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MEASUREMENT OF CAPILLARY FRAGILITY: A USEFUL TOOL TO DIFFERENTIATE LIPEDEMA FROM OBESITY?

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ABSTRACT

Lipedema is a disproportional obesity featuring spontaneous or light pressure-induced pain and frequent hematoma formation due to even minor traumatic injuries. It is generally distinguished from general obesity primarily based on clinical hallmarks; however, this becomes difficult when appearing in a concomitant form (combination of obesity and lipedema). Our study group has recently demonstrated that lipedema-associated bruising is correlated with increased capillary fragility (CF) and also that CF could be significantly improved by complex decongestive physiotherapy (CDP). In this study, we measured CF in female subjects with lipedema (15) or non-complicated obesity (15) who were body mass index (BMI) and waist-to-hip ratio (WHR) matched. CF was evaluated with the vacuum suction method (VSM) using Parrot's angiosterrometer in both groups. Application of VSM resulted in a significantly higher number of petechiae in subjects with lipedema. Capillary fragility measurement appears to be a useful differential diagnostic tool between lipedema and obesity under these trial parameters.

Keywords: lipedema, obesity, capillary fragility, vacuum suction, angiosterrometry

Lipedema

Lipedema is a distinct clinical entity characterized by bilateral, symmetrical, biker's hosiery-shaped disproportional obesity (1-4). Arms are also quite commonly affected by fatty hypertrophy (2). Edema usually tends to have an orthostatic prolongation. This disorder is a real "hidden epidemic" with up to 11% of women or postpubertal girls affected to some degree (2). The relatively high prevalence of hormonal disturbances, especially thyroid abnormality, among lipedema patients may play a role as an aggravating factor (4). So far, no genetic factors have been identified although Bano et al has recently found MIC-1 mutation in family members suffering from lipedema (5). Studying morphological alterations in lipedema, Suga et al recently demonstrated massive CD68+ macrophage infiltration in lipedematous adipose tissue with loss of adipocytes and proliferation of adipose-derived stem cells (Ki67+CD34+) (6). These results may suggest massive adipogenesis and concomitant hypoxia that results in necrosis and macrophage recruitment (6).

It is easily distinguishable from other entities like lymphedema and phlebedema in the striking clinical features; however, its frequent combination with obesity makes the

diagnosis more complicated. Lipedematous fatty enlargement barely or never responds to diet and forced weight-loss unlike general obesity. The exact diagnosis should be preferably determined immediately but lack of further differential diagnostic procedures remains a challenge. Lipedema patients nearly always complain of pain upon palpation that worsens with aging. The other hallmark is frequent spontaneous or trauma-induced hematoma formation (2,4,7). In this background we found fairly high capillary fragility (CF) that could be efficiently decreased using complex decongestive physiotherapy (CDP) (7). Lipedema is also accompanied by local circulation abnormalities although major venous dysfunction is rarely found (8). In its clinical appearance the basic classification comprises columnar and lobar types (2). Severity-based description includes three distinct stages: stage I (normal skin surface, small nodular fatty tissue structure), stage II (uneven skin surface and harder, large nodular fatty tissue structure), stage III (lobular deformation due to increased fatty tissue with mattress phenomenon) (3). Transition from the less advanced to the most severe stage (stage I to III) may last for decades.

The peculiar fatty hypertrophy is presumably linked with capillary leakage inducing the production of interstitial fluid and lymph accumulation (7). Therefore, in early stages of lipedema, increased lymph flow may be detected using lymphscintigraphy, and this flow worsens over time as the overworked lymph vessels begin to fail in maintaining elevated transport capacity (9). Fluorescent microlymphography has diagnosed lymphatic microaneurysms and dilated vessels of the uppermost lymphatic network indicating that these lymph vessels are also involved (10).

