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REVIEW

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Estrogen receptors, hormonal imbalance, gynecomastia, hyperestrogenemia, and male breast cancer: a literature review

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Abstract

Male breast cancer (MBC) is a rare, malignant tumor. It occurs in men where it accounts for less than 1% of all breast cancers. This is linked with the hormonal imbalance of estrogen and androgen levels. The objective of this review is to provide the details about pathophysiology of gynecomastia (GM) caused by estrogen hormone imbalance along with the explanation of hyperestrogenemia caused by excessive estrogen, the treatment, the adjuvant, and preventive management of MBC currently used by clinical research. Treatment, prevention, and management strategies for MBC follow the similar protocols as for female breast cancer, but today's treatment strategies include hormone-manipulating chemotherapy and biologics. The use of gene metabolites or active isomers, hormonal therapy and resection are also illustrated in clinical cases. Regarding the treatment and prevention of MBC, it is expected that the treatment strategies will shift to personalized medicine in the future, as it is difficult to identify mutant genes and perform effective genetic screening. Nevertheless, through our narrative review, this article discusses the differences between male and female breast cancer, the relationship between male hormones and breast cancer, and potential future treatment strategies.

Keywords

Male breast cancer; Estrogen; Gynecomastia; Hyperestrogenemia

1. Introduction

Male breast cancer (MBC) is a rare malignant disease which may occur in men at any age. It accounts for less than 1% of all cancers in men and less than 1% of all breast cancers [1]. Breast Cancer in male is often triggered by aging, exposures of radiation and a strong family history of breast cancers. However, it is mainly due to the hormonal imbalances. In particular, the mutations in the breast cancer gene 2 (BRCA2) are epidemiologic and risk factors for the development of breast cancer and it can lead to the development of secondary cancers as well [2]. Although MBC is a rare disease whose incidence has been on the rise for 25 years, but it is less studied than other cancers [3]. Being a rare disease, there has been a lack of awareness and a dearth of randomized control trials (RCT) to understand the disease. So, the management guidelines which are available are primarily based on the results of clinical trials of male breast cancer in women. As a result, there limited evidence supports the breast cancer screening or measures to reduce the mortality in men [4]. Although, MBC is a rare and often neglected disease in men, the patients with MBC present a clinically complex situation. In this regard, germline mutations in BRCA2 androgen receptor (AR) based targeted drugs, the benign toxicity profile or early action of seviteronel and the biosynthetic pathways of steroids are currently being studied [5]. It is usually painless and localization of the lesion. Adjuvant treatment with drugs or chemotherapy, mastectomy and endocrine therapy are preferred mode of treatment especially for the tissue to a posterior mass [6]. The diagnosis of MBC is based on the similarities to breast cancer in women with palpable masses, lymph node enlargement, ulceration or discharge and skin changes such as redness. Mammography or ultrasound should be performed to evaluate the regional lymph nodes and a biopsy is done for the final diagnosis [7].

Generally, the pathophysiology of MBCs is related to an imbalance in the estrogen and androgen profiles of the patient. Changes in testosterone and estrogen levels contribute to the gender-specific changes in the body having a direct impact on the functionality of immune cells. They regulate autoimmune diseases and alter the immune system of T-cell subsets and monocyte B-cells [8]. The sex hormones like estrogen and androgen contribute to the pathogenesis of cancer by modulating the immune signaling activity of tumor cells and tumor-associated white blood cells. Therefore, sex hormones may act as potential therapeutic agents for enhancement of anti-tumor immune responses and for elimination of malignant cells [9, 10]. Breast cancer in male is often due to high estrogen levels, which can lead to hyperplasia and increases the risk of breast cancer. Obesity or rapid weight gain, high blood cholesterol, gallstones, non-insulin-dependent diabetes,

or chronic liver disease influence the estrogen levels in men [11]. The MBC treatment strategy is like that for female breast cancer. It typically involves the surgical removal of the tumor followed by hormonal, radiation or cytotoxic therapy. However, the correspondence with female breast cancer is still unclear and tamoxifen (TAM) treatment for MBC may decrease the libido leading to sexual dysfunction. It reduces the compliance of therapy in male patients. Therefore, DNA repair methods by using protein variants, medical genetics methods by involving protein geobiology, predictive diagnostics for functional changes associated with mutations that disrupt protein-ligand interactions and the development of potential biomarkers based on bioinvestigation are preferred therapeutic approaches [12].

