levels of estrogens (estradiol)
- Tumour markers for germ cell neoplasms (β-hCG)
- Levels of adrenal androgens (serum DHEA-sulphate or urinary 17-ketosteroids)

Radiologic examination*
- Mammogram
- Breast ultrasonography

*Radiologic examination is not recommended for routine evaluation of gynaecomastia (see text for detailed discussion). Abbreviations: DHEA, dehydroepiandrosterone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

Diagnostic evaluation of gynaecomastia

The goal of clinical evaluation of a male patient with gynaecomastia is to differentiate gynaecomastia from fatty breasts (lipomastia or pseudo-gynaecomastia), rule out breast cancer, and determine the possible cause of the gynaecomastia.[2]

After the diagnostic evaluation has been completed, about 25% of patients are found to have idiopathic gynaecomastia, and another 25% have acute or persistent pubertal gynaecomastia.[157] Drugs might account for 25%, primary hypogonadism for 8%, cirrhosis or malnutrition for 10%, testicular tumours for 3%, secondary hypogonadism for 2%, hyperthyroidism for 1% and renal disease for 1% of cases.[4,157]

To determine the underlying cause of gynaecomastia, a detailed history should be obtained regarding the onset and duration of the breast enlargement, associated breast pain or sensitivity, systemic symptoms (of hypogonadism and/or thyroid, liver or kidney disease) and weight gain or loss in the previous few months (Box 3). Medication use, including recreational drugs and over-the-counter supplements, must be specifically ascertained, as drugs might be the cause of up to 25% of all cases of gynaecomastia.[4,157] The investigating clinician should also look for possible signs of occupational or accidental exposure to estrogens. Of note, no underlying cause is ever identified in many men with gynaecomastia.

Physical examination

True glandular breast tissue (gynaecomastia) can be distinguished from fatty breasts by comparing subareolar tissue with adjacent subcutaneous fat (such as that in the anterior axillary fold). Gynaecomastia is felt as symmetric, firm glandular tissue under the nipple. Galactorrhoea (milky breast discharge) is uncommon in men with gynaecomastia but could be seen in some men with prolactinomas with considerably raised serum levels of prolactin.[164]

On general physical examination, the degree of virilization and secondary sexual development should be carefully noted in addition to examining the thyroid and looking for signs of chronic kidney or liver disease. Careful breast examination should be performed to rule out fatty breasts and breast cancer, and to assess for breast tenderness. On examination of the genitalia, the amount and distribution of pubic hair, phallus size and development and testicular size should be noted and testicular masses should be looked for.

Other tests

Laboratory testing might not be necessary in a boy with pubertal gynaecomastia or a man with long-standing asymptomatic gynaecomastia incidentally noted on physical examination, if history and physical examination are otherwise normal.[1,2,165] Obtaining a morning serum level of testosterone (preferably bioavailable) and LH, determination of FSH and prolactin levels, and routine liver, kidney and thyroid function tests are reasonable if dysfunction is suspected clinically. In men with recent-onset breast enlargement or with breast pain or tenderness, serum levels of estrogens and hCG should be measured to rule out estrogen-secreting tumours, hCG-secreting tumours or germ cell tumours.

Routine mammograms and breast ultrasonography are not recommended in the evaluation of gynaecomastia as breast cancer is very uncommon in men; these imaging studies should only be performed if breast cancer is clinically suspected.[165–167] In selected patients, a testicular ultrasonograph or abdominal CT scan could be performed if a testicular or adrenal mass are suspected as a result of history, physical examination or laboratory testing.

Management of gynaecomastia

In a male patient with lipomastia (also known as pseudogynaecomastia or fatty breasts), weight loss should be recommended. If this strategy fails or the patient is bothered by the lipomastia, plastic surgery is a reasonable option. No treatment is necessary in asymptomatic boys with pubertal gynaecomastia or in men with long-standing asymptomatic gynaecomastia.[1,2,165] In male patients with new-onset or progressive gynaecomastia, or with associated breast pain or tenderness, further evaluation to determine the probable cause of gynaecomastia should be undertaken, as detailed in the previous section. If a reversible cause of gynaecomastia is suspected (for example, medications, recreational drugs, occupational exposure to estrogens or hyperthyroidism), the medication

or source of gynaecomastia should be withdrawn or avoided, respectively, if at all possible. An improvement in gynaecomastia is then usually seen within a few weeks. If gynaecomastia does not improve after several months, or the exposure cannot be safely withdrawn, medical therapy for gynaecomastia can be tried.[1,2]

Treatment is indicated in any male patient with symptomatic gynaecomastia, with breast pain, sensitivity or tenderness, or for cosmetic reasons (as breast enlargement can cause considerable social anxiety in many young men).[1,2]

Medical therapy

As gynaecomastia is usually the result of an imbalance of androgens and estrogens, medical therapy for gynaecomastia is based on decreasing estrogen production (using aromatase inhibitors), or action (with antiestrogens) and/or increasing the levels of androgens (with the use of systemic or topical androgens).[1,2] However, well-designed prospective studies on the medical treatment of gynaecomastia are lacking, and empiric therapy is often used.

