

LIPDEMA IS ASSOCIATED WITH INCREASED AORTIC STIFFNESS

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ABSTRACT

Lipedema is a disproportional obesity due to unknown pathomechanism. Its major hallmark is frequent hematoma formation related to increased capillary fragility and reduced venoarterial reflex. Beyond microangiopathy, both venous and lymphatic dysfunction have also been documented. However, arterial circulation in lipedema has not been examined, and therefore we explored aortic elastic properties by echocardiography. Fourteen women with and 14 without lipedema were included in the study. Each subject consented to blood pressure measurement, physical examination, and transthoracic echocardiography. Aortic stiffness index (β), distensibility, and strain were evaluated from aortic diameter and blood pressure data. Mean systolic (30.0 ± 3.2 vs. 25.5 ± 3.6 , $P < 0.05$) and diastolic (27.8 ± 3.3 vs. 22.3 ± 3.1) aortic diameters (in mm) and aortic stiffness index (9.05 ± 7.45 vs. 3.76 ± 1.22 , $P < 0.05$) were significantly higher, while aortic strain (0.082 ± 0.04 vs. 0.143 ± 0.038 , $P < 0.05$) and distensibility (2.24 ± 1.07 vs. 4.38 ± 1.61 , $P < 0.05$) were significantly lower in lipedematous patients compared to controls. Thus, lipedema is characterized with increased aortic stiffness.

Keywords: lipedema, aortic stiffness, echocardiography, blood pressure

Lipedema was first described by Allen and Hines more than seven decades ago but its pathomechanism has remained enigmatic (1). It is a disproportional obesity that nearly always affects women and is characterized by bilateral, symmetrical, biker's hosiery-shaped fatty swelling of the legs with sparing of the feet (2-4). Arms are also commonly affected by adipose hypertrophy. However, during progression, the characteristic "stove-pipe" legs emerge and as a result of orthostatic prolongation, a sharp demarcation between normal and abnormal tissue at the ankle occurs with the filling of retromalleolar sulcus, giving the "pantaloons" appearance (Fig. 1).

The skin is usually normal in texture and appearance, without the dermal thickening or induration common in lymphedema. At most, one in ten women or postpubertal girls may exhibit involvement to some degree (5). Lipedema is presumably associated with genetic background, but, to date, none of the examined genes have proved to be responsible for the phenotypic appearance (6). It is easily distinguishable from lymphedema and phleboedema by clinical features (2,4,5), and hormonal abnormalities can commonly be detected (2,4,5). Lipedema is often combined with morbid obesity, although lipedematous tissue hardly or never responds to diet and forced weight loss. Lipedema patients nearly always complain of spontaneous or mild



Fig. 1. Lipedema: clinical appearance.

injury evoked pain upon palpation that worsens with aging. Another hallmark is frequent hematoma formation due to even minor trauma (2,4,5). This feature is depicted in increased capillary fragility (CF) and partially with decreased venoarterial reflex (VAR) (7,8). Lipedema is accompanied by local lymphatic and venous abnormalities (e.g., irregularly dilated lymphatics, lymphatic microaneurysms, and varicosity), however major venous dysfunction is rarely found (9-11).

The peculiar enlargement of subcutaneous fat is linked with microangiopathy and altered microcirculation leading to increased permeability and protein-rich fluid extravasation, both of which further enhance the amount of lymph produced. Therefore, in early stages, an increased lymph flow may be

visualized by lymphoscintigraphy, and this worsens with aging (10). As soon as overload of lymphatics occurs, lymph vessels are unable to maintain their function and altered microcirculation leads to impaired lymph transport capacity and accumulation of lymph fluid. Lymph stasis induces fibrosis leading to non-pitting edema characterized by Stemmer's sign (5).

Despite alterations in capillaries, lymphatics, and veins, the function and morphology of large arteries have not previously been studied and therefore, not been examined in relation to lipedema. The markedly reduced elasticity of the skin and the poor venoarterial reflex in conjunction with robust fatty enlargement also substantially weakens venous calf pumping activity leading to further impaired venous and lymphatic function. Massively enlarged adipose tissue and accompanying edema may increase vascular resistance affecting arterial function. Some data suggest that body weight and fat distribution are related to higher arterial stiffness (12), and these data have stimulated our examination of aortic elasticity in lipedema.

