Obesity and chronic inflammation in phlebological and lymphatic diseases

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Keywords
Obesity-associated functional venous insufficiency, obesity-associated lymphoedema, visceral obesity, chronic inflammation, insulin resistance

Summary
The prevalence of obesity has continued to increase considerably during the past 15 years. Particularly noticeable is the marked increase in morbid obesity, which is in turn particularly pronounced among the elderly. Since the prevalence of venous thromboembolism, chronic venous insufficiency and secondary lymphoedema also increases with age, the number of patients with venous or lymphatic diseases, who are also severely obese and often multimorbid, rises disproportionately. Obesity, especially of the visceral type, exacerbates all oedema diseases, increases the risk of thromboembolic diseases and post-thrombotic syndrome and may be the sole cause of obesity-associated functional venous insufficiency without evidence of obstruction or reflux. Obesity-associated lymphoedema now accounts for the largest share of secondary lymphoedemas. More than 50 percent of patients are obese, with their subsequent secondary lymphoedema usually resulting from obesity rather than the lipoedema. Weight reduction improves the symptomatology in all clinical presentations. Beside mechanical factors, such as an increase in intra-abdominal and intertriginous pressure, which in turn leads to an increase in venous pressure in leg vessels, these relationships are mainly caused by the metabolic, chronic inflammatory and prothrombotic processes that result from the increase of visceral adipose tissue. These processes can be identified by low levels of adiponectin and high levels of leptin, insulin, intact proinsulin, PAI-1 and proinflammatory cytokines (IL-6, IL-8, TNF-α). Therapeutic measures must therefore be aimed primarily at reducing visceral obesity and with it hyperinsulinemia or insulin resistance as well as at fighting chronic inflammation.

Schlüsselwörter
Adipositas-assoziierte funktionelle Veneninsuffizienz, Adipositas-assoziiertes Lymphödem, viszerale Adipositas, chronische Inflammation, Insulinresistenz

Zusammenfassung
Die Prävalenz der Adipositas ist in den letzten 15 Jahren weiter stark angestiegen. Dabei fällt besonders die deutliche Zunahme der morbiden Adipositas auf, die wiederum bei den Älteren besonders ausgeprägt ist. Da mit dem Alter auch venöse Thromboembolien, chronisch venöse Insuffizienz und sekundäre Lymphödeme zunehmen, steigt die Zahl der Patienten mit venösen oder lymphatischen Erkrankungen, die gleichzeitig schwer adipös und häufig multimorbide sind, überproportional an. Die Adipositas, vor allem die viszerale, verschlechtert alle Ödemerkrankungen, erhöht das Risiko für thromboembolische Erkrankungen und postthrombotisches Syndrom und kann alleinige Ursache sein für die Adipositas-assoziierte funktionelle Veneninsuffizienz ohne Nachweis von Obstruktion oder Reflux. Das Adipositas-assoziierte Lymphödem stellt inzwischen den größten Anteil unter den sekundären Lymphödemen. Mehr als 50 Prozent der Lipödempatientinnen sind adipös, die bei ihnen im Verlauf zu beobachtenden sekundären Lymphödeme in der Regel Folge der Adipositas, nicht des Lipödems. Die Symptomatik wird bei allen Krankheitsbildern durch Gewichtsreduktion gebessert. Neben mechanischen Faktoren wie der Erhöhung des intraabdominalen und intertriginösen Drucks, der wiederum zu einer venösen Drucksteigerung in den Beingefäßen führt, sind es vor allem die durch die Zunahme des viszeralen Fettgewebes verursachten metabolischen, chronisch inflammatorischen und prothrombotischen Prozesse, die für diese Zusammenhänge verantwortlich sind, erkennbar an niedrigen Spiegeln von Adiponektin und hohen von Leptin, Insulin, intaktem Proinsulin, PAI-1 sowie proinflammatorischen Zytokinen (Il-6, Il-8, TNF-α). Therapeutische Maßnahmen müssen also in erster Linie auf die Reduktion der viszeralen Adipositas und damit der Hyperinsulinämie bzw. der Insulinresistenz sowie auf die Bekämpfung der chronischen Entzündung abzielen.

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Introduction

In Germany, men with a normal bodyweight are already a minority from the age of 30 to 35 years, while overweight women do not dominate until the age of 55 years.

At the end of their working life, 74.2% of men and 56.3% of women are overweight. While the number of overweight individuals has been stagnant for several years, the proportion of obese people increased from 12% in 2000 to 15% in 2009 and up to 23.6% in 2015. Most notably, the proportion of people with morbid obesity (BMI ≥ 40) aged over 65 increased between 1999 and 2013 by 300% for men and by 175% for women (1). Since the prevalence of thromboembolic events, chronic venous insufficiency (2) and secondary lymphoedema also increases with age, the number of patients with these conditions, who are also severely obese, is steadily increasing. The development of overweight and obesity is favoured by family predisposition or genetic causes (3, 4), medications, endocrine and mental illnesses as well as by a low social and educational status (5). The rapid spread of the obesity epidemic is above all caused by today's lifestyle, which is characterized by the constant availability of mostly unhealthy food, frequent „snacking" (6), lack of exercise due to a sedentary lifestyle in a closed environment, chronic stress (7) and lack of sleep (8–10).