In prolonged courses of lipedema, lymph vessels are unable to sustain their function, and altered microcirculation leads to impaired lymph transport capacity and accumulation of lymph fluid. The high protein and fat content of lymph fluid can induce a low-grade inflammation and subsequent fibrosis leading to non-pitting edema characterized by Stemmer's sign (2,7).

The widely accepted and now evidence-based conservative approach for lipedema is CDP comprising manual lymph drainage (MLD), multilayered compression with short-stretch bandages, regular walk-training (exercises), and meticulous skin care (11,12). Manual lymph drainage (MLD) is a standard and effective therapeutical tool against various forms of primary and secondary lymphedemas. Pressotherapy (IPC) is an adjunctive treatment to MLD, that mainly reduces edema and improves venous flow (12). Multilayered compression bandaging plays a crucial role in the further reduction of leg volume enhancing the continuous self-massage using the active involvement of muscle pumps. Higher efficacy can be achieved using gentle forms of liposuction (13).

Obesity

Obesity is most commonly caused by a combination of excessive dietary caloric intake, lack of physical activity, and genetic susceptibility, although some cases are caused primarily by genetic background, endocrine disorders, medications, or psychiatric illness (14). Complications may include cardiovascular disorders, diabetes mellitus, cancers, cholelithiasis, fatty liver and cirrhosis, osteoarthritis, reproductive disorders in men and women, psychologic disorders, and premature death. Diagnosis is mostly based on BMI (calculated from height and weight), waist circumference (WC), and waist-to-hip ratio (WHR). Blood pressure, fasting plasma glucose, and lipid levels should be measured. The most frequently used anthropometric measures are BMI and WC. Unlike WHR, they do not give reliable information on body structure and morbidity. BMI and WC are reasonable surrogate measures of body and visceral fat, respectively but they lack sensitivity and specificity when applied to individuals.

WHR is calculated by measuring the smaller circumference of the natural waist, usually just above the belly button, and dividing by the hip circumference at its widest part of the buttocks or hip. The WHR has been used as an indicator or measure of the health of a person and the risk of developing serious health conditions. Research shows that people with "apple-shaped" bodies (with more weight around the waist) face more health risks than those with "pear-shaped" bodies who carry more weight around the hips. If obesity is redefined using WHR instead of BMI, the proportion of people categorized as at risk of heart attack worldwide increases threefold (15).

A novel clinical staging system is based on simple clinical assessments that include medical history, clinical and functional assessments as well as simple routine diagnostic investigations that are easily and widely available (14). Rather than simply categorizing patients based on anthropometric measures, the proposed staging system would provide a measure for presence and severity of risk factors, comorbidities, and functional limitations that would serve as a guide to management.

Previous studies have shown similar detrimental associations of truncal adipose tissue, independently of BMI or total body fat, on large vessel properties such as arterial stiffness and on cardiovascular risk factors such as insulin resistance and dyslipidemia. Recent experimental and prospective studies suggest a pathophysiological role for capillary recruitment in the development of insulin resistance and hypertension. No such correlation is suspected in case of non-truncal, pear-shaped (hip and leg affection) obesity.

Obesity may be a primary cause of microvascular dysfunction and this has several pathophysiological consequences. First, it may constitute a pathway through which obesity increases blood pressure and decreases insulin sensitivity. In addition, it may directly contribute to obesity-associated microangiopathy. Indeed, the individuals are associated with impaired microvascular function and the pathophysiological mechanism behind the relationship between obesity and microvascular dysfunction is probably multifactorial (16,17). Adipose tissue secretes substances, such as free fatty acids (FFAs), tumor necrosis factor-alpha (TNF-alpha), and adiponectin that can influence microvascular function. An increase in FFAs impairs vascular function in resistance vessels in humans and in microvasculature in rats. Fasting FFA levels were not associated with microvascular function in a recent study but this does not exclude a role for FFA dynamics in modulating microvascular function.

