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Mini Review

Is Lipedema a Unique Entity?

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Abstract

Lipedema is a disease with high prevalence but low recognition. It is often misdiagnosed and underdiagnosed. Obesity and lymphoedema are the most common differential diagnoses and can also coexist in patient with lipedema. Its broad range of presentation and fat distribution types contribute to this confusion. It is likely that lipedema symptom variations and presentation forms are often associated with hormonal variations, chronic low-grade systemic inflammation, and wide polygenic variations. This paper presents a theory regarding the clinical evolution of lipedema clinical and its involvement with other diseases, suggesting a three-phase approach for treatment.

Keywords: *Lipedema; Obesity; Lymphoedema*

Introduction

Though it was first described 1940 by Allen and Hines [1,2], little is understood about lipedema [3]. This adipose tissue disorder is also known as "adiposis dolorosa" (painful fat), Allen-Hines syndrome and lipofilia membralis [4,5]. Obese women with lipedema are often misdiagnosed with lymphoedema [6]. One of the most common misconceptions about lipedema is that the patients suffer from lifestyle- or diet-induced obesity [3]. Some patients have both obesity and lipedema; however, lipedema is an entity distinct from obesity. It may be misdiagnosed as primary obesity because of overlapping clinical presentations. The phenotype suggests a condition that is distinct from obesity and is associated with pain, tenderness, and easy bruising in affected areas [7].

Lipedema presents with a wide range of symptoms and impacts on quality of life. Rapprich., *et al.* administered a questionnaire to measure symptoms associated with lipedema using a visual analogue scale in 25 patients before and after surgical treatment [8]. The scores ranged from 0 to 150 and mean score before treatment was 92 (± 21.3) and 39.0 (± 23.2) after 6 months of treatment, suggesting that there was a wide range of impairment caused by the disease. Clinical evolution of fat deposition and other symptoms, related to inflammatory aspects, and its correlation with external factors can be seen in figure 1, describing a three-phase treatment consisting of clinical treatment, self-awareness and surgical treatment.

Genetics

High prevalence genetic diseases have more often polygenic contribution

If estimates are correct, the incidence of lipedema is 1 in 9 adult women [3]. This high prevalence may explain why lipedema the genetics is not yet fully understood.