Among MBC patients, 70% receive radiation therapy, 44% receive chemotherapy, and 62% of the patients with estrogen receptor-positive disease receive endocrine therapy. The survival following MBC is associated with older age or Black race, higher disease and tumor stage, mastectomy, progesterone receptor-positive tumors and endocrine therapy [13]. The breast cancer in postmenopausal women and MBC have same therapeutic treatments. Estrogen regulates various pathological and physiological behaviors within the male and female body. Endogenous estrogen 17β-estradiol (E2), executed by estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) of the nuclear estrogen receptor (ER), has a fundamental role in breast cancer formation and progression [14]. The E2 assists in the activation of many chemical carcinogens, including benzo(a)pyrene, 7,12-dimethylbenz(a)anthracene and aflatoxins by epoxidation. Activated E2 is an anticancer agent that prevents breast cancer by inhibiting nuclear DNA-dependent RNA synthesis in the body. It acts as a potential antioxidant from a therapeutic perspective in breast cancer. The anti-estrogen TAM can prevent the formation of epoxides of E2 [15].

Better understanding of the immune system's role in sex hormones has led to the increased interest in the rare disorders MBC and its associated gynecomastia and hyperestrogenemia, especially in men. This review details ERs and MBC along with estrogen hormone imbalance and gynecomastia, the hyperestrogenemia due to excess estrogen and future treatment and management of MBC. The purpose of this review is to describe (1) the relationship between MBC and estrogen, (2) clinical cases of gynecomastia due to estrogen imbalance (3) clinical cases of hyperestrogenemia due excessive secretion of estrogen and (4) to discuss surgical treatment, adjuvant and preventive management of MBC. Because, this research focuses on understanding estrogen and ERs, thus the clinical case studies focus on cases of estrogen imbalance and estrogen hypersecretion.

2. Estrogen receptor and MBC

Estrogen has a well-established physiological role in the female endometrium. It is based on the steroid hormones, namely progesterone and androgen. It acts in the female endometrium by synthesizing progesterone receptors (PRs) and prepares the endometrium by interaction with the ER [16]. In women, ER is an essential component of the regulatory network that controls the muscles and muscle dysfunction in the body. It acts as a body maintenance metabolism mechanism for the prevention of muscle loss and alternative treatment option for disease [17]. In men, ER is also associated with resting energy expenditure and weight control. Energy expenditure and balance are related to estrogen action, including changes in the distribution of adipose tissue, homeostatic regulation of body weight and induction of satiety. This resembles with postmenopausal women and is associated with the risk of developing cardiometabolic disease [18]. However, for men, estrogen is a sex hormone that has been known for more than 90 years. Early studies have shown that estrogen is harmful to male reproduction but that the synthesis of estrogen in the testes is dependent on high concentrations of 17β-estradiol for normal male reproductive function [19]. The male genital tract has also been shown to broadly expresses ERs from neonatal to adulthood life. The primary ERs may be involved in in male reproduction and infertility, as it is essential for male fertility, epididymis, and prostate development. This indicates that estrogen also plays an important physiological role in men and shapes evolutionary concepts [20]. However, the optimal treatment for MBC is still unclear and related research is lacking. The patients of MBC respond to hormonal manipulation or chemotherapy and prognosis is managed based on biological treatment strategies [21]. ERα and ERβ are transcription factors that regulate the complex physiological processes in humans. Aberrant ER signaling leads to cancer, metabolic and cardiovascular diseases, neurodegeneration, inflammation and osteoporosis [22]. In the relationship between estrogen and breast cancer, elastosis is strongly linked with the expression of ERα. The correlation between the amount of elastosis, age, grade, mitotic activity index and progesterone receptor (PgR) is associated with the development of breast cancer in women. But in MBC, the less clinically useful ERα tissue biomarker has been shown to have a sex difference [23].