In addition, in rats acute TNF-alpha elevation impairs insulin-induced capillary recruitment and glucose uptake, and in humans it concomitantly impairs insulin-induced endothelium-dependent vasodilatation in resistance vessels and glucose uptake. Adiponectin levels are reduced in obesity, and adiponectin has a vasoprotective effect as demonstrated by associations between hypoadiponectinemia and impaired endothelial function in resistance vessels. Although not yet fully established in a clinical setting, endothelial and microvascular dysfunction, characterized by decreased responses to endothelial-derived relaxing factors (essentially, but not only nitric oxide) and alterations of hemodynamic parameters such as the number of perfused capillaries and baseline red blood cell velocity, respectively, have been hypothesized as primary causes of insulin resistance. In type 2 diabetes mellitus microvascular dysfunction has been well characterized in the coronary bed and the skin, but in young uncomplicated overweight/obese persons, the extent of microvascular damage tested by non-invasive nailfold videocapillaroscopy and its interrelationship with clinical-anthropometrical-laboratorial parameters remains to be determined (18). Obesity without any medical complications has relatively normal capillary fragility but when associated with conditions like diabetes, cardiac insufficiency,

hypertension, or renal insufficiency then capillary fragility might increase (16- 18).

The primary treatment for obesity includes exercise and dieting. To supplement this, or in case of failure, anti-obesity drugs may be taken to reduce appetite or inhibit fat absorption. In severe cases, surgery (e.g., bariatric surgery) is performed or an intra-gastric balloon is placed to reduce stomach volume.

There is a strong need for finding a new, reliable tool to differentiate lipedema from obesity and to promote the earliest diagnosis because therapeutical algorithms are distinguishable. Current knowledge allows speculation that lipedema and non-truncal obesity vary in the degree of capillary fragility. Thus, the goal of the comparative trial was to measure CF in lipedema and obese subjects.

PATIENTS AND METHODS

Sample Characteristics

This comparative study included 15 women [median age: 59.53 years (range: 38-82 years)] with lipedema and 15 obese women [median age: 51.13 years (range: 33-64 years)] without the clinical signs of bilateral leg lipedema. Both legs were examined throughout the trial in both groups. Patients were first seen at the Lymphedema Outpatient Care Unit of the Department of Dermatology and Allergology, University of Szeged. None of the recruited subjects were under treatment at the time of capillary fragility measurement. Measurement was started after a written informed consent approved by the Institutional Review Board of Albert Szent-Györgyi Clinical Centre, University of Szeged, Hungary.

All obese subjects were carefully selected on the basis of specific criteria to rule out any condition that might interfere with microvessel function and thereby lead to false results.

The criteria for recruitment of obese persons considered included a BMI >30 and the lack of biker's hosiery shape or painful fatty edema suggesting lipedema. In addition, other exclusion criteria included: no treated or untreated hypertension; vasculitis or active autoimmune disease; thighs with active inflammatory involvement; evidence of diabetes mellitus; intake of venotonic drugs within the last month; intake of corticosteroid therapy (systemic or topical on thighs); and use of compression therapy.

CF Assessment

CF was evaluated using a vacuum suction chamber (Parrot's angiosterrometer) as described elsewhere (7) using the following modifications. Briefly, standardization included continuous room temperature at 22 °C and an obligatory 10-min-rest in supine position before Parrot's angiosterrometry. In each case, the skin of the flexor part of both thighs (the border of the upper and middle one-third) was sucked with Parrot's angiosterrometer for the period of 1 minute. The negative pressure in the glass chamber was 300 mmHg (*Fig. 1*). Finally, the number of petechiae was counted within the glass suction cup of the instrument by the same two non-independent readers using Dermlight DL 100 dermoscope (3Gen Inc, San Juan Capistrano, CA, USA) (19). The application of limited negative pressure for a short period on the skin may break and damage some of the most altered and fragile uppermost capillary loops. The range of diameters of visible petechiae was between 100 and 1000 µm. In both groups we considered right and left legs separately and comparisons were made within the identical groups (right obese leg vs right lipedematous leg and left obese leg vs left lipedematous leg).

