Chapter

Estrogen as a Contributing Factor to the Development of Lipedema

Sara Al-Ghadban, Mary L. Teeler and Bruce A. Bunnell

Abstract

Lipedema is an underdiagnosed painful adipose tissue disorder that occurs almost exclusively in women, with onset manifesting at puberty or at times of hormonal change. Unlike many fat disorders, diet and exercise have little to no impact on the prevention or progression of this disease. Estrogens control the distribution of body fat and food intake, regulate leptin expression, increase insulin sensitivity, and reduce inflammation through signaling pathways mediated by its receptors, estrogen receptor alpha (ERα) and ERβ. This review will focus on understanding the role of estrogen in the pathogenesis of the disease and envisage potential hormonal therapy for lipedema patients.

Keywords: lipedema, adipose tissue, estrogen, adipogenesis, inflammation

1. Introduction

Lipedema is a chronic underrecognized adipose tissue (AT) disorder distinguished by the symmetrical accumulation of painful fat in the lower body, predominantly in the thighs. The clinical presentation of lipedema resembles that of obesity, lymphedema, and other AT disorders, so it is often misdiagnosed and mistreated [1–4]. Lipedema is diagnosed by a thorough physical examination in conjunction with the patient's family and medical histories. Healthcare providers identify lipedema through the following criteria: bilateral and symmetrical distribution of subcutaneous fat predominantly in the legs that excludes the hands or feet, minimal pitting edema and a negative Stemmer's sign which can indicate edema followed by a set of detailed criteria that characterize regionalization of fat accumulation and pain, time of change in fat distribution, and diet resistance to discern the type and stage of the patient.

There are five different types of lipedema, which are based upon the regions of prominent fat deposition. Type 1: the fat builds up in the buttocks and hip; Type 2: the fat spreads from the buttocks to the knees with fat folds around the inside of the knee; Type 3: the fat extends to the hips and ankles, the feet are not affected; Type 4: the fat is increased in the upper arms sparing the wrist and Type 5: the fat accumulates in the lower legs only [2, 5, 6]. Patients may present with more than one type depending on the progression of the disorder. Additionally, patients present at three different stages, depending on the severity of fat accumulation and the onset of other symptoms [2, 5–7]. Stage 1: the skin is smooth with small fat lobules; Stage 2: the skin has indentations with pearl-sized fat nodules and Stage 3: the skin has large extrusions with overhanging fat causing tissue deformities. Lymphedema may also develop collaterally at any stage of the disorder but does not alone qualify a case of lipedema [2]. Unlike many AT disorders, lipedema is largely irresponsive

to lifestyle interventions such as diet and exercise, but liposuction and decongestive therapy are effective treatment options [1]. While neither are curative, liposuction is widely accepted as the better treatment option for its ability to provide long-term improvement to appearances, functionality, mobility and bruising while reducing edema, spontaneous pain, sensitivity to pressure. Combined decongestive therapy (CDT) such as pre- or post-operative lymphatic drainage or use of compression garments in recovery weeks may be conducted in support of the procedure [2, 4].

Lipedema predominantly affects females and often manifests during time of hormone fluctuations, during puberty, childbirth, or menopause [7, 8], indicating that estrogen and estrogen signaling play a role in the pathogenesis of lipedema via direct impacts on adipocytes and immune cells, and/or secondary effects on the brain control centers [9, 10]. However, the exact mechanism(s) of action remain unclear [11, 12]. Although lipedema is a common disease (11% of women worldwide), no data are yet available to demonstrate the prevalence of lipedema in pre- and post-menopausal or pregnant women. In addition, cases of lipedema in males are very rare; however, men who develop lipedema tend to have high levels of estrogen but low testosterone levels [2, 5, 6]. Understanding the mechanisms of the life-long transitions of estrogen levels and interactions with AT will define the pathogenesis of lipedema more thoroughly while identifying novel diagnostic and treatment options.

This review will describe the potential role of estrogen in the development of lipedema. The effect(s) of estrogens on the immune system will be described, the association of estrogen signaling on tissue adipogenesis and inflammation will be explored and the application of estrogen as a potential therapy in preventing the progression of this disease will be discussed.