"Estrogen dominance" is an endocrine immune disorder that occurs in diseases, caused by the binding of thyroid hormones and the deregulation of B and T cells due to the imbalance of sex hormones, due to elevation of estrogen, and due to castration or clinical effects [24]. This is called estrogen dominance syndrome, when the amount of estrogen is greater than the amount of testosterone and progesterone, the lipotoxic effect that inhibit matrix formation are impaired. It directly influences bone health, through changes in adipogenesis and differentiation, bone marrow stem cells and osteoblast-associated ERs [25]. For this reason, mastectomy is the most common surgery for men and may be a way to prevent metastasis to axillary lymph nodes. Mastectomy in patients with MBC is performed when breast tissue has spread to the nipple, or to a terminal mass near the nipple [26]. Since ERα in MBC is almost always positive in all cases of MBC, inhibition of ERα is used as an adjuvant treatment. Moreover, the androgen receptor (AR) has also attracted attention as target for breast cancer treatment [27].

3. Estrogen imbalance and gynecomastia

An overproduction of estrogen or deficiency of androgen leads to gynecomastia (GM). Other causes include non-endocrine diseases, including liver failure and chronic kidney disease [28]. It is one of the risk factors for developing MBC, along with diabetes, obesity, Klinefelter's syndrome and orchitis. Gynecomastia was detected by a discharge record survey of the US Veterans Arrairs Medical Care System and was characterized by lower risk factors than women, who do not develop MBC within an average of 75 months. But they are difficult to identify as a high-risk group [29]. However, in addition to a systemic examination the GM requires a testicular checkup along with the treatment of underlying condition. Treatment includes the use of testosterone for hypogonadism and TAM may also be used for the same purpose. Although medications such as clomiphene, danazol, letrozole and anastrozole can be used but it is difficult to expect significant treatment results in the case of chronic diseases [30]. The GM is a palpable enlargement of the male breast which results into enlargement of breast tissues. It accounts for 80% of all the cases of Klinefelter's syndrome and makes it important to explore its pathophysiology [31]. Especially in adolescents, GM is caused by an imbalance of androgens and estrogens along with changes in growth hormone, insulin-like growth factor-I, prolactin, and the aromatase enzyme. It can also occur due to obesity, which is common during puberty or by medications and hypogonadism. However, GM can develop other diseases as well, like liver and kidney failure, thyrotoxicosis, Klinefelter's syndrome and tumors, which require medical attention [32–35]. It is noticeable that GM in adolescence regresses over the period of 1–3 years. But it can cause significant tenderness and embarrassment, accompanied by psychological stress and depression in the adolescent. Treatment with anti-estrogenic agents can be used to reduce the size of the breasts or managed with the use of medicines in the early stages of the disease. Selective surgical removal may be used in special conditions for cosmetic purposes [36–39].