Anthropometric Measures

Body mass index was calculated as weight (in kg)/height^2 (in meters).

Waist-to-hip ratio was evaluated using a measuring tape. Hip circumference at the

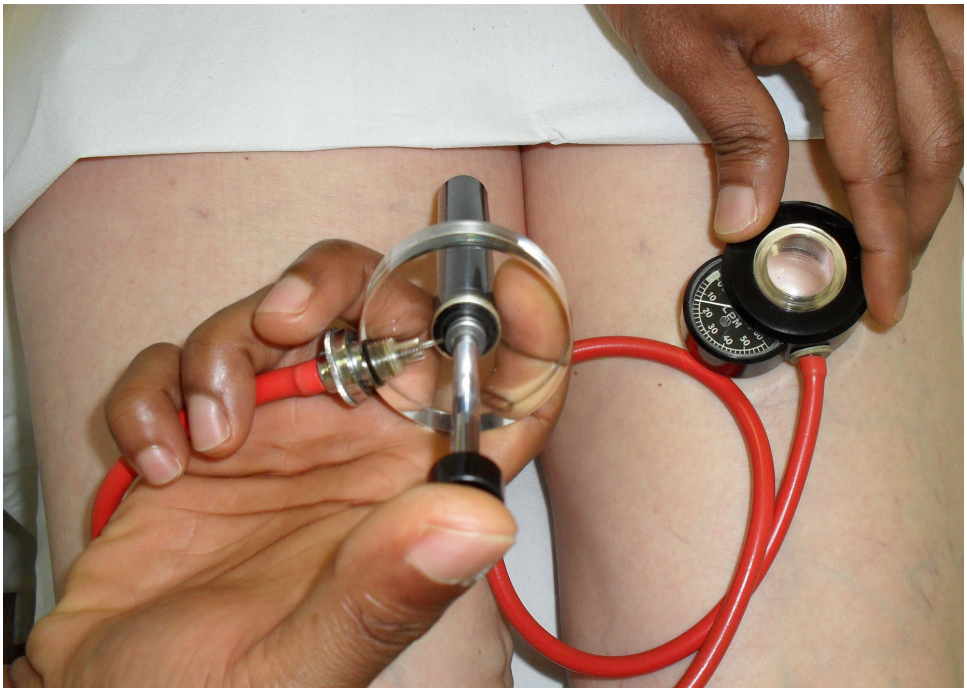

Fig. 1. Photograph demonstrating the application of the Parrot's angiosterrometer vacuum method at upper level of the distal one-third of the right thigh flexor surface.

level of the two bony prominences (anterior iliac spines) felt in the front of the hips, then waist circumference were measured. Waist circumference (cm) was divided by hip circumference (cm).

Statistical Analysis

Kolmogorov-Smirnov test found normal distribution in both groups so statistical analysis was performed with two-sided (two-sampled) t-test.

RESULTS

There was no statistical difference regarding mean age (p=0.28), body weight (p=0.211), height (p=0.293), BMI (p=0.358) and WHR (p=0.869).

On examination mean number of petechiae was 13.38±10.23 in the right leg and 13.44±11.53 in the left leg of lipedema patients and 2.47±3.09 in the right leg and 2.33±2.35 in the left leg of obese women. Difference appeared to be significant in both comparisons (p=0.01 and p=0.02; respectively). *Fig. 2* illustrates typical results of vacuum suction method induced petechiae in obese and lipedema women.

DISCUSSION

Lipedema is a chronically progressive, bilateral, symmetrical accumulation of fat in the subcutaneous tissue with orthostatic edema, which occurs almost exclusively in women. General obesity is characterized by accumulation of excess body fat which usually can be seen throughout the body including the legs. Importantly for this study, lipedema and not obesity tends to be associated with frequent hematoma formation even after minor traumatic injuries due to increased capillary fragility.

