Investigation of gynaecomastia in men

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Case scenarios are used in this section to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

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Case scenario

Clinton is a 76-year-old Caucasian man with a history of hyperaldosteronism. He has come to see you, his GP, because of tenderness in both of his nipples. Clinton's other past medical history includes type 2 diabetes mellitus, obstructive sleep apnoea, gastro-oesophageal reflux disease, fatty liver disease and obesity. Three months ago, he was diagnosed with bilateral idiopathic primary hyperaldosteronism confirmed on a saline suppression test and adrenal vein sampling. He was commenced on spironolactone to manage his hypertension and hypokalaemia.

Clinton is taking metformin, omeprazole, perindopril, metoprolol, aspirin and rosuvastatin in addition to spironolactone. He has no allergies. He is a lifelong nonsmoker and drinks three standard drinks per night, five nights a week. On examination, Clinton's blood pressure is 130/80 mmHg and pulse rate is 90 beats per minute. His weight is 115 kg, height 1.68 m and body mass index (BMI) 40.7 kg/m^2. Breast examination reveals symmetrical breast fullness bilaterally. There is no redness or skin changes on visual examination. On palpation, there are no breast masses or lymphadenopathy. Behind each areola there is a palpable firm and tender, mobile, 1 cm diameter, rubbery-feeling ridge.

What is gynaecomastia?

Gynaecomastia is a proliferation of glandular tissue under the areola. The glandular tissue proliferation usually occurs because of an imbalance between oestrogenic and androgenic hormones. Other hormones such as prolactin, thyroxine, cortisol, human chorionic gonadotrophin and leptin have also been implicated.[1] Hyperprolactinaemia itself is rarely a cause of gynaecomastia, as up to 20% of men with elevated prolactin levels report galactorrhoea alone (without gynaecomastia).[2]

On examination, gynaecomastia appears as firm tissue beneath the areola. It is usually symmetrical, mobile and tender on palpation in the early proliferative phases. Due to the systemic pathophysiology of gynaecomastia, it is commonly bilateral rather than unilateral.

The histological changes seen in men with gynaecomastia are similar to the glandular structures and development seen in pubertal females. Initially there is ductal epithelial hyperplasia, which undergoes extensive branching and proliferation. The surrounding breast stroma also increases and proliferates with increased adipose tissue, connective tissue and fibroblast activity. During this rapid proliferation stage, tenderness is usually present. After about 12 months, the ductal and breast tissue proliferation reduce, and a process of fibrosis occurs reducing the number of ductal glands and increasing the amount of stromal and fibrotic tissue. The physical appearance of gynaecomastia is more difficult to reverse once the tenderness has settled and this fibrotic process has begun.

How common is gynaecomastia?

Reports of the prevalence of gynaecomastia in men are variable. A cross-sectional population study of 214 hospitalised men aged 27 to 92 years reported an overall prevalence of 65%, with most patients (72%) being between the age of 50 and 69 years.[3] Higher rates of gynaecomastia in men were associated with a higher BMI.[3] Another retrospective study that reviewed CT scans undertaken at a radiology department found a prevalence of 25.6%.[4] Most cases involved bilateral gynaecomastia, with only one instance of unilateral disease reported.

Table 1. Pathophysiological mechanisms of gynaecomastia

Pathophysiological mechanism	Examples
Increased oestrogen activity	• Increased production of oestrogen • Exogenous oestrogen exposure or use of oestrogenic mimic drugs • Familial or sporadic aromatase excess syndrome
Changes to serum concentration of free sex steroid hormones due to changes in sex hormone binding globulin levels	• Higher aromatisation of androgens to oestrogen – Ageing – Obesity – Hyperthyroidism – Liver disease – Refeeding after starvation
Decreased androgen activity	• Primary testicular failure • Secondary testicular failure • Miscellaneous diseases – Chronic renal failure (Leydig cell dysfunction) – Chronic liver failure – HIV (presumably due to fat redistribution from older generation antiretroviral therapy, which causes lipodystrophy)
Changes in the target cell response to androgens and oestrogens	Decreased androgen action (e.g. androgen receptor defects)