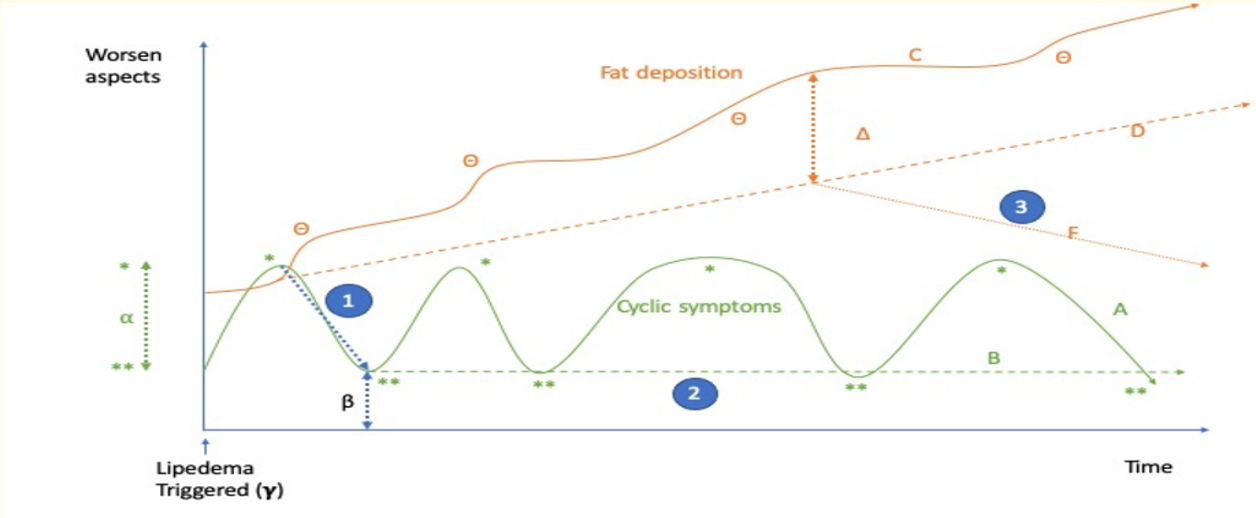

Figure 1: *A) Cyclic worsening and improvement of symptoms can be seen during life (α), with peaks (*) and troughs (**). This phenomenon is probably associated with chronic low-grade systemic inflammation triggered mainly by external factors such as acute inflammation or inflammatory food intake. After treatment of low-grade systemic inflammation (1), which I consider to be the first phase of lipedema treatment, there is an improvement in lipedema symptoms. Treating low-grade systemic inflammation (1) can lower symptoms but cannot cure all symptoms (remaining symptoms: β). Despite symptomatic improvement, achieving baseline for symptoms is very rare only with clinical treatment, although it is possible. B) The dashed green line shows what can be achieved with self-awareness of inflammatory triggers and avoiding them during life (2). I consider self-awareness of the disease and its triggers as the second phase of the treatment. C) After initial trigger of lipedema (γ) with hormonal variation (often puberty, pregnancy or menopause), fat deposition always increases (Orange lines C and D); however, during inflammatory peaks (*), there is a higher deposition of fat (Θ). D) Avoiding other inflammatory peaks (B) will not stop fat deposition (D) but will lower fat deposition over time (Δ), lowering risk of lipedema complications. F) To reduce fat deposition (3), which I consider the third phase of treatment, we have fewer options, including surgical liposuction and ketogenic diet, both of which are associated with mixed results, probably because of the polygenic nature of the disease with large variation of expression. (Based on clinical and empirical data obtained in a focused approach with lipedema patients).*

The precise etiology is also not yet understood; however, we know that genetic and hormonal factors may be involved [6]. It was proposed that lipedema is a genetic condition with either X-linked dominant inheritance or more likely, autosomal dominant inheritance with sex limitation [7].

Polygenic diseases are caused by the joint contribution of a number of independently acting or interacting polymorphic genes; the individual contribution of each gene may be small or even unnoticeable. The carriage of certain combinations of genes can determine the occurrence of clinically heterogeneous forms of the disease as well as treatment efficacy. Because such disorders depend on the simultaneous presence of several genes, they are not inherited as simply single-gene diseases.

The recognition that rare alleles are important contributors to common complex human diseases is a major paradigm shift in human genetics [9]. Each "risk variant" is postulated to confer a small degree of risk; however, it fails to explain the vast majority of genetic heritability for human disease [9]. Marked genetic heterogeneity correlates with multiple levels of causation in many common human diseases.

These levels of causation are complex and occur in the following combinations: rare, individual mutations that when combined contribute to the development of common diseases; the accumulation of several rare, individual mutations within the same gene that contribute to the development of the same common disease among different individuals; the accumulation of several rare, individual mutations within the same gene that contribute to the development of different phenotypic variations of the same common disease within different individuals; and the development of the same common disease in different individuals through different mutations.[9] Many common human diseases and traits cluster in families and are believed to be influenced by several genetic and environmental factors. Increased understanding of the role of genetic heterogeneity and the mechanisms through which it produces common disease phenotypes will facilitate the development of effective prevention and treatment methods for these diseases [10].

Hormones

There was a recent description of the association of hormone deficiency due to a Pit-1 mutation and lipedema in a family, as well as lipedema in an unrelated man with growth hormone and testosterone deficiency but no family history [11].

Recently Szél., *et al.* proposed a lipedema theory in which lipedema is an estrogen-regulated polygenetic disease, manifesting in parallel with feminine hormonal changes and leads to vasculopathy and lymphangiopathy. Inflammation of peripheral nerves and sympathetic innervation abnormalities of the subcutaneous adipose tissue also involving estrogen may be responsible for neuropathy. Furthermore, adipocyte hyperproliferation is likely to be a secondary phenomenon maintaining a vicious cycle [12].

Systemic inflammation

Low grade or mild inflammation could explain lipedema symptom variations, prognosis and evolution through time. Inflammation is a hallmark of many human diseases [13].

Cancer is by far the most often-studied, and it is now widely recognized that outcomes in patients with cancer are not determined by tumour characteristics alone, but that patient-related factors are also critical to outcomes. In the last decade, it has become increasingly apparent that cancer-associated inflammation is a key determinant of disease progression and survival in most cancers [14]. Human blood leukocyte response to acute systemic inflammation includes the transient dysregulation of leukocyte bioenergetics and modulation of translational machinery [13]. The systemic inflammatory response has been proven to have a prognostic value for colon cancer [15] and there is evidence to suggest that the presence of a systemic inflammatory response is a major factor underlying patient decline [16].

Chronic noncommunicable diseases (CNCDs), including cardiovascular conditions (mainly heart diseases and stroke), some cancers, chronic respiratory conditions, and type 2 diabetes, affect people of all nationalities and classes and are reaching epidemic proportions worldwide [17]. From a historical perspective, inflammation has been considered to be the natural host response to an acute infectious episode, whereas chronic inflammation has been considered a sign of chronic infection. It has now become clear that low-grade chronic inflammation is a key player in the pathogenesis of most CNCDs [17]. There has been an increasing appreciation of the role of inflammation both in the pathogenesis of atherosclerosis and as a key factor in insulin resistance. Low-grade chronic inflammation is characterized by increased systemic levels of some cytokines and C-reactive protein (CRP) and a number of studies have confirmed an association between low-grade systemic inflammation on one hand and atherosclerosis and type 2 diabetes on the other [17].