Two-dimensional transthoracic echocardiography (2DE) is a valuable and non-invasive method for assessment of aortic stiffness index (β), distensibility, and strain as a reliable characteristics of arterial elasticity (13,14). The current study was designed to measure these parameters of elasticity in women with and without lipedema.

PATIENTS AND METHODS

Study Population

The study included 14 women with and 14 without lipedema. All of them were referred to our outpatient clinic for routine cardiological examination, whereas lipedema patients were first seen at the lymphedema outpatient care unit in the Department of Dermatology and Allergology (*Table 1* displays patient demographics). All patients

TABLE 1
Patient Demographics

	Lipedema	Control	P value
Age (years)	40.3±9	35.5±8.1	> 0.05
BMI (kg/m ²)	27.6±1.7	27.2±3.3	> 0.05
Diabetes mellitus	0	0	> 0.05
Lipid metabolism disorder	0	0	> 0.05
Hypertension	4	3	> 0.05
Anemia	0	0	> 0.05

underwent physical examination, 2DE, and blood pressure measurement. Patients with coronary or valvular heart disease, atrial fibrillation or other arrhythmias, heart failure, unstable angina pectoris, or acute myocardial infarction were excluded. Body mass index (BMI) was calculated by dividing the participant's weight in kilograms by the square of his/her height in meters. The following classification was used: overweight (BMI 25-29.9 kg/m²), grade 1 obesity (BMI 30-34.9 kg/m²), grade 2 obesity (BMI 35-39.9 kg/m²) and grade 3 obesity (BMI greater than 40 kg/m²) (12). Informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a prior approval by the institution's Human Research Committee.

Blood Pressure Measurement

After clinical and demographic data recording, systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in the supine position with a mercury cuff sphygmomanometer from the left arm after 10 min of rest. The first and the fifth Korotkoff sounds were taken for the SBP and DBP. Stimulants were not used or consumed during the 30 minutes prior to the blood pressure measurements. The average of

three consecutive measurements was accepted as the blood pressure measurement.

Transthoracic Echocardiography

All subjects underwent a complete 2DE and Doppler study using a Toshiba Powervision 8000 and Aplio echocardiography equipments (Toshiba, Tokyo, Japan) in the left lateral decubitus position from multiple windows. 2-dimensional echocardiography-guided M-mode tracings were used to measure systolic and diastolic ascending aortic diameters (SD and DD, respectively) using the leading-to-leading edge technique at a level of 3 cm above the aortic valve from parasternal long-axis view, according to a method described previously (14). Gain, depth, and sector angles were set in an individualized manner to provide the best measurement. The SD and DD were measured at the maximum anterior motion of the aorta and at the peak of QRS complex on the simultaneously recorded ECG, respectively (Fig. 2).

Evaluation of Aortic Stiffness, Distensibility and Strain

Aortic stiffness index (β) was used as a characteristic of aortic elasticity, which represents the slope of the exponential