Causes of gynaecomastia[1,5]

- Physiological (25%)
  - Newborns
  - Puberty
  - Advanced age
- Medications/iatrogenic/substance abuse (10–25%) (see Table 2)
- Chronic organ disease (8% cirrhosis; 1% renal failure)
  - Chronic liver disease
  - Chronic kidney disease
- Male hypogonadism (8% primary; 2% secondary)
  - Primary or secondary hypogonadism due to reduced production of androgens (e.g. Klinefelter's syndrome)
- Tumours (3%)
  - Testicular cancers
  - Leydig cell tumours
  - Adrenal adenomas or carcinomas
  - Ectopic or paraneoplastic secretion of human chorionic gonadotrophin
  - Hyperprolactinaemia due to pituitary suppression of gonadotrophins, which causes secondary hypogonadism in men
- Hyperthyroidism (1%)
  - Multinodular goitre or adenoma
  - Graves' disease
- Rare causes (2%)
  - Enzymatic defects of testosterone production
  - Androgen-insensitivity syndromes
  - True hermaphroditism
  - Aromatase excess syndrome
  - Familial prepubertal gynaecomastia
- Idiopathic (25%)

What causes gynaecomastia?

Gynaecomastia may have many different causes, and may be physiological, pathological or idiopathic (Box).[1,5] As many as 25% of cases are thought to be idiopathic.[1] Physiological gynaecomastia occurs in neonates, pubertal boys and older men.[6] This trimodal distribution reflects periods in which the oestrogen to testosterone ratio is slightly elevated. Newborn babies have high maternal transplacental exposure of oestrogen which usually resolves four weeks postpartum. In adolescent boys, a second peak occurs due to increased oestrogen concentrations and delayed testosterone production. Increased tissue sensitivity to oestrogen also occurs at this stage.[7] Up to two-thirds of adolescent boys may develop gynaecomastia at some point during puberty, although this resolves spontaneously by the end of puberty in the vast majority and does not require medical or surgical intervention.[8] In men over 50 years of age, declining serum testosterone levels with age may contribute to the rise in gynaecomastia.

The pathophysiology underpinning gynaecomastia may be due to a single cause or be multifactorial. The pathophysiological mechanisms can be generally categorised into increased oestrogenic activity, changes to serum concentration of free sex steroid hormones due to changes in sex hormone binding globulin (SHBG) levels, decreased androgen activity or changes in target cell responses to androgens or oestrogens (Table 1).[5]

What are some red flags?

A primary breast malignancy is an important differential diagnosis. Gynaecomastia must be differentiated from a breast lump due to cancer. This may be possible on clinical examination but if suspicions remain a mammogram and/or breast ultrasound should be ordered. There is a high prevalence of gynaecomastia in men with Klinefelter's syndrome and it should be noted that these patients have a 20- to 50-fold increased risk of breast cancer. However, in most cases of gynaecomastia, clinical history and examination will indicate a benign cause and imaging is not required.

Testicular malignancies may cause gynaecomastia through secretion of beta-human chorionic gonadotrophin (beta-hCG). Other tumour markers for testicular malignancy are alpha-fetoprotein and lactate dehydrogenase, which do not drive gynaecomastia but are mentioned due to their potential association with beta-hCG secretion. High androstenedione levels may be associated with an adrenal carcinoma.[7] Other malignancies to consider include those causing ectopic beta-hCG production. Leydig cell tumours of the testis are usually benign and present with gynaecomastia caused by excessive oestrogen secretion. Abuse of hormones for performance enhancement or dependency behaviours are also causes to consider.