The pathophysiological clinical case studies of GM are shown in Table 1. It is caused by an increase in the circulating or localized breast tissue ratio of androgens to estrogen but the estrogen secretion being the primary cause. Estrogen develops the breast tissues, while androgens have an antiproliferative action on them. Men secrete 6–10 μg of estradiol and 2.5 μg of estrogen per day from the testes [40]. In the presence of Leydig cell tumor (LCT), the release of estrogen induces GM, which results in reduced sperm production. This may lead to erectile dysfunction due to suppression of gonadotropin secretion and steroid hormones production [41]. This association of GM with granulomatous lobular mastitis (GLM) is presented in a clinical case of a 48-year-old man. GLM is an autoimmune disease, which is associated with bacterial or fungal infections along with oral contraceptives and hyperprolactinemia. Clinically, this is similar to breast cancer and characterized by a high rate of local recurrence. This phenomenon is due to the effects of androgens and estrogen on the development of the mammary glands in men [42]. It has been suggested that the GM can also be described as thyrotoxicosis with sex hormone imbalance. This was demonstrated in a 49-year-old clinical case, in which the increased expression of sex hormone-binding globulin (SHBG) protein after thiamazole and levothyroxine treatment of thyrotoxicosis led to the development of GM. This clinical study demonstrated that SHBG leads to a decrease in the level of testosterone [43]. The personalized treatment of GM includes weight reduction, mental stabilization, pharmacotherapy by using TAM and elective surgical treatments such as liposuction [44]. The first concurrent case of GM and GLM has been reported for GM. A male patient diagnosed with GM with hyperprolactinemia complicated by a rare GLM was treated with bromocriptine. Hyperprolactinemia with low serum testosterone and elevated levels of prolactin and estradiol was identified. Galactorrhea and breast masses were abolished by bromocriptine treatment at 2.5 mg per day for 3 months [45] in that patient. In a clinical case study of a hyperprolactinemic adolescent with obese GM and galactorrhea, increasing the bromocriptine dose from 2.5 mg/day to 7.5 mg/day resulted in a significant decrease in the levels of galactorrhea and prolactin [46]. In particular, diabetes is a risk factor for low androgen levels thus the signaling and diagnosis of GM should be discussed in older men who are on anti-diabetic medications. Among the eight classes of drugs used for diabetes, only dipeptidyl peptidase-4 (DPP-4) detected a signal from GM. Furthermore, among all the anti-diabetic drugs used, the signals were only identified for sitagliptin and vildagliptin [47]. Medication is the mainstay of chemical modulation-based therapies that utilizes pathophysiologic changes in GM. Androgens and aromatase inhibitors, mainly TAM or estrogen antagonists are used for the treatment of GM. Antiretroviral therapy is an oral regimen of anastrozole, cabotegravir, rilpivirine, tenofovir disoproxil fumarate, lamivudine and doravirine. It is associated with fatigue and weight gain due to the reduced physical activity and reduces the swelling and pain in GM besides reduction of breast enlargement [48]. Studies comparing the characteristics of GM by age indicate that fibrotic GM may be more common in adolescents and young adults. It is also more likely to occur in older patients with good hematologic status. Further, the patients with pigmented GM had a higher recurrence rate in comparison to the patients with fibrotic GM. This is due to the reason that the recurrence rate was not increased in patients using anti-androgen or steroid/immunosuppressive therapy in the clinical strata of 13–17, 18–30, 31–49 and 50–83 years of age [49]. In a 19-year-old clinical case, medical surgery was used as a treatment for adolescent GM because of its low recurrence rate. Liposuction and subcutaneous mastectomy were performed together along with adjuvant treatment by using TAM. However, three years later, the patient recurred and underwent a second surgery that was diagnosed as recurrent gynecomastia [50].

4. Excessive estrogen and hyperestrogenemia

Germline mutations in several genes, including BRCA2, the androgen receptor gene and phosphatase tensin homolog (PTEN), increase the risk of development of MBC up to tenfold. This creates problems with the biosynthesis of

TABLE 1. Summary of a pathophysiologic clinical case for GM patients studies.