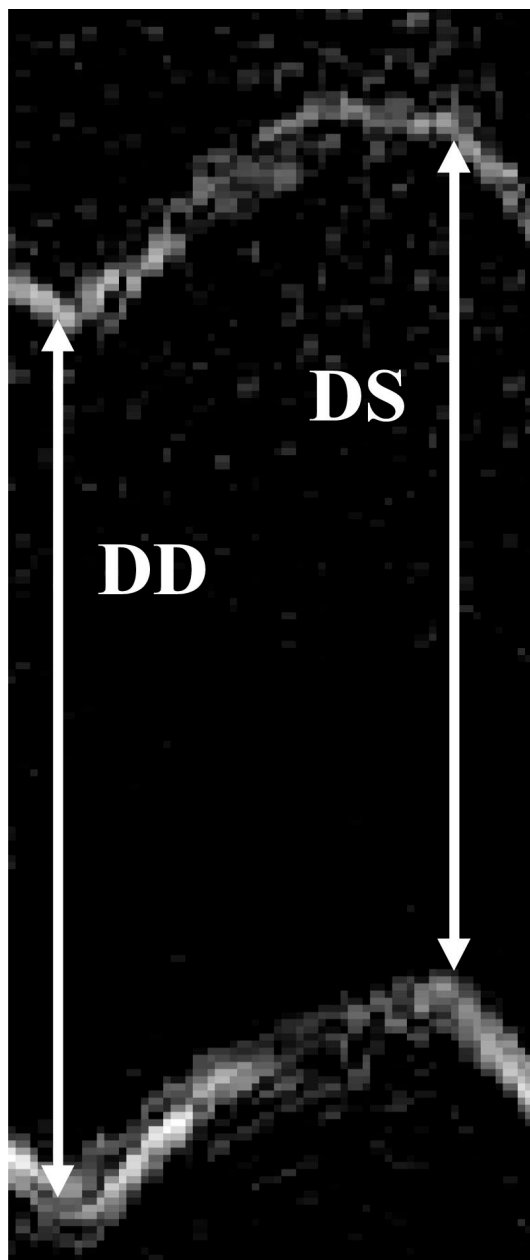


Fig. 2. Measurement of systolic (DS) and diastolic (DD) diameters of the ascending aorta are shown on the M-mode tracing obtained at a level 3 cm above the aortic valve.

function relating the relative arterial pressure and the distention ratio of the artery and characterizes the entire deformation behavior

of the vascular wall. The following formula was used to calculate:

$(\beta) = \ln(\text{SBP}/\text{DBP})/(\text{DD}/\text{DS})$, where DD is the pulsatile change in aortic diameter (SD minus DD) and 'ln' is the natural logarithm (15). The inverse of stiffness is compliance (distensibility), which describes the ease of systolic aortic expansion and is calculated as follows: $2 \times (\text{SD} - \text{DD})/(\text{SBP} - \text{DBP}) \times \text{DD}$. Aortic strain expressed as a percentage change of the aortic root was calculated as $(\text{SD} - \text{DD})/\text{DD}$.

Statistical Analysis

Data are reported as means \pm standard deviation; 95% confidence limits are also included. We applied Mann-Whitney and Fisher's exact tests using SPSS 12.0 software. A probability value $P < 0.05$ was accepted as statistically significant.

RESULTS

Patient Characteristics

There was no significant difference between patient and control groups as to age (40 ± 9 vs. 36 ± 7 years, $P > 0.05$) and mean BMI values (27.6 ± 1.7 vs. 27.2 ± 3.3 kg/m², $P > 0.05$). None had relevant risk factors including lipid metabolism disturbance, diabetes mellitus, or anemia (Table 1).

Transthoracic Echocardiography

Mean systolic and diastolic aortic diameters and aortic stiffness index were significantly higher, while aortic strain and distensibility were considerably lower in lipedematous patients compared to control subjects (Table 2). Individual systolic blood pressures are displayed in Fig. 3 and aortic stiffness indices are presented in Fig. 4.

DISCUSSION

The present study has clearly shown that

TABLE 2
Echocardiographic Data, Aortic Dimensions and Elastic Properties
in Lipoedema Patients and Controls

	Lipoedema Group	Controls
LV end-diastolic diameter (mm)	49.4 ± 3.4	48.4 ± 3.0
LV end-systolic diameter (mm)	30.8 ± 2.8	30.1 ± 3.5
Interventricular septum (mm)	9.4 ± 1.1	9.4 ± 0.8
LV posterior wall (mm)	9.0 ± 1.0	9.1 ± 1.0
LV ejection fraction (%)	67.4 ± 5.9	68.1 ± 5.4
Aortic systolic diameter (SD, mm)	30.0 ± 3.2 *	25.5 ± 3.6
Aortic diastolic diameter (DD, mm)	27.8 ± 3.3 *	22.3 ± 3.1
SD-DD (mm)	2.20 ± 0.92 *	3.21 ± 0.87
Systolic blood pressure (SBP, mm Hg)	135.4 ± 9.9	129.6 ± 13.9
Diastolic blood pressure (DBP, mm Hg)	79.1 ± 12.4	77.9 ± 8.6
SBP-DBP (mm Hg)	56.3 ± 12.8	51.7 ± 13.1
Aortic strain	0.082 ± 0.040 *	0.143 ± 0.038
Aortic distensibility (cm ² /dynes 10 ⁻⁶)	2.24 ± 1.07 *	4.38 ± 1.61
Aortic stiffness index (β)	9.5 ± 7.45 *	3.76 ± 1.22

* p <0.05 vs. controls; Abbreviations: LV: ejection fraction

aortic stiffness is increased in lipoedematous patients compared to healthy individuals within a similar age group suggesting early vascular remodeling. Increased arterial stiffness is an important risk factor for cardiovascular mortality in distinct diseases (16). The evidence demonstrated that pulsatile changes in ascending aortic vessel diameter can be indirectly registered during routine 2DE (13) instead of using direct invasive methods. Aortic elastic properties rely on aortic and blood pressure data. These non-invasive measurements have been confirmed as the determinants of aortic distensibility, with a high degree of accuracy (13).