2. Estrogens and estrogen receptors in lipedema

Estrogens are hormones that regulate adipose tissue metabolism by controlling food intake, energy expenditure and body distribution. Estrogens have widespread effects on several organs around the body and therefore play a role in a variety of physiological functions and disorders. Estrogens can act on receptors in both the cytoplasm and the plasma membrane to mediate protein expression involving cell proliferation and metabolism [12]. Estrogens are present in three forms: estrone (E1), estradiol (E2), and estriol (E3). Estradiol is the most extensively studied, as it plays key roles in reproductive phase functioning and a large variety of chronic disorders. There are three receptors that have distinct presences and functions around the body. Alterations in estrogen activity or the absence of estrogen receptors (ER) results in the accumulation of subcutaneous adipose tissue (SAT), a phenomenon observed in lipedema patients [5, 9, 13, 14]. Szél et al. hypothesized that alteration in ERs is involved in the regulation of appetite and weight gain which might explain why lipedema patients accumulate fat and have difficulty losing it with diet and exercise [10]. Furthermore, Yi et al. showed that estrogen regulates the expression of leptin, a hormone that controls hunger and body weight, in adipocytes via ERs [15] supporting the hypothesis that lipedema is a hormonal disease.

Estrogen exerts its function through the estrogen receptor alpha (ERα) and beta (ERβ). Both ERα and ERβ receptors appear in significantly high concentrations in SAT of premenopausal women, as signaling from estrogens mediates adipose deposition throughout the body [9, 16]. However, ERα expression is reduced in the SAT of clinically obese females and postmenopausal women treated with estradiol compared to their normal-weight counterparts [14, 17, 18]. Interestingly, Erβ, which serves an antagonistic role on ERα-mediated gene expression, is highly

expressed in postmenopausal women in comparison to premenopausal women [19]. Such findings raise the question of whether a correlation of the concentrations of estrogen receptors in adipose tissue could elucidate a similar relationship between estrogen receptor concentrations in lipedema AT. Additionally, a study conducted by Gavin et al. discovered described that the concentration of ERα is decreased and ERβ concentration is increased in the lower extremities of overweight patients, associating the variable concentrations to sexual dimorphisms in regionalized fat deposition for individuals [20]. As discussed earlier, fat accumulates in the lower extremities of lipedema patients, implying a potential role of ER in its pathogenesis. Furthermore, Dieudonné and colleagues evaluated the expression of ERs in preadipocytes and adipocytes in a cohort of lean subjects and determined that males and females statistically share similar levels of both ERα and ERβ within intraabdominal AT (IAT) and SAT [14]. Females have slightly higher concentrations of ERα and ERβ globally than males. However, when induced with estradiol, expression of ERα in the SAT in females increased significantly more than in IAT. In these same conditions, the SAT in females have a significantly increased expression of ERβ while all other levels of ERβ (IAT in females, SAT and IAT in males) remained the same. Cases of increased regionalized lipid accumulation are closely correlated to estrogen deficiency [21–24]. In contrast, in an estrogen-sufficient state, excess fat is stored in the gluteal-femoral region, rather than the abdominal region. One mechanism has been postulated as a factor in this association is the acute administration of estrogens to postmenopausal women which reduced basal lipolysis in SAT, particularly in the femoral region, further supporting a role for estrogens in regional fat deposition in lipedema patients [25].

The third estrogen receptor, G protein-coupled estrogen receptor (GPER) is expressed on the membrane at lower concentrations in adipose tissue but nonetheless, with several important effects. GPER has been widely studied in regulation of body weight, inflammation, insulin sensitivity, and metabolic dysfunction [26–29]. Several studies demonstrated that mice lacking GPER demonstrate an increase in adiposity (mass and adipocyte size) and decrease in energy expenditure compared to their wild type mice [29–31]. Studies have also shown that the lack of GPER or ERα expression in mice show similar characteristic of metabolic syndrome such as inflammation, obesity, glucose intolerance and insulin resistance [26, 31–34]. Although the actions of estrogens on GPER have not yet been fully elucidated, examining the crosstalk between ERs and estrogen will help understand their function in the development of lipedema.

