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Current state of knowledge about spironolactone-induded gynecomastia. Review 2024

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Abstract: Spironolactone, a potassium-sparing diuretic, acts as an aldosterone antagonist but also has anti-androgen properties, leading to increased estrogen levels in the body. It can

cause gynecomastia in men by blocking the production of androgens, preventing androgens from binding to specific receptors, and rising levels of both total and free estrogen. Numerous scientific articles and clinical cases have been analyzed and confirmed this statement. Evidence for gynecomastia with mineralocorticoid receptor antagonist usage was of high quality.Clinicians are advised to monitor patients taking these medications for developing gynecomastia and to consider this risk in the therapeutic decision-making process.

Aim of the study: The aim of this manuscript is to summarize the current knowledge on the impact of spironolactone therapy on the development of gynecomastia in patients.

Material and method :Electronic databases (e.g., PubMed, EMBASE, Google Scholar) were searched for articles published up to April 30, 2024. The search was conducted using keywords such as "spironolactone and gynecomastia," "antiandrogens AND gynecomastia," and "drug-induced gynecomastia." It is important to note that many of the studies referenced below also examined the impact of other medications on the development of gynecomastia, such as potassium canrenoate and 5-alpha-reductase inhibitors. However, this paper focuses solely on the effects of spironolactone.

Keywords: Gynecomastia, Spironolactone, Drug-induced gynecomastia, Breast enlargement, Estrogen, Androgen

Introduction

This paper focuses on spironolactone therapy and its associated adverse effects on gynecomastia. Due to the increasing number of patients using this medication and the importance of understanding its side effects, an extensive analysis of the available literature and online sources was conducted to investigate the mechanisms and incidence of drug-induced gynecomastia. This study discusses the findings from searches of numerous databases, scientific articles, and other available materials to present the current state of knowledge on this phenomenon, its pathophysiology, and clinical implications. The evidence indicating that the use of mineralocorticoid receptor antagonists is associated with gynecomastia was of high quality[1].

Spironolocatone and gynecomastia

The study will begin by presenting information on the two fundamental concepts of this study: what spironolactone and gynecomastia is.

Spironolactone is a widely used medication from the group of aldosterone antagonists, used in various cardiovascular diseases. Its main uses include the treatment of primary hypertension, primary hyperaldosteronism, and cirrhosis of the liver with accompanying ascites and edema. Spironolactone exerts its pharmacological action by antagonizing aldosterone at aldosterone-sensitive sodium/potassium channels located in the distal tubule of the nephron. This interaction results in increased level of water and sodium, while simultaneously reducing potassium excretion[2]. Regarding its secondary role as an antiandrogen, spironolactone is frequently utilized off-label to manage hyperandrogenism in women and the associated symptoms, such as acne vulgaris, hirsutism, and alopecia [3].

This medicine has numerous side effects of which the physician should be aware, including fluid and electrolyte imbalances such as hyperkalemia and hyponatremia, mild acidosis, and transient increases in serum urea nitrogen levels. Concurrent use of spironolactone with non-steroidal anti-inflammatory drugs (NSAIDs) exacerbates the risk of nephrotoxicity, while NSAIDs may also attenuate the hypotensive effects of diuretics. One of the common adverse effects is disorders of the reproductive system and breasts, including gynecomastia, which has been reported at a frequency of $\geq 1/100$ to $< 1/10$ [4].