Lipoedema is a peculiar form of adipose tissue deposition in a disproportional fat accumulation in a biker's hosiery shape and is complicated by venous and lymphatic insufficiency and also microangiopathy. Generalized obesity is known to be associated with structural (altered aortic size) and

functional (decreased aortic elasticity) vascular abnormalities, where aortic enlargement may represent an adaptation process to accommodate the increased blood volume. Wildman et al found that excess weight begins to affect the vascular system at a very early stage of vascular aging (17). We have recently shown that obesity is associated with aortic enlargement and increased stiffness regardless of the age of patients (12).

Various mechanisms can be attributed to obesity-linked aortic stiffening including visceral adipose tissue throughout insulin resistance development (18). Hyperinsulinemia can be associated with increased sodium reabsorption (19), a stimulated sympathetic nervous system (20), and atherosclerosis (21,22). In the obesity-related insulin resistant state, the endothelium dependent vasodilator effects of insulin is weakened (23,24). Higher levels of nonesterified fatty acids have been found to

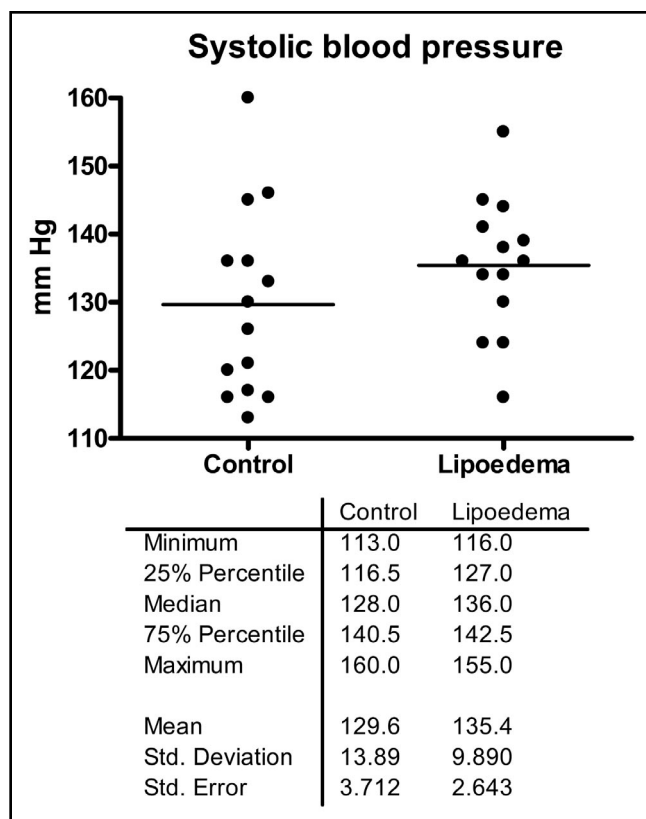


Fig. 3. Individual systolic blood pressures of lipoedema patients and controls.

be associated with central obesity by increasing α -adrenergic reactivity, vascular tone, and blood pressure (25). Increased BMI has been associated with permanent low-grade inflammation and concomitantly increased expression of proinflammatory cytokines resulting in wall stiffening (26,27).

One of the major hallmarks of lipoedema is excessive bruising. Hematoma formation is presumably triggered by increased CF and possibly by impaired venoarterial reflex (VAR) (7,8). Capillary fragility measurement with a vacuum suction chamber, the Parrot's angiostrometer, has clarified remarkable CF in the background of frequent hematoma formation (7). Decongestive lymphatic therapy (DLT) in combination with intermittent pneumatic compression (IPC) significantly decreased CF.

