

Overview on Epidemiology, Causes and Management of Gynecomastia

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ABSTRACT

Background: Gynecomastia is characterized by the benign enlargement of male breast tissue, a condition witnessed across varied age brackets and influenced by several factors. While its global prevalence and causative factors have been comprehensively documented, there is a notable gap in understanding its specific implications within Saudi Arabia.

Objective: The study aims to provide a comprehensive review of the etiology, epidemiology, and management strategies of gynecomastia, emphasizing its manifestation in the context of Saudi Arabia.

Methodology: A comprehensive literature review was undertaken, sourcing articles and studies from established databases such as PubMed and Google Scholar, facilitated by targeted internet searches, with particular emphasis of Saudi Arabia studies

Results: Gynecomastia's incidence notably peaks during puberty and in the older demographic, with various medications, lifestyle choices, and environmental factors contributing to its onset. Within Saudi Arabia, a 15-year case series reflected gynecomastia as the predominant benign male breast lesion, constituting 54% of such cases. Another study pinpointed the prevalence of pubertal gynecomastia at 34% in Riyadh. In terms of treatment, hormonal therapies like tamoxifen and raloxifene, aromatase inhibitors, and certain androgens have been employed, albeit with varying degrees of efficacy. Surgical avenues such as liposuction and mastectomy present more conclusive solutions for the affected when pharmacotherapy is ineffective.

Conclusion: Gynecomastia is a significant condition with diverse influencing factors. In Saudi Arabia, despite limited data, gynecomastia emerges as a pressing health concern. There exist a range of medical and surgical interventions, ensuring a holistic approach to patient care and management.

Keyword: Gynecomastisa, Saudi Arabia, Epidemiology, Causes, Management.

Introduction

Gynecomastia, a condition characterized by the benign enlargement of male breast tissue, remains a topic of significant medical and social attention due to its implications on a patient's self-image and psychological health. This condition sees fluctuating

Prevalence across different age groups. It can manifest transiently in neonates owing to maternal estrogen influence, with reports indicating its occurrence in as many as 60-90% of newborns [1]. Similarly, hormonal changes during puberty trigger gynecomastia in about

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50-60% of adolescent boys, predominantly between ages 13 to 14[2]. Although it often resolves on its own in a year or two, it's a prominent concern during this delicate phase of life. The condition's prevalence also rises among older men, impacting 50-70% of those aged 50 to 69[3]. The etiology of gynecomastia primarily traces back to an imbalance between the activities of estrogens, which stimulate breast tissue growth, and androgens, which inhibit it. Several factors can precipitate this imbalance. Physiological shifts in hormonal levels during neonatal, puberty, and aging periods serve as typical examples [2]. Medications, including agents like spironolactone, cimetidine, specific antipsychotics, and some antiretroviral drugs, have been implicated in inducing gynecomastia [4]. Endocrine disorders such as hyperthyroidism, hypogonadism, and tumors producing elevated levels of hCG also contribute to its occurrence [5]. Diseases affecting hormone metabolism and excretion, like liver disorders (both acute and chronic) and renal failure, are associated with gynecomastia [6]. In many older men, however, the exact cause remains unknown after rigorous medical investigations, leading to the classification of such cases as idiopathic [7]. In terms of management, the strategy usually hinges on its root cause, severity, and patient considerations. Many cases, especially those arising during puberty, tend to resolve spontaneously, suggesting observation might be suitable for some [2]. Medical management might involve drugs like tamoxifen and raloxifene. These selective estrogen receptor modulators have shown efficacy in reducing breast size in gynecomastia patients [8].

Pathophysiology of Gynecomastia

Gynecomastia arises from the intricate interplay of hormonal dynamics, predominantly between estrogens, which stimulate breast tissue, and androgens, which inhibit breast tissue. At the cellular level, when estrogen binds to its receptors in male breast tissue, it leads to ductal epithelial proliferation and augments connective tissue content of the breast. On the other hand, androgens, like testosterone, hinder these estrogenic actions by obstructing the growth of the breast epithelial cells [9]. The tissue response to this imbalance is further modulated by the local expression of enzymes such as aromatase, which converts testosterone to estrogen, and 5-alpha reductase, which converts testosterone to its more potent derivative, dihydrotestosterone. An increase in the activity of aromatase in the male breast can enhance local estrogen production, thereby promoting