2.1 Estrogen and adipogenesis

Estrogens have been shown to play a role in gender and regional adiposity. Several studies revealed that women have ~10% more early stage preadipocytes in abdominal SAT and ~35% more in femoral SAT [35, 36]. However, only ERα is expressed in preadipocytes, suggesting a role for estrogen in adipogenesis that is not mediated by the antagonistic mechanisms of ERα and ERβ [16]. Lacasa et al. found the mechanisms involved by which estrogen stimulates preadipocyte proliferation, supporting a role of estrogen in adipogenesis [13, 37]. However, Eaton et al. postulated that local adipocyte-produced estrogen may play a role in preventing preadipocyte differentiation based on data from two studies where treatment of preadipocytes with estrogen, both in vitro and in vivo, inhibited adipogenesis and lipogenic gene expression [13, 38]. The distribution of preadipocytes and adipocytes along with the expression of estrogen receptors on differentiated adipocytes could play a role in the pathogenesis of lipedema, as regionalized and sexually distinct adipocyte hypertrophy is one of the central defining characteristics of the disorder.

Activation of ERα, ERβ, and GPER on adipocytes elicit an intranuclear response, causing up or down-regulation in the expression and activity of proteins such as leptin and lipoprotein lipase (LPL), which are involved in lipid regulation in the body [39, 40]. Through this regulation of protein expression, estrogen partially mediates weight control and lipogenesis-lipolysis mechanisms. Moreover, several studies have shown that estrogen treatment altered the expression of several genes involved in lipogenesis. A study conducted by Homma et al. revealed a negatively controlled estrogen response element in the LPL gene, indicating that estrogen decreases activity of LPL, a protein that regulates lipid uptake by adipocytes and leads to lipogenesis, which inhibits adipose deposition [41]. Another study has shown that estrogen stimulates the expression of leptin in human breast tissue [42]; thus, estrogen might play an important in the regulation of adipose tissue. We have shown that leptin gene expression is increased in adipocytes differentiated in vitro from adipose-derived stem cells obtained from obese lipedema patients compared to the same cells from healthy controls [43]; however, the effect of estrogen on the expression of leptin in lipedema has yet to be determined. Additionally, ERβ has been shown to be a negative regulator of peroxisome proliferator-activated receptor γ (PPARγ), a key transcription factor highly expressed in AT and controls the expression of LPL, glucose transporter type 4 (Glut 4) and leptin; thus, a decrease in ERβ expression increases adipogenesis which is detected in lipedema SAT [43]. However, further studies will be needed to study the correlation between the loss of ERs expression and the increase adiposity in AT disorders.

2.2 Estrogen and inflammation

Estrogen exerts regulatory effects on the immune system through ER-dependent and independent pathways [44], which can be both positive and negative depending on a wide array of factors such as the level of estrogen, expression of ERs, cell types and the environment [45]. Lipedema AT is characterized by hypertrophic adipocytes and activated immune cells such as macrophages and mast cells [46–48]; thus, direct, and indirect cellular interaction through auto- and paracrine secretions of inflammatory cytokines via the ER signal transduction pathway have an immense impact on the tissue function [7, 19, 35]. Several studies have shown that a decrease in estrogen levels results in increased expression of pro-inflammatory cytokines, including interleukins (IL)-6, IL1-β and Tumor Necrosis Factor-alpha (TNF-α) as is the case with women undergoing menopause or oophorectomy [49]. On the other hand, in the case of pregnant women or in women taking ectopic estrogens, suppressed immune responses are observed [48]. Hence, as estrogen levels fluctuate in lipedema patients during their lifetime, the inflammatory signals in the tissue may as well. This correlation between estrogen levels and onset of inflammation could provide insight into the pathophysiology of lipedema-associated inflammation.

3. Potential hormonal therapy

Estrogen is widely known as a central regulator of fat metabolism and regional deposition. In premenopausal women, estrogen is synthesized in the ovaries during menstruation [19]; however, it is depleted as they age. In adipose tissue, androgens are aromatized into estrogens to restore hormonal levels and prevent the progression of hormonal-related diseases [17, 19, 50]. One study found increased aromatase activity in a group of obese individuals, supporting a correlation between this shift of hormone production and metabolic disease [51]. However, estrogen deficiency or depletion, such as in the case of ovariectomy, polycystic ovary syndrome (PCOS), or the lack of a functional aromatase gene, causes weight gain which is associated