Study	Patient's condition	Diagnosis	Therapeutic trait	Findings
Han *et al*. [43]	A 48-year-old man	GLM of right breast, GM	Anti-infection treatment for 3 days, Lesion incision	Strong opposition to glucocorticoid treatment due to the side effects of steroid hormone. GMs can be caused by GLMs.
Mohammadnia *et al*. [44]	A 49-year-old man	GM	Thiamazole 30 mg once a day, 1 month later, added in levothyroxine 100 ng once daily	Regulation of sex hormone plasma levels by SHBG, stimulation of HepG2 by thyroid hormone administration and expression of HNF4A suggest that SHBG is involved in metabolic processes other than thyrotoxicosis.
Yin *et al*. [45]	A 20-year-old man, 1-year history of breast enlargement and galactorrhea	GLM	3 months of treatment with bromocriptine at 2.5 mg once a day	Galactorrhea disappearance of breast lumps and normalization of serum prolactin levels by prescribing bromocriptine.
Jaruratanasirikul and Janejindamai [46]	A 15-year-old boy, obese, had gynecomastia and galactorrhea	Hyperprola-ctinemia	Bromocriptine 2.5 mg/day, then increased to 7.5 mg/day	Elimination of galactorrhea and reduced prolactin levels (<10 ng/mL).
Senkoro *et al*. [48]	A 56-year-old man	GM	anastrozole 1mg once a day, gained weight but decreased breast enlargement, reduced breast swelling and pain. Medication—antiretroviral therapy (cabotegravir, rilpivirine, tenofovir disoproxil fu-marate + lamivudine + doravirine)	Treatment of GM involves the use of estrogen antagonists, androgens and aromatase inhibitors and TAM is an estrogen antagonist that induces the activity of cytochrome P450 3A4 (CYP3A4).
Jabori *et al*. [50]	A 19-year-old boy	GM	Liposuction, mastectomy and adjuvant treatment with tamoxifen	Despite the surgical treatment having a low recurrence rate, the patient recurred three years later and underwent a second surgery and recurrent gynecomastia was diagnosed.

GLM: granulomatous lobular mastitis; GM: gynecomastia; SHBG: sex hormone-binding globulin; HepG2: hepatoblastoma cell lines; HNF4A: hepatocyte nuclear factor-4α; TAM: tamoxifen.

estrogen following gonadal mutations. Key enzymes in estrogen biosynthesis include the c.1-34T>C 5′ promoter region polymorphism of cytochrome P450c17 (CYP17), which is associated with risk of male breast cancer; hemochromatosis gene (HFE) mutations; and mismatch repair genes human MutS homologues2 (hMSH2), human mutL homolog1 (hMLH1), human postmeiotic segregation1 (hPMS1), human postmeiotic segregation2 (hPMS2) and PTEN mutations. It is associated with cowden syndrome (CS) and accounts for 5–10% of all cancers [51]. CS is a multiple Hamartoma syndrome associated with germline mutations in the PTEN tumor suppressor gene. It is characterized by facial papules, oral papillomatosis and hyperkeratosis, mucosal lesions, gastrointestinal and thyroid hyperplasia and asymptomatic hyperplasia of the right cerebellum beginning at age 10. Diagnosis is based on early symptoms and regular examinations. In particular, the skin lesions are the most characteristic features. It is essential to identify the mucocutaneous symptoms and make a quick judgment based on clinical symptom reports [52]. Estrogen, the parent of the gene mutations associated with CS is highly correlated with the diagnosis of MBC. Indirect indicators of high estrogen levels include low high density lipoprotein (HDL) (<40 mg/dL), low albumin (<4 g/dL) and high body mass index (BMI) (>25). Eleven out of 12 MBC patients had at least one high estrogen marker, specifically 11 positive ER, 8 positive

PR, 3 low HDL, 4 low albumin and 9 obese BMI [53]. The survival rate of MBC is lower than female breast cancer. It also has late diagnosis with localized progression and resistance to treatment by metastatic cases. However, hormonal therapy like treatment with anti-estrogens, steroids and non-steroidal aromatase inhibitors alone or in combination with luteinizing hormone-releasing hormone (LHRH)-agonists, fulvestrant and other hormonal agents has been shown to be effective in the treatment of patients with signs of hyperestrogenemia and also in the management of prognostic signs. For example, stage 3 cancer, low differentiation of tumor cells, moderate to severe morbid obesity or regional lymph node N2–3 status [54].