Several theories have been postulated regarding the etiology of lipoedema. Földi and Földi have proposed that microangiopathy in the area of the affected adipose tissue sets off the condition leading to increased permeability to proteins (5,8). Hypoxia is known to be a major induction factor for angiogenesis and, in the eye, pathological angiogenesis in the retina leads to catastrophic loss of vision in retinopathy of maturity, diabetic retinopathy. The principal feature of these newly formed capillary vessels in these disorders is also fragility. Angiogenesis is controlled by several factors, including vascular endothelial growth factor (VEGF), and accordingly, abnormally high serum VEGF levels might be predicted in the presence of intensive angiogenesis and concomitant CF. A study examining effects of shock-wave therapy in

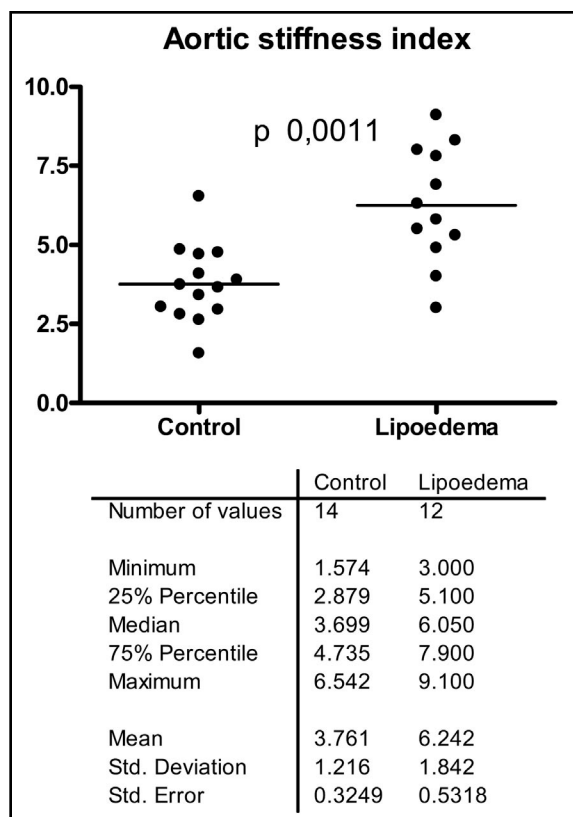


Fig. 4. Individual aortic stiffness indices of lipoedema patients and controls.

patients with lipoedema or cellulite found nearly 4-fold higher plasma mean VEGF levels at baseline compared to non-lipoedematous individuals (28). Other observations relate to immunohistochemical findings (29). In lipoedema, adipocytes undergo necrosis and are scavenged by macrophages. Hypoxia induced by excessive adipose hypertrophy has been proposed to cause adipose metabolic dysfunction and the production of adipose tissue cytokines related to inflammatory reaction might also be operative in lipoedema. Furthermore, adipocyte enlargement and Ki67 and CD34 positivity were also observed, which are associated with cell proliferation, and adipose stem/progenitor cells, respectively.

Observed and suspected pathological features of lipoedema suggest a possible

explanation for the increased aortic stiffness. Lipoedematous adipose tissue as in generalized morbid obesity may enhance peripheral vascular resistance causing increasing aortic stiffness (12). Additionally, at the microvascular level, localized hypertension accompanying arteriolar remodeling and capillary hyperpermeability can lead to microangiopathy interacting with macrovascular function. Expansion of the lipoedematous microvascular network and its fragility might be explained as a compensatory response to constant stimuli from local tissue pressure and vascular resistance. Thus, the known interaction of macro- and microcirculations observed in other disorders could account for the coexistence of raised CF and aortic stiffness in lipoedema (30).

To our knowledge, this is the first

measurement of aortic stiffness in lipedema patients, and we found remarkable alterations in aortic elastic properties.