What is Gynecomastia? Gynecomastia is not a disease in itself but is a symptom of a hormonal imbalance with multiple causes, endocrine, tumor, drug, or idiopathic when all other causes are eliminated[5].It is the most common breast disorder in men, typically characterized by symmetrical, generalized enlargement of the mammary glands. This condition results from the benign proliferation of glandular tissue, which includes ductal epithelial proliferation, periductal inflammatory cell infiltration, and an increase in subareolar adipose tissue[6]. Estrogens stimulate breast tissue growth, whereas androgen inhibits it[7]. The main pathophysiology of gynecomastia is an imbalance between the estrogens and androgens can be induced by various clinical conditions, such as elevated levels of free estradiol relative to free testosterone in plasma, locally increased aromatase activity, and excessive sensitivity of breast tissue to estrogens. Another mechanism leading to gynecomastia involves the blockade of androgen receptors by exogenous factors such as antiandrogen drugs, including spironolactone, which is the pathomechanism we will focus on in this paper[8]. Other conditions that should be considered as potential causes of gynecomastia include pathological cirrhosis/liver disease, starvation, male hypogonadism (primary testicular neoplasms like germ cell tumors, Leydig cell tumors, sex-cord tumors, hyperthyroidism or secondary like renal failure and dialysis feminizing adrenocortical tumors[9]. Drugs can be associated with gynecomastia, some more than others. According to some sources, drug-induced gynecomastia accounts for about 20%–25% of all new cases in adults [10]. It is also worth mentioning that gynecomastia can be accompanied by a concurrent proliferation of fatty tissue. However, these two conditions should be differentiated, and the proliferation of fatty tissue alone should be referred to as lipomastia [11].

The impact of spironolactone on androgen metabolism

Breast tissue contains androgen and estrogen receptors, which can respectively inhibit growth or stimulate proliferation and differentiation of breast tissue. Spironolactone can lead to the development of gynecomastia through various mechanisms:

1. Increased peripheral conversion of testosterone to estradiol.

2. Displacement of testosterone from sex hormone-binding globulin (SHBG), increasing the metabolic clearance of testosterone.

3. Binding to peripheral androgen receptors to competitively inhibit testosterone and dihydrotestosterone.

4. Inhibition of the enzymes 17α-hydroxylase and 17,20-desmolase, which play crucial roles in the testosterone biosynthesis pathway, limiting testosterone production and concurrently increasing estrogen levels due to enhanced peripheral conversion of testosterone to estradiol [12].

These mechanisms can result in pathological gynecomastia, breast tenderness, and pain in men, as confirmed by scientific studies. Spironolactone is one of the drugs with the strongest evidence linking it to gynecomastia, indicating a robust scientific basis that spironolactone indeed contributes to the development of this condition in men[13]. Gynecomastia can develop in a month after starting spironolactone treatment [14]. In the Randomized Aldactone Evaluation Study (RALES), 10% of male participants who received spironolactone at a dose of 25 mg/day reported gynecomastia and/or breast pain as adverse events [15]. The incidence of spironolactone-induced gynecomastia is dose-dependent, with rates reaching up to 52% at a dosage of 150 mg/day. Additionally, the occurrence of gynecomastia is associated with the duration of therapy, and it is typically reversible upon discontinuation of the medication [16].

Discussion :

In the study "Pathophysiology of Spironolactone-Induced Gynecomastia" by Rose LI, Underwood RH, Newmark SR, Kisch ES, and Williams GH, it was found that gynecomastia induced by spironolactone is associated with hormonal imbalances. Patients using spironolactone exhibited significant gynecomastia, defined as the presence of glandular breast tissue in one or both breasts, particularly in the subareolar area. This condition was absent in the control group, which did not receive spironolactone. Among patients who developed gynecomastia while on spironolactone, blood testosterone levels were lower, and estradiol levels were higher compared to the control group, where testosterone and estradiol levels remained within normal ranges. Additionally, endogenous estradiol production was elevated in those taking spironolactone compared to the control group, while no statistically significant difference was observed in testosterone production. The symptoms of gynecomastia resolved after discontinuing the drug. The study highlights the importance of monitoring hormone levels in patients treated with spironolactone[17].