Hyperestrogenemia further promotes the risk of breast adenocarcinoma in patients with other MBC risk factors, such as hormonal imbalances of androgens and estrogens, BRCA1 gene mutations and inversions of chromosome 9 [55]. A 30-year-old man diagnosed with hyperestrogenemia had plasma estrone, estradiol and cortisol that were not suppressed by high dose of dexamethasone. After adrenalectomy, an increased aromatase activity was observed. Quantitative reverse transcription-polymerase chain reaction (RT-PCR) showed a weak and non-significant rise in total aromatase mRNA in comparison to normal adrenal tissue. This suggests that the rapid overexpression of aromatase is not necessary for biochemical estrogenic hyperestrogenism [56]. However, the patients with progressive myodystrophy (PMD) are characterized by markedly elevated blood estradiol. In these patients hyperestrogenemia may play an adaptive role under the genetically determined muscular dystrophic process. Some patients with PMD have hypoestrogenemia, hypotestosteroneemia, hyperprolactinemia, hypoprolactinemia and reduced luteinizing hormone (LH) levels, which can lead to decreased libido and sexual dysfunction [57]. This hyperestrogenemia can stem from obesity, which is the root cause of chronic disease. Obesity leads to abnormalities in steroid and polypeptide hormone secretion, particularly hyperestrogenemia and hypogonadism in men. It also results into decreased SHBG levels in men and women, elevated insulin, blunted stimulatory effects of prolactin, growth hormone and vasopressin along with elevated basal levels of beta-endorphin and blunted stimulatory and inhibitory effects. This shows that obesity leads to a whole range of hormonal abnormalities that can be reversed or restored through weight control [58]. Obesity in men is associated with aromatase activity as well. In normal circumstances, aromatase plays an important role in male health. It is especially effective for type 2 diabetes, metabolic syndrome, obesity and aging. It is required to convert testosterone to estradiol in addition to reducing testosterone and increasing estrogen levels. This leads to insulin resistance and glucose transporter type 4 (GLUT4) down regulation and hence suggesting that the hormonal products of aromatase activity are potential therapeutic agents for ERs [59–61]. Table 2 summarizes the clinical case studies with hyperestrogenemia.

5. Targeted therapies for MBC

Breast cancer is the second leading cause of cancer death. Systemic treatments for breast cancer include cytotoxic, hormonal and immunotherapeutic agents. The drugs are used as adjuvants, neoadjuvants and for the treatment of the metastatic environment. However, over the course of treatment, resistance may occur. There are also chances of host, tumor and drug interactions with P-glycoprotein along with emergence of multidrug resistance protein families. This has led to the importance of new treatment strategies that incorporate new effective chemotherapeutic agents, systemic treatment with hormonal agents and biologics, surgery and radiotherapy [62, 63]. Treatment of MBC patients follows the similar precautions as given for postmenopausal breast cancer in women, with surgery or systemic therapy and radiation. ERs and progesterone receptors (ER/PR) help predict the treatment options for cancer. Human epidermal growth factor receptor 2 (HER2) has many compounds (trastuzumab, Herceptin, Genentech, South San Francisco, CA) and a tyrosine kinase inhibitor (lapatinib) in the clinic and may be a positive therapy for HER2+ breast cancer, making it a targeted therapy for MBC patients (HER2+/ER+ or HER2+/ER-MBC). Similarly, lapatinib (Tykerb) is being explored as a potential treatment for patients with trastuzumab-resistant MBC [64–66]. In general, genetic counseling and germline genetic testing for cancer predisposition genes is recommended for patients suffering from MBC and routine breast magnetic resonance imaging is not recommended. Patients with MBC who have metastatic or advanced disease should receive endocrine therapy as first-line treatment and those with early disease should receive the medications for osteoporosis to prevent the bone loss. In early stage of MBC, TAM is used for 5 years, followed by a gonadotropin agonist/antagonist plus aromatase inhibitor, if TAM is contraindicated and an additional 5 years of treatment if there is a risk of recurrence [67–71].