Medical therapy of gynaecomastia will probably be most effective if used in patients with recent (within 2 years) onset of breast enlargement. After 2 years, the stroma becomes mostly fibrotic, making medical therapy largely ineffective in men with long-standing gynaecomastia.[4,6]

Antiestrogens such as tamoxifen and raloxifene block estrogen action in breast tissue but might have an estrogen agonist action at other tissues (hence the term selective estrogen receptor modulators). Tamoxifen has often been used as a first-line medication (off-label use), and has been effective in many cases of gynaecomastia, including men with prostate cancer[58,168–170] and boys with persistent pubertal gynaecomastia.[171–173] Tamoxifen doses of 10–20 mg daily used for 3–9 months have shown efficacy of up to 90% for the resolution of gynaecomastia.[58,168–173] If the gynaecomastia recurs, a second course of treatment might be used, after ruling out any reversible and/or secondary cause of the recurrent breast enlargement. Raloxifene is effective in treating pubertal gynaecomastia in up to 90% of boys.[172] Clomiphene improved gynaecomastia in only 42% of boys with pubertal gynaecomastia, and is less effective than either tamoxifen or raloxifene.[174] In men with prostate cancer about to start antiandrogen therapy, tamoxifen prophylaxis might be considered to prevent the development of gynaecomastia.[170,175,176]

Aromatase inhibitors (such as anastrozole and testolactone) have been less effective than antiestrogens in treating pubertal gynaecomastia[177,178] and in men with prostate cancer who develop gynaecomastia.[168] They might have an important role in selected patients with increased aromatization of androgens to estrogens, as in familial aromatase excess syndrome, patients with Peutz–Jeghers syndrome or Carney complex with aromatase excess due to testicular tumours, or in men who develop gynaecomastia while they are receiving testosterone (or possibly hCG) therapy.[81,155]

Testosterone therapy usually improves gynaecomastia in men with hypogonadism.[179] However, as testosterone is aromatizable to estrogens, testosterone therapy can cause gynaecomastia in some men (especially in men with borderline testosterone levels and in men with obesity, adipose tissue being the primary site of aromatization).[179] Nonaromatizable androgens such as dihydrotestosterone have been used topically in the treatment of gynaecomastia; percutaneous dihydrotestosterone was effective in men with HIV-associated gynaecomastia[180] and in men with persistent idiopathic gynecomastia.[181] However, dihydrotestosterone gel is unavailable in the USA.

Radiation treatment of the breast tissue has been tried in the past for the treatment of pubertal gynaecomastia; owing to the increased risk of breast cancer related to radiation exposure, this strategy is not recommended. However, prophylactic breast radiation has been successfully used in older men (mostly >50 years of age) with prostate cancer to prevent or decrease new-onset gynaecomastia or breast pain and tenderness after starting antiandrogen therapy,[182] but it is less effective than tamoxifen therapy.[169,176]

Surgery for gynaecomastia

In men with long-standing, symptomatic gynaecomastia, medical therapy will probably be ineffective, and surgery can be considered. Surgery might also be considered if a patient does not respond to medical therapy, is unable to tolerate it or declines treatment, or if the patient prefers surgery for cosmetic reasons or wants immediate correction of gynaecomastia. Surgery could involve suction lipectomy or removal of glandular breast tissue through a periareolar incision.[183–185] A comprehensive workup should be performed before surgery to rule out any underlying cause of gynaecomastia and to prevent possible recurrence after surgery.

Conclusions

Gynaecomastia is a common and usually benign condition, but could rarely be associated with serious underlying systemic or hormonal disease. A careful history and physical examination with limited laboratory testing are usually an adequate workup for most patients; radiological tests are rarely helpful. Treatment of underlying disorders, withdrawal of drugs that might cause gynaecomastia, medical therapy and surgery could be used in selected patients who are symptomatic or have recent-onset gynaecomastia. Further research could clarify the interactions between sex steroids, drugs and nonsteroidal hormones in the pathogenesis of gynaecomastia, and might eventually lead to additional treatments for the condition.

Review criteria

We searched PubMed and Google Scholar for all relevant articles using the search terms “gynaecomastia” and “gynecomastia”. The search was not limited by publication date. In addition, a manual search of references from selected reports was also performed. All article types were considered (original studies, reviews, editorials). Articles in English were studied in full, but only the abstracts were considered for studies written in languages other than English.

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Author contributions

H.S.N. researched data for the article, contributed to discussion of the content and wrote the article. H.E.C. researched data for the article, contributed to discussion of the content and reviewed/edited the manuscript before submission.