gynecomastia. Concurrently, a decrease in 5-alpha reductase activity can lead to reduced local concentrations of dihydrotestosterone, an inhibitor of breast tissue growth, further tipping the balance in favor of tissue proliferation [5]. The consequent changes in the male breast tissue due to these hormonal imbalances are characterized by ductal epithelial hyperplasia, an increase in ductal length and diameter, stromal edema, increased vascularity, and collagen deposition. Over time, this proliferative phase, which is potentially reversible, can progress to a fibrous phase where there is an irreversible increase in dense connective tissue, leading to a firmer and more fibrotic breast mass [2]. While the initial stages of gynecomastia are often associated with tenderness, the fibrotic stages are typically asymptomatic apart from the palpable enlargement. A clear understanding of this pathophysiology is essential for appropriate clinical management and for setting therapeutic expectations.

Causes

Gynecomastia can be attributed to a myriad of causes that range from physiological changes to pathological conditions and exposure to certain medications and substances. Understanding these causes provides a foundation for both its management and the development of future treatment options.

Physiological Causes:

- Neonatal Period: A significant proportion of newborn male's exhibit transient breast enlargement. This is primarily due to the transplacental transfer of maternal estrogens. Fortunately, this neonatal gynecomastia typically resolves within a few weeks after birth [1].
- Puberty: The hormonal flux that characterizes puberty can lead to a temporary imbalance between estrogen and testosterone levels. This imbalance can result in gynecomastia, affecting up to 60% of adolescent boys. The condition usually resolves spontaneously within one to two years [2].
- Aging: Older men, especially those between ages 50 and 80, can experience gynecomastia due to a natural decline in testosterone production. With age, there is also an increase in adipose tissue, which can convert testosterone into estrogen, further promoting breast tissue growth [3].

Pathological Causes:

- Hypogonadism: Conditions such as Klinefelter syndrome or pituitary insufficiency can lead to reduced testosterone production, which in turn can cause gynecomastia [10].

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- Tumors: Tumors of the testes, adrenal glands, or pituitary can produce hormones that alter the male estrogen-testosterone balance, resulting in gynecomastia [5].

- Liver Disease: Cirrhosis or liver failure can lead to an altered estrogen-androgen metabolism, thereby leading to gynecomastia [11].

- Renal Failure: Chronic kidney disease can alter hormone levels, which might result in gynecomastia.

- Thyroid Diseases: Hyperthyroidism, a condition where the thyroid gland produces excessive thyroid hormone, can lead to gynecomastia due to its impact on the hormonal milieu [12].

Medication-Induced Causes:

- Several medications have been associated with gynecomastia. These include anti-androgens used to treat prostate enlargement or cancer, some antiretroviral drugs, anti-anxiety medications, certain antibiotics, and medications for heart conditions such as digoxin and calcium channel blockers [13].

- Chemotherapy for cancer can sometimes cause gynecomastia, as can drugs that influence the endocrine system like corticosteroids [7].

Substance Use: Consumption of alcohol, especially in excessive amounts, can decrease testosterone levels and increase estrogen levels, leading to gynecomastia. Additionally, substances such as marijuana, heroin, methadone, and amphetamines have been linked to gynecomastia [4].

Other Causes: Conditions like malnutrition or starvation can cause testosterone levels to drop, which can lead to gynecomastia once normal nutrition resumes. A heightened estrogenic state can also be induced by exposure to exogenous estrogens from occupational, environmental, or other sources [14]. Understanding the underlying cause of gynecomastia is essential for its appropriate management. Early diagnosis can prevent unnecessary distress for the patient and guide the healthcare provider in determining the most effective treatment strategy.