Z-endoxifen is an emerging drug treatment option for MBC. TAM, an ER modulator, is an endocrine agent that is quite effective for the treatment of MBC. N-Desmethyltamoxifen (NDT) is the primary TAM metabolite which undergoes cytochrome P450 2D6 (CYP2D6)-dependent biotransformation to the secondary metabolite endoxifen. Endoxifene is a more potent anti-estrogen than TAM having anti-tumor potential. Its active isomer Z-endoxifene has anti-tumor activity and is orally bioavailable [72]. Based on the clinicopathologic features of MBC, the cytotoxic chemotherapy and endocrine therapies, including TAM, aromatase inhibitors and gonadotropin releasing hormone agonist (GnRH) analogs have a potent role today as HER2-directed therapy. They are also famous for being used as targeted agents, as poly ADP ribose polymerase (PARP) inhibitors and angiogenesis inhibitors [73]. Everolimus is a drug for the treatment of ER-positive breast cancer with positive results in clinical trials. A 43-year-old man's low back hip pain and a lump in his left breast led to a diagnosis of left breast cancer. He was treated with temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor and the results showed improvement in left breast cancer along with achievement of a synergistic effect with MBC hormone therapy for everolimus, one of the mTOR inhibitors [74]. The high heterogeneity of breast cancer is reflected in the treatment of MBC, with different detection and classification methods for patient prognosis and treatment. As the identification of specific

TABLE 2. Summary of studies of a pivotal clinical case for hyperestrogenemia.

Study	Subject	Diagnosis	Materials and methods	Findings
Tariq *et al.* [53]	A 13-year retrospective review of the MBC	MBC, high estrogen level	A 13-year retrospective review of MBC cases, analyzed according to estrogen markers: low HDL (<40 mg/dL), low albumin (<4 g/dL) and high BMI (>25)	All MBC patients have hyestrogenemia precursors and 11 out of 12 MBC patients have at least one marker of high estrogen.
Yevhen [54]	Clinical trial of hormone therapy in 168 patients with MBC	MBC, feminization syndrome	Anti-estrogens, steroids and non-steroidal aromatase inhibitors alone, in combination with LHRH-agonists, fulvestrant and other hormonal agents	Feminization syndrome (hyperestrogenemia, stage III of cancer, low differentiation of tumor cells, status of regional lymph nodes N2–3, medium, severe and morbid obesity) patients therapeutic.
Bouraïma *et al.* [56]	Diagnosis of a 30-year-old MBC patient	MBC	Analysis of prognostic symptoms following adrenalectomy for feminizing adrenocortical tumors (aromatase activity)	Overexpression of aromatase is not a prerequisite for clinical and biochemical hyperadrenocorticism and aromatase promoter can be utilized in the adrenal cortex.
Zavadenko [57]	The patient's age ranged from 21 to 45; Becker's PMD patients in 11, Erb-Roth's PMD in 9 and 10 with Landouzy-Dejerine's PMD	PMD	Blood serum LH, FSH, prolactin, testosterone and estradiol were measured by RIA	Hyperestrogenemia plays an adaptive role in the conditions of the genetically determined muscular dystrophy process and neuroendocrine changes cause sexual disorders in patients with PMD (including arrested sexual development, decreased libido, objective signs of masculinization and feminization and sexual dysfunction).

MBC: male breast cancer; PMD: progressive myodystrophy; LHRH: luteinizing hormone-releasing hormone; HDL: high density lipoprotein; BMI: body mass index; LH: luteinizing hormone; FSH: follicle-stimulationg hormone; RIA: rich Internet application.

mutations associated with breast tumors becomes more difficult and effective genetic screening becomes available, personalized medicine and preventive care strategies are changing treatment regime [75]. More than 83% of ER/PR-positive cases of MBC are treated with the hormonal therapy TAM which is a common adjuvant treatment. Since people over the age of 60 suffer from MBC and is mostly receptor-positive, it is more important to improve prognosis with early diagnosis. Hence, the community and health professionals should be educated about it. A team approach involving the oncologists, surgery, radiology, nutrition, and mental health is recommended. Adjuvant treatment with the commonly used RT, hormonal therapy (HT) and chemotherapy (CT) is associated with reduced recurrence and increased survival rates [76, 77].