Regular physical activity offers protection against and may be useful as a treatment for a wide variety of, chronic diseases associated with low-grade inflammation [18]. It is currently understood that exercise can improve symptoms in lipedema, despite not decreasing fat accumulation, and it is used as supporting treatment [19]. The protective effects of regular exercise against diseases such as cardiovascular disease, type 2 diabetes, colon cancer, and breast cancer have been reviewed extensively [18,20-22]. Recent findings demonstrate that physical activity induces an increase in the systemic levels of a number of cytokines with anti-inflammatory properties [23,24] and

skeletal muscle has recently been identified as an endocrine organ that produces and releases cytokines (also called myokines) [25,26]. The discovery of contracting muscle as a cytokine-producing organ creates a new paradigm: Skeletal muscle is an endocrine organ that, during contraction, stimulates the production and release of myokines that may influence metabolism and modify cytokine production in tissue and organs [17].

Chronic low-grade systemic inflammation and its consequences

Acute inflammation can trigger chronic low-grade inflammation that persists for a long time and generates positive feedback, initiating and perpetuating lipedema symptoms.

In response to an acute infection or trauma, levels of cytokines and cytokines inhibitors increase [24]. The initial cytokines that appear in the circulation in response to an acute infection are the following: TNF-α, IL-1β, IL-6, IL-1 receptor antagonist (IL-lra) and soluble TNFα-receptors (sTNF-R), and IL-10. The systemic response known as the acute-phase response includes the production of a large number of hepatocyte-derived acute phase proteins, including C-reactive protein (CRP) that is a sensitive marker of systemic inflammation. The response can be mimicked by the injection of the cytokines TNF-α, IL-1β, and IL-6 into laboratory animals or humans [24,27]. Chronic low-grade systemic inflammation has been characterized by a 2- to 3-fold elevation in the systemic levels of proinflammatory and anti-inflammatory cytokines, natural occurring cytokine antagonists, and CRP [22,28]. In the latter case, the stimuli for the cytokine production are not known; however, it is assumed that the origin of TNF in chronic low-grade systemic inflammation is primarily adipose tissue [29-32].

Type 2 diabetes, obesity, and cardiovascular disease are related to a state of low-grade systemic inflammation [33-36]. Despite the fact that the changes in acute-phase reactants are much smaller than those in acute infections, the chronicity of low-grade inflammation is strongly associated with increasing age, lifestyle factors such as smoking and obesity, together with increased risk of cardiovascular disease and type 2 diabetes [28,30,37]. Plasma concentrations of IL-6 [38] and TNF-α have been shown in several studies to predict the risk of myocardial infarction [38] and CRP has emerged as a much stronger independent risk factor for cardiovascular disease than low-density lipoprotein cholesterol levels [22,39,40].

A number of studies suggest that IL-6 enhances lipolysis as well as fat oxidation [17,41,42].

Subclinical elevations of IL-6, CRP, orosomucoid, and sialic acid are related to the development of diabetes in middle-aged adults [43]. It is increasingly recognized that low-grade systemic inflammation precedes and predicts the development of both diabetes and atherothrombotic diseases. The mild inflammatory state is closely related to obesity and insulin resistance. It appears to be related to lipedema as well. Adipocytes, especially in the obese, secrete a number of proinflammatory cytokines [44] some of which have been shown to directly inhibit insulin signaling [45]. Adipocytokines probably act through master proinflammatory regulators such as those of the nuclear factor-κB [45] and the c-Jun NH_2-terminal kinase (JNK)/AP-1 signaling pathways [45] to modulate the expression of genes coding for many inflammatory proteins and to alter insulin signaling. These actions have two basic consequences: first, to augment and perpetuate the proinflammatory diathesis; and second, to decrease insulin sensitivity. Some adipocytokines may also cause vasoconstriction [44]. Vasoconstriction appears to diminish insulin action [46].

Obesity also decreases adipocyte expression of adiponectin, which has anti-inflammatory and insulin-sensitizing effects [46]. The important role for adipocytokines in this process may explain the somewhat stronger inflammation score-incident diabetes association we found with higher BMI.

Smoking generates systemic inflammation that is related to subsequent chronic pulmonary inflammation and to the proinflammatory molecules in cigarette smoke [47,48]. Smokers in the study of Duncan., *et al.* had notably higher inflammation scores [43]. Smoking appears to activate proinflammatory macro-regulatory molecules differentially, with one study showing blunted activation of JNK [47]

which has recently been suggested to be important in weight gain and obesity-related diabetes [49]. Furthermore, nicotine, through the nicotinic receptor, has recently been shown to have anti-inflammatory effects [48,50-52]. If adipocytes have nicotinic receptors similar to those recently shown to exist on macrophages, then smoking, by generating an overall proinflammatory state, could selectively inhibit the effects of inflammation on adipocyte metabolism and adipocytokine production, a mechanism that might explain the observed heterogeneity.

Conclusion

Lipedema appears to be a polygenic disease that is closely associated with and dependent on hormone expression and chronic low-grade inflammation. Proinflammatory and anti-inflammatory factors appear to influence lipedema symptoms. Treatment should include inflammatory manifestations using a three-phase approach: controlling low grade inflammation, self-awareness of inflammatory triggers and surgical liposuction and/or ketogenic and anti-inflammatory diet.

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