Epidemiology of Gynecomastia

Gynecomastia, the benign enlargement of male breast tissue, is a common condition that has been extensively studied. Understanding its epidemiology helps shed light on its prevalence, influencing factors, and distribution across various age groups and populations. Age-related Prevalence: Gynecomastia frequently occurs during puberty, with a peak incidence at around 14 years of age. It's estimated that up to 70% of adolescents will experience some form of the condition, although it often resolves on its own within one to two years [1]. In older adults, especially

men aged 50 to 69, the prevalence is estimated to be as high as 65%, with the increase in age-associated factors such as a decline in testosterone and an increase in adipose tissue playing significant roles [15]. U.S. data indicates that 36% of young adult males and 57% of senior males experience this condition in various degrees of severity. Hence, it's prevalent among approximately one-third of adult males and half of the elderly male population. During puberty, 30-60% of boys might experience gynecomastia, but it typically subsides on its own. Only 8% of these boys will still have the condition after three years. Gynecomastia manifests bilaterally in 30-50% of these cases, meaning it can also occur on just one side. In individuals with Klinefelter syndrome, about 80% present with gynecomastia [16-18]. Factors Influencing Prevalence: Various factors can influence the prevalence of gynecomastia. Medications, especially those that affect the endocrine system, are known culprits. For example, antiandrogens used in the treatment of prostate enlargement and cancer, certain antiretroviral drugs, and even some antibiotics and anti-ulcer medications have been associated with gynecomastia [4]. Lifestyle and environmental factors, such as alcohol consumption, exposure to estrogens, and the use of recreational drugs like marijuana, can also play a role [7]. The number of individuals showing symptoms of gynecomastia is considerably less. In a study examining 214 hospitalized men aged between 27 and 92, 65% were found to have gynecomastia, characterized by a nodule size exceeding 2 cm. Yet, none exhibited any symptoms. Differences in prevalence results across various studies are due to differing definitions based on palpable breast tissue size and distinctions in study populations, such as age and whether they're from primary care or specialized clinics [2, 19].

Data from Saudi Arabia: There is not many studies that focused on prevalence of gynecomastia in Saudi Arabia, however there are number of studies which we can use to give us hint about the situation of this condition in the country. In a case series study by Jamal A. A. (2001). Aimed to evaluate the profile and patterns of male and female breast diseases in Saudi Arabia over a period of 15 years, between 1984 and 2000. Out of 1084 examined breast lesions, benign lesions in females accounted for 57% of all lesions, with fibroadenoma being the most common at 47%. Female malignant lesions constituted 32.5% of all lesions, predominantly characterized by ductal carcinoma at 88%. For males, 87% of the lesions were benign, with gynecomastia being the most common,

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representing 54% of all male breast lesions. However, carcinomas in males made up 3% of all breast carcinomas. The study highlights the predominance of benign conditions like fibroadenoma in females and gynecomastia in males, while also emphasizing the significance of ductal carcinoma in the evaluated population [20]. Another study by Al Jurayyan, N. A. M. (2012). Delved into the pattern of endocrine disorders in children seen at the Paediatric Endocrine Clinic of King Khalid University Hospital in Riyadh, Saudi Arabia, from 1989 to 2009. Amongst the numerous endocrine disorders observed, gynecomastia was notably prevalent in pubertal boys, accounting for six patients. In these cases, gynecomastia was determined to be physiological. Interestingly, one 8-year-old boy diagnosed with gynecomastia was found to have an oestrogen-secreting adrenocortical adenoma, linking the tumor to the development of the condition in this particular case [21]. In a study conducted by Shirah, et al. (2016), they retrospectively analyzed the surgical outcomes of 74 male patients diagnosed and treated for gynecomastia in their hospital. The study found that the prevalence of gynecomastia among male patients at their hospital was 0.17%. Interestingly, 5 of these patients (6.76%) had an incidental finding of ductal carcinoma in situ (DCIS) in their histopathology specimens. The study emphasizes the significance of thorough histopathological examination of resected gynecomastia tissue in all patients, regardless of age, due to the potential for malignant variants [22]. Al Alwan, I., et al. (2013) conducted a cross-sectional study of 542 healthy male school children and adolescents in Riyadh, Saudi Arabia, the prevalence of pubertal gynecomastia was determined to be 34%, peaking at age 14. Participants with gynecomastia were typically older, had lower gonad stages, and exhibited increased anthropometric measures like height, weight, and BMI. They also had elevated levels of lipids, including triglycerides, HDL, and LDL. Notably, testosterone and estradiol levels were significantly higher in those with gynecomastia. The study identified BMI, HDL cholesterol, and gonad stage (especially Stage III with an odds ratio of 6.40) as the primary factors associated with the development of pubertal gynecomastia in this population [23].