6. Future directions

While much has been written about the effects of estrogen on MBC, GM and hyperestrogenemia there is still a strong need of randomized clinical trials and research on breast disease in men. Studies are required, especially to translate the clinical results in different age groups or experimental studies to develop the treatment protocols. Firstly, the breast cancer in men is vague and difficult to identify, so there are no programs or systematic indicators or processes in place for early detection. Therefore, they follow women's advocacy systems and are managed by women's follow-up systems.

Secondly, there is a lack of evidence for MBC in sexual dysfunction and clinical trials are also needed for this. This is associated with long-term safety concerns and the review and depiction of effective management and treatment-based scenarios are highly appreciated to overcome sexual disorders [78].

As the MBC can recur despite surgical treatments, so the adjuvant treatment or management methods with decreased risk of recurrence should be studied epidemiologically. To reduce the risk of recurrence, the prevention strategies should include ongoing self-examination or professional diagnosis.

This has also been noted in clinical case studies of the

patients who have experienced recurrence following the surgical treatment. Hence, targeted therapies that look at MBC characteristics at the genetic and molecular levels are in the spotlight today. These new therapeutic strategies are based on the identification of molecular alterations using gene panel sequencing in the clinics or the implementation of accurate medicine based on data updates according to genomic topography [79].

7. Conclusions

Sex hormone health factors should be considered in the treatment of MBC. Since MBC is a rare disease with difficult early diagnosis and extremely low incidence, it is necessary to understand the pathogenesis of the disease based on clinical cases and to acquire rapid treatment strategies through regular diagnosis. Estrogen is a sex hormone that is also present in men and GM is caused by an estrogen imbalance, and excess estrogen causes hyperestrogenemia. This is initiated by estrogen and ERs, indicating that sex hormones also have a relationship with the immune system. Treatment of MBC is divided into two main categories: surgical treatment and the adjuvant treatment to prevent and maintain the disease due to the high risk of recurrence. Surgical treatment with nipple dissection was thought to completely remove MBC. However, clinical trials have shown that it can recur, and most cases occur in older people. Therefore, new treatment paradigms are needed. Changing treatment paradigms and the abundance of new drugs require further research and clinical trials.

ABBREVIATIONS

MBC, male breast cancer; GM, gynecomastia; BRCA2, breast cancer gene 2; RCT, randomized control trials; AR, androgen receptor; TAM, tamoxifen; E2, 17β-estradiol; ERα, estrogen receptor alpha; ERβ, estrogen receptor beta; ER, estrogen receptor; PRs, progesterone receptors; PgR, progesterone receptor; LCT, leydig cell tumor; GLM, granulomatous lobular mastitis; SHBG, sex hormone-binding globulin; DPP-4, dipeptidyl peptidase-4; PTEN, phosphatase tensin homolog; CYP17, cytochrome P450c17; HFE, hemochromatosis gene; hMSH2, human MutS homologues 2; hMLH1, human mutL homolog 1; hPMS1, human postmeiotic segregation 1; hPMS2, human postmeiotic segregation 2; CS, cowden syndrome; HDL, high density lipoprotein; BMI, body mass index; RT-PCR, reverse transcription-polymerase chain reaction; LHRH, luteinizing hormone-releasing hormone; LH, luteinizing hormone; GLUT4, Glucose transporter type 4; ER/PR, ERs and progesterone receptors; HER2, human epidermal growth factor receptor 2; NDT, n-desmethyltamoxifen; CYP2D6, cytochrome P450 2D6; GnRH, gonadotropin releasing hormone agonist; PARP, poly ADP ribose polymerase; mTOR, mammalian target of rapamycin; HT, hormonal therapy; CT, chemotherapy.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

YP and KHK—conceptualization, writing–review, validation; YP—methodology, software; formal analysis, investigation, resources, data curation, writing-original draft preparation; editing, visualization; KHK—supervision. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

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