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REFERENCES

- Allen, EV, EA Hines: Lipedema of the legs: A syndrome characterized by fat legs and orthostatic edema. *Mayo Clin. Proc.* 15 (1940), 184-187.
- Langendoen, SI, L Habbema L, TE Nijsten, et al: Lipoedema: from clinical presentation to therapy. A review of the literature. *Br. J. Dermatol.* 161 (2009), 980-986.
- Szolnoky, G, L Kemény: Lipoedema: From clinical presentation to therapy. Further aspects. *Br. J. Dermatol.* 162 (2010), 889.
- Fife, CE, EA Maus, MJ Carter: Lipedema: a frequently misdiagnosed and misunderstood fatty deposition syndrome. *Adv. Skin. Wound Care* 23 (2010): 81-92.
- Földi, M, S Kubik: *Textbook of Lymphology*. Urban and Fischer Publisher, 2005.
- Child, AH, KD Gordon, P Sharpe, et al: Lipedema: An inherited condition. *Am. J. Med. Genet. A.* 152 (2010), 970-976.
- Szolnoky, G, N Nagy, RK Kovács, et al: Complex decongestive physiotherapy reduces capillary fragility in lipedema. *Lymphology* 41 (2008), 161-166.
- Földi, E, M Földi: A comparative study to measure veno-arterial reflex in lipedema. In: *Lipoedema and Cellulitis*. Viavital Publisher 2001: 80-86.
- Harwood, CA, RH Bull, J Evans, et al: Lymphatic and venous function in lipoedema. *Br. J. Dermatol.* 134 (1996), 1-6.
- Brauer, WJ: Altersbezogene Funktionslymphszintigraphie beim Lipödem und Lipolymphödem. *LymphForsch* 4 (2000): 74-77.
- Amann-Vesti, BR, UK Franzeck, A Bollinger: Microlymphatic aneurysms in patients with lipedema. *Lymphology* 34 (2001), 170-175.
- Nemes, A, H Gavallér, E Csajbók É, et al: Obesity is associated with aortic enlargement and increased stiffness: An echocardiographic study. *Int. J. Cardiovasc. Imaging* 24 (2008), 165-171.
- Stefanadis, C, C Stratos, H Boudoulas, et al: Distensibility of the ascending aorta: Comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. *Eur. Heart J.* 11 (1990), 990-996.
- Nemes, A, TW Galema, ML Geleijnse, et al: Aortic valve replacement for aortic stenosis is associated with improved aortic distensibility at long-term follow-up. *Am. Heart J.* 153 (2007), 147-151.
- Henry, WL, A DeMaria, R Gramiak R, et al: Report of the American Society of Echocardiography Committee on nomenclature and standards in two-dimensional echocardiography. *Circulation* 62 (1980), 212-217.
- Nemes, A, T Forster, M Csanády, et al: Indices of aortic distensibility and coronary flow velocity reserve in patients with different grades of aortic atherosclerosis. *Int. J. Cardiovasc. Imaging* 20 (2004), 271-277.
- Wildman, RP, RH Mackey, A Bostom, et al: Measures of obesity are associated with vascular stiffness in young and older adults. *Hypertension* 42 (2003), 468-473.
- Brunzell, JD, JE Hokanson: Dyslipidemia of central obesity and insulin resistance. *Diabetes Care* 22(Suppl 3) (1999), C10-C13.
- Stenvinkel, P, J Bolinder, A Alvestrand: Effects of insulin on renal haemodynamics and the proximal and distal tubular sodium handling in healthy subjects. *Diabetologia* 35 (1992), 1042-1048.
- Young, JB: Effect of experimental hyperinsulinemia on sympathetic nervous system activity in the rat. *Life Sci.* 43 (1988), 193-200.
- Ulrich, P, A Cerami: Protein glycation, diabetes, and aging. *Recent Prog. Horm. Res.* 56 (2001), 1-21.
- DeFronzo, RA, E Ferrannini: Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14 (1994), 173-194.
- Kahn, BB, JS Flier: Obesity and insulin resistance. *J. Clin. Invest.* 106 (2000), 473-481.
- Arcaro, G, A Cretti, S Balzano, et al: Insulin

- causes endothelial dysfunction in humans: sites and mechanisms. *Circulation* 105 (2002), 576-582.
25. Egan, BM, G Lu, EL Greene: Vascular effects of non-esterified fatty acids: Implications for the cardiovascular risk factor cluster. *Prostaglandins Leukot. Essent. Fatty Acids* 60 (1999), 411-420.
 26. Weyer, C, JS Yudkin, CD Stehouwer, et al: Humoral markers of inflammation and endothelial dysfunction in relation to adiposity and in vivo insulin action in Pima Indians. *Atherosclerosis* 161 (2002), 233-242.
 27. Visser, M, LM Bouter, GM McQuillan, et al: Elevated C-reactive protein levels in overweight and obese adults. *JAMA* 282 (1999), 2131-2135.
 28. Siems W, T Grune, P Voss, et al: Anti-fibrosclerotic effects of shock wave therapy in lipodema and cellulite. *Biofactors* 24 (2005), 275-282.
 29. Suga, H, J Araki, N Aoi, et al: Adipose tissue remodeling in lipedema: adipocyte death and concurrent regeneration. *J. Cutan. Pathol.* 36 (2009), 1293-1298.
 30. Feihl, F, L Liaudet, B Waeber: The macrocirculation and microcirculation of hypertension. *Curr. Hypertens. Rep.* 11 (2009), 182-189.

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