Medical Management of Gynecomastia: Gynecomastia is the enlargement of the male breast tissue, often caused by an imbalance between estrogen and androgens. While many cases can resolve spontaneously, certain persistent or distressing instances necessitate medical intervention.

1. **Hormonal Treatment:** Tamoxifen, a selective estrogen receptor modulator, has demonstrated efficacy in managing gynecomastia. In randomized controlled trials, tamoxifen has been effective in reducing breast glandular tissue and associated pain, especially in pubertal males [24]. Another selective estrogen receptor modulator, raloxifene, has shown similar efficacy but is primarily used for osteoporosis [25]. While these agents have demonstrated efficacy, it's worth noting that their use in gynecomastia remains off-label.

2. **Aromatase Inhibitors:** Anastrozole and letrozole, both aromatase inhibitors, have seen use in gynecomastia, particularly when induced by therapies for prostate cancer. They function by inhibiting the conversion of androgens to estrogens. However, some studies suggest these might be less effective than tamoxifen, especially in cases of pubertal gynecomastia [26].

3. **Androgens:** Danazol, a synthetic derivative of testosterone, works by inhibiting the pituitary output of LH and FSH, which in turn decreases testosterone and its conversion to estradiol. Historically, it's been utilized for gynecomastia. However, due to side effects like weight gain and liver function alterations, it has become a less preferred option [27].

4. **Treatment of Underlying Causes:** For gynecomastia induced by specific medications, cessation or switching to an alternative can often reverse the condition. In instances where gynecomastia is a result of hyperthyroidism, thyroid hormone replacement therapy can be beneficial. For cases stemming from liver cirrhosis, liver transplantation, albeit a more radical solution, can be curative [2]. It is worth noting that Medical management might not be universally effective. Often, it's more suitable for gynecomastia that's painful or of recent onset rather than cases with a significant fibrotic component or those seeking care for purely cosmetic concerns [28]. Treatment duration can vary, ranging from a few months to longer. Continuous monitoring during therapy is essential to assess efficacy and identify any potential side effects. Once therapeutic goals are achieved, a gradual tapering of the medication is recommended to mitigate recurrence [3].

Surgical Management of Gynecomastia: In situations where medical management is ineffective or not optimal, surgical intervention becomes the preferred course of action.

1. **Liposuction:** Liposuction is the primary method for cases dominated by fatty tissue rather than glandular enlargement [29]. Through tiny incisions, excess fat is

aspirated, thereby reducing breast size. The technique has evolved, and now ultrasonic or laser-assisted liposuction can help in breaking down the fat more effectively [30].

2. Mastectomy: For patients with more significant glandular tissue or skin redundancy, a subcutaneous mastectomy might be necessary. This involves removal of the glandular tissue while preserving the skin envelope, nipple, and areola [31]. There are various techniques, ranging from semi-circular periareolar incisions to more extended inframammary incisions, depending on the grade of gynecomastia and the surgeon's preference [32].

3. Skin Reduction: In patients with severe gynecomastia, especially after massive weight loss, there's often excess skin that needs addressing. Techniques range from periareolar tightening (the "doughnut" approach) to more extensive procedures that might leave longer scars but offer better contouring [33].

4. Combination Therapy: In several cases, a combination of liposuction and direct tissue excision is optimal. This allows for the removal of both fatty and glandular components, giving the best aesthetic result [33].

5. Post-Operative Care: Compression garments are typically worn for several weeks post-surgery to reduce swelling and optimize skin retraction. Drains might be placed to prevent fluid accumulation, especially in more extensive dissections [34]. Regular follow-ups ensure proper healing and early identification of complications like seromas or hematoma. Surgery does carry the general risks of anesthesia, infection, and scarring. It's crucial to set realistic expectations with patients and discuss potential complications and the possibility of needing revision surgery.

Conclusion

The surgical management of gynecomastia offers a more definitive solution for patients seeking relief from the condition. The method chosen often depends on the grade of gynecomastia, the relative components of fat and glandular tissue, and patient-surgeon preference. As with any surgical intervention, a thorough consultation and understanding of the risks and benefits are essential.

Conflict of Interest

None

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