with comorbidity, cardiovascular disease, and other diseases; thus, hormone replacement therapy (HRT) was shown to be an effective treatment [52–57]. In the context of AT, administration of exogenous estradiol to premenopausal women decreases LPL activity in AT of the lower extremities, which are primarily affected in lipedema [58]. However, another study conducted by Lindberg et al. found that the treatment of postmenopausal women with oral ethinyl estradiol (50 μg/day) for three weeks increased adipose tissue LPL activity in femoral adipocytes [59]. Other studies expand on this, finding that estrogen treatment of adipocytes decreased the expression of genes related to adipogenesis and lipogenesis such as PPAR-γ and LPL [19, 38, 58]. Furthermore, administering estrogen resulted in a significant decrease in LPL activity in adipose tissue [52]. Similarly, Pederson et al. discovered that estrogen treatment almost doubled insulin binding affinity in rat adipocytes. Control rats had 11% weight gain in 7 days whereas estrogen treated rats gained only 4% in the same period. Adipocytes were significantly larger in control rats compared to adipocytes from estrogen substituted rats. Interactions of estrogens with androgens to mediate these processes were also discovered, with two studies observing the effects of HRT that further substantiate an association between androgens and weight gain [54, 60]. Davis et al. reported that administering androgens with estrogens in hormone replacement therapy seemed to antagonize or reduce the effects of estrogens on fat deposition and weight loss. Likewise, Gamberini et al. reported administration of antiandrogens with the typical estrogen dosage results in more efficient weight loss. While the effects of androgens in lipedema cases have been underdefined in this literature review, the pathophysiological effect of androgen therapy implies a treatment option for cases of lipedema. Clinical research has also found that women receiving estrogen HRT have relatively increased protection from metabolic syndrome and decreased AT deposition in the intra-abdominal region [13, 61–64]. Additionally, as mentioned above, post-menopausal clinical subjects developed high levels of inflammatory cytokines had associated decreases in such levels following estrogen treatments [13]. All these data confirm that the physiological impact of estrogen is altered as females passes through reproductive benchmarks, and thus estrogen may be a potential treatment of Lipedema patients.

Furthermore, it has been proposed that activation of ERα can induce the browning of white adipocytes, referred to as beiging, through induction of lipolysis mediated by adipose tissue triglyceride lipase [65]. It is known that premenopausal women have more brown adipose tissue (BAT) and are more sensitive to brown adipose tissue activation than men or postmenopausal women. Selective activation of ERα by pyrazole triol (selective ERα agonist) increased markers of beiging in vitro [65]. The results of this study indicated that selective activation of ERα in adipocytes can induce beiging through the induction of adenosine monophosphate-activated protein kinase (AMPK) mediated lipolysis providing free fatty acids as an energy source to activate Uncoupling protein (UCP)-1 [66]. Another study conducted Yepuru et al. demonstrated that activation of ERβ increases mitochondrial function and energy expenditure; thus, ERβ ligands have anti-obesity and antimetabolic disease effects [67] and might be more beneficial than estradiol treatment which unselectively activates both ERs. In vitro and in vivo studies have suggested that selective ERβ ligand reduces the expression of genes associated with white adipose tissue and promote the expression of genes associated with brown adipose tissue. This ligand additionally increases the mitochondrial oxygen consumption without an increase in physical activity [68]. Additional research is needed to gain insight into whether selectively activating of one estrogen receptor over another confers more benefits than activating both unselectively. Given these results on the selective activation of estrogen receptors, there is an increased effort to characterize specific molecular pathways to induce white adipose tissue browning; thus, presenting another potential treatment for lipedema patients.

4. Conclusion

Lipedema is a severe chronic adipose tissue disorder that affects women worldwide. Although the pathophysiology of the disease has not been fully elucidated, several lines of evidence have suggested estrogen dysfunction may be central to the development of lipedema. The loss of estrogen can additionally induce cardiovascular disease and create an insulin resistant dyslipidemia state that can have long term implications on the metabolic profile of a patient. Thus, studying the role played by estrogen in the processes are involved in the pathogenesis, AT inflammation, fibrosis, and angiogenesis, will provide researchers insights into the mechanism involved in the development of the disease and will help direct future study on hormonal therapy as a form of treatment for lipedema. Through these efforts, the correlation revealed between hormones and adipogenesis in AT will lead to evaluate lipedema as a hormonal disease.

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Conflict of interest

The authors declare no conflict of interest.

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