In 2021, a meta-analysis of 14 randomized controlled clinical trials involving 3,745 participants demonstrated that individuals taking spironolactone have significantly higher odds of developing gynecomastia compared to control groups (OR = 8.39, 95% CI: 5.03 to 13.99). The study concluded that spironolactone can induce gynecomastia through several mechanisms: increased peripheral conversion of testosterone to estradiol, displacement of testosterone from sex hormone-binding globulin (SHBG), or binding to peripheral androgen receptors, thereby competitively inhibiting testosterone and dihydrotestosterone. The meta-analysis confirms that spironolactone and 5-alpha-reductase inhibitors are associated with an increased risk of gynecomastia, although this risk is less pronounced compared to that associated with antiandrogens[18].
A clinical study observed 30 healthy men over a 10-month period. Before starting spironolactone therapy, participants' testosterone and estrogen levels were measured. In this randomized, double-blind study, gynecomastia developed in 3 out of 10 men receiving 100 mg/day of spironolactone and in 5 out of 8 men receiving 200 mg/day of spironolactone. The presence of gynecomastia was clinically determined and confirmed by thermography. Two metabolic clearance studies utilizing either ^{3}H-testosterone or ^{3}H-androstenedione were conducted: (1) immediately before the initiation of spironolactone treatment and (2) either on the final day of the 10-month treatment period or upon the development of gynecomastia. Concentrations of testosterone, estradiol, estriol, luteinizing hormone (LH), follicle-stimulating hormone (FSH). A total of eighteen individuals received spironolactone, with ten in the low-dose group and eight in the high-dose group. Of these, eight individuals developed gynecomastia. No cases were reported in the placebo group. The incidence of gynecomastia was 30% in the low-dose group and 62% in the high-dose group. Spironolactone did not significantly affect the metabolic clearance of androstenedione and testosterone. Gynecomastia resolved in all subjects afterdiscontinuing spironolactone[14]

In another prospective study, it was hypothesized that spironolactone-induced gynecomastia might be caused by the binding of canrenone, an active metabolite of the drug, to tissue androgen receptors. Six out of nine healthy young men developed gynecomastia after taking 400 mg of spironolactone daily for 24 weeks. These men had lower testosterone levels and higher estradiol levels. This hormonal imbalance is a significant factor in the development of gynecomastia[19].

In a separate prospective study, spironolactone or potassium canrenoate (a metabolite of spironolactone) was administered for 6 months to 44 individuals with liver cirrhosis and ascites. In this study, gynecomastia was defined as a palpable, discrete nodule of firm tissue under the areola with a diameter of at least 2 cm. Fourteen patients received 100 mg/day of spironolactone, and all of them developed gynecomastia. In this study, testosterone, estradiol, LH, and FSH levels did not change significantly [20].

The Randomized Aldactone Evaluation Study (RALES) investigated the effects of spironolactone on morbidity and mortality in patients with severe heart failure. Spironolactone was generally well-tolerated. However, the study did report an increased incidence of hyperkalemia (elevated potassium levels) and gynecomastia. In a study involving 1,663 patients with heart failure, who were randomly assigned to receive either spironolactone at a dose of 25 mg per day or a placebo for 24 months, gynecomastia was reported in 10% of patients in the spironolactone group compared to 1% in the placebo group [21]

The article "Drug-induced gynecomastia: An evidence-based review" by Deepinder F and Braunstein GD provides a comprehensive overview of the mechanisms and prevalence of

gynecomastia caused by various medications. In this study atients with gynecomastia had lower testosterone levels and higher estradiol levels compared to the control group. The study suggests that spironolactone-induced gynecomastia is the result of a hormonal imbalance, where estrogens predominate. Treatment involves discontinuing spironolactone, which leads to the resolution of symptoms. Estradiol levels decrease, and testosterone levels significantly increase 3–6 months after stopping spironolactone.[13]

The literature analysis also included Case Reports:

In a 2021 case, a 75-year-old man with heart failure reported painful symptoms in his right breast during a routine check-up, which had been ongoing for 6 months. The patient was taking multiple medications, including spironolactone at a dose of 100 mg per day. Fine needle aspiration cytology of the right breast confirmed symptoms of gynecomastia[22]

A case of a 62-year-old patient with diagnosed coronary artery disease and ischemic left ventricular dysfunction, in whom an advanced gynecomastia was found during a physical examination. The patient had been treated with spironolactone at a dose of 25 mg per day for 8 years.The article emphasizes the importance of distinguishing gynecomastia from other conditions that may present similarly, such as breast cancer, and highlights the multidisciplinary approach required for effective management [23]

In another clinical case described, a 41-year-old patient was taking spironolactone at a dose of 50 mg per day for 2 years as part of a treatment regimen for decompensated liver cirrhosis with portal hypertension [24].