Rarer causes include enzymatic defects in testosterone production, androgen insensitivity syndromes or aromatase excess

Table 2. Medications associated with gynaecomastia[9-11]

Medication*	Approximate time of onset
Strong evidence	
Spironolactone	Variable
Cimetidine	4 to 12 months
Ketoconazole	1 to 32 months
Human growth hormone	1 week to 6 months
Oestrogen	Variable
Human chorionic gonadotrophin	Variable
Antiandrogens (e.g. flutamide, bicalutamide, cyproterone acetate)	3 to 5 months
Gonadotrophin-releasing hormone analogues (e.g. goserelin, leuprorelin)	Variable
5-alpha-reductase inhibitors (e.g. dutasteride, finasteride)	2.5 years
Fair evidence	
Risperidone	3 months to 3 years
Verapamil	1 to 18 months
Nifedipine	6 to 30 months
Omeprazole	2.9 months
HIV medications	Variable
Alkylating agents	2 to 9 months
Anabolic steroids	1 month to 5 years
Alcohol	10 days to years
Opioids (e.g. heroin, methadone)	Variable
Others	
Marijuana	Variable (lower quality evidence, but known clinical association)

* This list is not exhaustive as gynaecomastia is a rare adverse effect that has been associated with a wide range of medications.

syndrome, which are usually diagnosed at a younger age due to presentations with ambiguous genitalia or deficient virilisation.

Which medications are associated with iatrogenic gynaecomastia in men?

Medications cause 10 to 25% of all cases of gynaecomastia in men.[9] Medications may cause an imbalance of the oestrogen to testosterone ratio through several means including antiandrogenic effects, increased oestrogenic effects, increased SHBG concentrations, increased serum prolactin levels and other unknown mechanisms. A list of medications causing gynaecomastia is provided in Table 2.[9-11]

Spironolactone is a potent mineralocorticoid receptor blocker, but also displays marked affinity for progesterone and androgen receptors. The Randomized Aldactone Evaluation Study reported that 10% of men who were treated with spironolactone 50 mg daily reported gynaecomastia or breast pain.[12] Eplerenone is a selective mineralocorticoid receptor blocker with 100-fold lower affinity for progesterone and androgen receptors than nonselective mineralocorticoid receptor blockers.[13] Its use in hyperaldosteronism in Australia is limited by higher cost and non-PBS reimbursement status for this specific purpose.

Clinton continues on spironolactone to manage his primary hyperaldosteronism as there are no other nonsurgical options. Eplerenone is not considered due to cost. Clinton switches from omeprazole to pantoprazole to exclude medications that may be contributing to his gynaecomastia.

Are there any lifestyle changes that would reduce Clinton's gynaecomastia?

The cause of Clinton's gynaecomastia is most likely multifactorial. The use of spironolactone to treat his primary hyperaldosteronism is a significant contributing cause, but there are also other factors such as his obesity, excessive alcohol consumption and the potential of undiagnosed liver cirrhosis in the context of fatty liver disease.

Lipomastia or pseudogynaecomastia is a condition that is commonly mistaken for gynaecomastia. Lipomastia occurs when excessive body weight predisposes to fat accumulation in the breast tissues, giving the appearance of pseudogynaecomastia. This contrasts with the proliferation of glandular tissue under the areola in true gynaecomastia. However, obesity increases the aromatisation of androgens to oestrogens by adipose tissue, which in turn increases the oestrogen to testosterone ratio to potentially cause gynaecomastia. Engaging with healthy dietary habits, physical activity and aiming for weight loss reduces the aromatisation and may lead to improvements of gynaecomastia.

End stage liver disease and cirrhosis increase the production of androstenedione from the zona reticularis layer of the adrenal cortex. Liver cirrhosis increases the conversion of androstenedione to oestrogen, which also further disrupts the oestrogen to testosterone ratio in the systemic circulation. Clinton should be educated to reduce his alcohol consumption as it increases aromatisation of androgens and hence increases the concentration of oestrogen relative to testosterone.

Due to his type 2 diabetes, Clinton may be at risk of diabetic nephropathy. In patients on maintenance haemodialysis, gynaecomastia has a reported prevalence of 50%.[14] Patients with end-stage kidney disease have elevated plasma luteinising hormone (LH) and follicle stimulating hormone (FSH) levels, in the context of low testosterone levels.[15] Reduced renal clearance of LH and persistently poor testicular testosterone production contribute to a high oestrogen to testosterone ratio, which predisposes a patient to gynaecomastia.