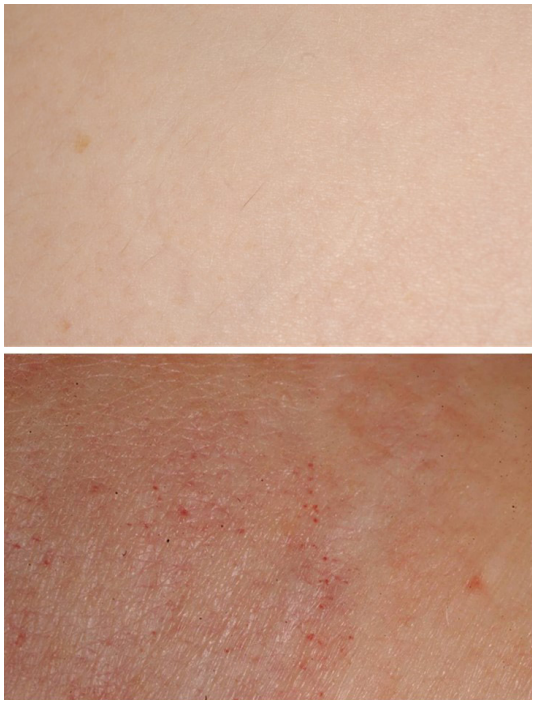

Fig. 2. Vacuum suction with the angiosterrometer was unable to induce petechia formation on the right thigh of a 46-year old obese woman (Top) compared to numerous induced petechiae on the left thigh of a 56-year old woman with lipedema (Bottom).

In lipedema, the pathological fat deposit, distribution and peculiar enlargement of subcutaneous fat is presumably linked with microangiopathy and altered microcirculation leading to increased permeability and protein-rich fluid extravasation, which further enhances the amount of lymph formed.

In general obesity, the cause of capillary malfunction has not yet been fully clarified; however, endothelial dysfunction has been assumed in most published studies, and again fat distribution has been found to be the main determinant. Thus WHR, a clinical marker representing abdominal obesity, seems to be better correlated with endothelial dysfunction than BMI. Obesity without relevant comorbidities less frequently results in relevant capillary dysfunction.

Our study indicates the possibility to differentiate lipedema from general obesity on the basis of capillary fragility using the vacuum suction method. Other published methods mostly distinguish lymphedema from obesity (19,20).

Our design used a vacuum suction chamber (Parrot's angiosterrometer) for capillary fragility measurements because it is very simple, cheap, quick, and easily applicable (non-invasive). However, the measurement requires standardization (room temperature, timing, same test site) and adequate magnification at reading ruptured capillaries is mandatory. It exerts an adjustable suction to the examined skin and was found to be an excellent technique for determination of capillary fragility in lipedema. We carefully selected the control group due to the fact that obesity very often was associated with complicating factors such as diabetes or hypertension that affect the microcirculation and would lead to false results. This greatly reduced our potential subject population and may also reduce the applicability of our study to the larger population. We observed that the number of petechiae recorded in lipedema was substantially higher than in the control group. This finding is consistent with higher capillary fragility in lipedema compared to non-complicated obese cases. Capillary fragility is the propensity to capillary wall rupture. The application of limited negative pressure for a short period breaks some of the most altered and fragile uppermost capillary loops. The range of diameters of visible petechiae is between 100 and 1000 µm. Diseases with microangiopathy including immune-mediated vasculitides, coagulopathy and certain medications (e.g., corticosteroids, platelet aggregation inhibitors, anticoagulants) strongly increase capillary fragility. We suggest that VSM is useful to differentiate lipedema from obesity without comorbidities and its use for diagnosis in the earliest stages of lipedema where proper therapeutical approaches for treatment or prevention of further worsening would be valuable.

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CONFLICT OF INTEREST AND DISCLOSURE

All authors declare that no competing financial interests exist.

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