A 76-year-old patient, chronically treated for hypertension and heart failure, also suffering from arrhythmia, had blood estrogen and testosterone levels within normal limits. During a physical examination, he was found to have gynecomastia classified as Tanner stage III. The patient was taking spironolactone at a dose of 25 mg per day. Spironolactone was replaced with eplerenone, which has greater selectivity for the aldosterone receptor and a lower incidence of gynecomastia than spironolactone. Within three months, the patient's breast-related symptoms resolved [25]

A case of a 52-year-old man with hypertension, who presented to his doctor due to easy fatigue and muscle weakness. Upon examination, his blood pressure was found to be normal, but he had low potassium levels. Consequently, spironolactone was added to his treatment regimen at a dose of 25 mg per day. After 12 months of therapy, the patient returned with tenderness and swelling of the right breast gland. These symptoms resolved within three months after discontinuing spironolactone [10].

A 58-year-old male with a known history of chronic liver disease (NASH) and ascites, managed with diuretics (spironolactone 50 mg and furosemide 20 mg) for the past eight months, presented with a painful swelling in the right breast persisting for the last ten days. Upon examination, a firm, the mobile lump was palpated beneath the right nipple, while the left breast appeared normal. The probable cause of the symptoms was attributed to spironolactone, which was subsequently discontinued. Following the cessation of spironolactone, the patient's pain and swelling began to subside and returned to normal within one month [26].

A 37-year-old patient was admitted to the hospital due to diffuse interstitial lung disease in the fibrosis stage. He had a long history of smoking. The patient was under the care of a cardiologist and was taking spironolactone at a dose of 50 mg daily for pulmonary hypertension associated with chronic cor pulmonale. During the clinical examination, bilateral gynecomastia was noted, which was confirmed by a breast ultrasound showing bilateral glandular hypertrophy. The renal, hepatic, thyroid, and cancer (HCG) assessments were within normal limits. Further hormonal tests revealed normal prolactin levels, but the testosterone level was at the lower end of the normal range, and the estradiol level was elevated. Other possible causes have been excluded. The patient did not report any decrease in libido or erectile dysfunction. Ultimately, the dose of spironolactone was reduced, and a thiazide diuretic was added [27].

An alternative to spironolactone

When a patient develops side effects from spironolactone therapy, we may consider other alternative medications like eplerenone, which does not bind to progesterone or androgen receptors, does not cause breast pain and gynecomastia [28]. Its potency is about 370 times less than spironolactone in blocking dihydrotestosterone-activating androgen receptors, thus resulting lesser incidence of gynecomastia [29]. Additional studies have confirmed that eplerenone reverses spironolactone-induced gynecomastia [30].

Disclosure

Breast tissue contains receptors for both estrogens and androgens, which play a critical role in regulating the proliferation or inhibition of growth and differentiation within the mammary gland. Gynecomastia can result from a marked decrease in circulating estrogen levels or an increase in androgen serum levels. Additionally, imbalances between estrogen and androgen levels, even when serum concentrations remain within normal ranges, can lead to such effects. The activity of estrogens and androgens can also be locally modulated in breast tissue through various mechanisms: increased local production or decreased inactivation of estrogens, decreased local production of androgens, or alterations in the number and/or activity of androgen or estrogen receptors. Spironolactone, acting as an anti-androgen, alters peripheral testosterone metabolism, causing changes in the testosterone/estradiol ratio, which may contribute to gynecomastia. This side effect appears to be related to both dose and duration of treatment and is usually reversible once treatment is discontinued. Many standardized studies and several clinical cases have confirmed this. It is necessary to take this conclusion into account in clinical practice when treating a patient with spironolactone, take into account other clinical conditions of the patient, and if symptoms of gynecomastia occur, discontinue or change the drug in question to eplerenone. The patient should be informed of possible side effects.

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Not applicable.

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