Furthermore, malnutrition is commonly seen in patients with chronic kidney disease and in those on dialysis, which further reduces systemic testosterone levels with relatively high oestrogen concentrations. A poor diet and prolonged starvation cause reduced gonadotrophin and testosterone levels, while the concentration of oestrogen is maintained by adrenal precursors such as androstenedione. Refeeding after starvation causes a sharp rise in FSH and LH concentrations, which increases androgens and oestrogens; the LH surge increases the aromatisation of testosterone to oestrogen.

Are there any over-the-counter medications or products that can cause gynaecomastia?

Tea tree oil, lavender oil and other plant-derived oils have been associated with gynaecomastia due to their weak oestrogenic properties.[16] These oils may also be found in skin care products or medications for insomnia that can be purchased over the counter. Other complementary or additive ingredients include Dong Quai and *Tribulus terrestris*.[17,18] Phyto-oestrogen exposure from soy products has been contentious in its role in causing gynaecomastia. In clinical trials, soy consumption of less than 300mg daily of isoflavones has not been associated with gynaecomastia.[19] However, in patients who consume commercially produced protein shakes or supplements, it is essential to review the ingredients for potential causes of gynaecomastia.

What pharmaceutical options are available?

Any primary underlying cause of gynaecomastia, such as hypogonadism, should be addressed, as testosterone replacement will alleviate symptoms. If gynaecomastia is caused by medication side effects, ceasing the offending medication may lead to regression of breast tissue.

Therapeutic options to manage gynaecomastia are only effective when the patient is most symptomatic, with tenderness and breast tissue swelling evident due to proliferation and hypertrophy of the glandular structures. Situations in which early pharmaceutical intervention may be indicated include breast pain, tenderness or significant psychological distress for the patient.

During the inflammatory phase, there may be some benefits of off-label use of selective oestrogen receptor modifiers (SERMs) such as tamoxifen 20mg daily for three months. There are limited studies using raloxifene. Partial benefit of gynaecomastia has been reported in 80% and complete regression in about 60% of patients taking SERMs.[20] Tamoxifen is generally well tolerated by men. In a review of tamoxifen use for gynaecomastia, the side-effect profile of the medication varied in men with prostate cancer, breast cancer, infertility and idiopathic gynaecomastia.[21] There were minimal side effects reported by men who used tamoxifen for infertility or idiopathic gynaecomastia. However, gastrointestinal side effects, such as constipation, diarrhoea, gastralgia and severe nausea, were commonly reported with use of tamoxifen by patients with advanced prostate cancer.[21]

Aromatase inhibitors (such as anastrozole) inhibit the aromatisation of androgens to oestrogens; however, studies have not shown significant efficacy in boys during puberty when compared with placebo.[22] After the inflammatory phase, the fibrotic phase occurs and symptoms of tenderness reduce. Once fibrotic tissue replaces inflammatory glandular tissue, the changes of gynaecomastia are generally pharmacologically irreversible.

A three-month trial of tamoxifen 20 mg daily had little effect in reducing Clinton's gynaecomastia. Clinton now has minimal breast pain and tenderness, but is still distressed by his physical appearance.

What other interventions would you consider for men with gynaecomastia?

After a 12-month history of gynaecomastia, most patients experience less pain and tenderness and enter the fibrotic stage. Fibrotic breast tissue can be managed definitively with surgical correction and excision.[23] In patients with prostate cancer who receive androgen deprivation therapy, prophylactic radiotherapy to breast buds to prevent the development of gynaecomastia has been reported.[24]

Clinton decides not to undergo surgical management of his gynaecomastia due to his anaesthetic risk. He continues spironolactone to manage his primary hyperaldosteronism. You organise counselling and clinical psychology review to provide support for his mental wellbeing.

Summary

Gynaecomastia represents a not uncommon but potentially distressing and embarrassing problem in boys and men. Many cases may be managed by reassurance and resolution with time, or by ceasing an offending medication. Other cases may require medical or even surgical intervention. It is important that GPs are aware of these issues and refer patients for specialist review where required. **ET**

References

A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

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