Obesity-associated diseases of veins and lymphatics

Obesity aggravates any existing oedema diseases or may cause them in the first place (11). It increases the risk of thromboembolic diseases and post-thrombotic syndrome (PTS) as well as the severity of chronic venous insufficiency (CVI), postthrombotic syndrome (PTS) and ulcus cruris (12).

Thromboembolism and post-thrombotic syndrome

In the Netherlands, in 2008, Abdollahi et al. observed in 454 consecutive patients with a first thrombosis a doubling of the risk of thrombosis at a BMI of 30 kg/m2 and higher (CI95: 1.5 vs. 3.4) as well as an increase in factors VIII and IX. The relative risk was similar for both sexes and all age groups; in absolute terms, the effect was greatest among the elderly (13). A prospective cohort study by Ageno et al. involving 83 consecutive thrombosis patients showed that a BMI > 28 kg/m2 is already a predictor for the early development of a post-thrombotic syndrome. After 12 months, PTS was observed in 24.1 percent; the mean BMI was significantly higher in this group (29.6 vs. 27.2 kg/m2, p = 0.022). The authors concluded that thrombosis patients should avoid weight gain and that a reduction could possibly help to prevent PTS (14).

CVI and ulcus cruris

The influence of body weight on the severity of CVI has been the subject of controversial debate in the literature, mainly because both CVI and BMI increase with age (2). In a large epidemiological study involving over 16,000 subjects, Chiesa et al. described a relationship between BMI, visible signs of CVI and increase in venous reflux (15). In contrast, a retrospective study by Padberg et al in 2003 (20 men, 39 legs, CEAP C4 to C6, BMI ≥ 40 kg/m2) found no evidence of venous reflux on duplex examination in two thirds of the patients despite typical skin changes (hyperpigmentation, lipodermatosclerosis up to hydrostatic ulcus cruris). With respect to the clinical findings (VCSS, venous clinical severity score), no differences were observed between patients with or without reflux (16). In a cross-sectional study from Serbia in 2013, the authors also described a strong correlation between obesity and CEAP-C stages that was independent of age, gender and other risk factors, but not between obesity and venous reflux (17). With the aid of duplex ultrasound examinations on more than 400 legs, Danielsson et al. also demonstrated that obese patients may exhibit CVI-typical skin changes even without venous reflux (18). They found a strong correlation between BMI and the severity of the clinical symptoms and described overweight as an independent risk factor for CVI-typical skin lesions. Over 50% of the obese patients had oedema and a florid or healed ulcer. In a study of ulcers, Obermayer et al. also described a share of 46% of obese and 35% of overweight patients (19). Overall, the proportion of the so-called venous hydrostatic ulcers without reflux is reported to be between 20 and over 60%, depending on the degree of obesity (16, 20). The skin lesions improve after weight loss (21, 22).

CVI-typical symptoms occurring in the context of obesity are summarised under the term „obesity-associated dependency syndrome," analogous to "immobility-induced dependency syndrome" in paralysed individuals (23, 24). Garzon and Obermayer were able to demonstrate that the intertriginous pressure in the groin already correlates with the leg vein pressure at a BMI as low as 25 kg/m^2 and that in obese patients it causes, in addition to the resulting obstruction of the leg veins due to the weight on the groin, a complete inactivation of the calf muscle pump when sitting, thereby preventing the relief of the in itself healthy, venous system, thus causing the venous pressure to increase. The authors see this as a possible explanation for the formation of hydrostatic ulcers (23). Since it is most likely that additional, particularly metabolic interrelationships contribute to the pathogenesis, the clinical picture is better described as secondary functional venous insufficiency without evidence of reflux or obstruction (11).

Lymphoedema and lipoedema

Compared to the general population with a proportion of obesity of around 20%, patients with lymphatic diseases are far more often overweight or obese (see also Bertsch, Tobias in this issue). In a study of 72 patients attending consultations at the Lymphatic Outpatient Clinic of the Venous Centre of the Ruhr University Bochum, Reich-Schupke observed a mean BMI of 38 kg/m^2, whith the proportion of obesity differing greatly depending on the lymphological diagnosis (25). In a lymphological population, Flaggl et al. found 24% of pa-

tients with normal weight (26). Obesity leads to a deterioration of primary lymphoedema (27), while secondary postoperative lymphoedemas are more prevalent, occur earlier and are more severe in obese persons (28). Most importantly, morbid obesity (BMI above 40 kg/m2) is now the most common cause of secondary lymphoedema, and forms its own entity as obesity-associated lymphoedema (29). It typically develops in the second half of life parallel to weight gain, particularly at the thighs, the genital region and abdominally in the area of fat folds, while the fibrosis on the lower legs is mildly pronounced and the Stemmer sign often only weakly detectable (29). Obesity-associated lymphoedema is often associated with skin lesions typical of secondary venous insufficiency (▶ Fig. 1).

For lipoedema, Schmeller et al. reported a proportion of patients with normal weight of 29% (30). The real proportion of adipose lipoedema patients is likely to be well over 50% (31). The secondary lymphoedema, which often develops in these patients over the further clinical course, is the result of obesity, not the lipoedema. Transitions appear to exist in both directions between the asymptomatic lipohypertrophy and the symptomatic, painful lipoedema, usually in phases of weight or hormonal changes (32, 33). Because of the additional fat masses at the thighs, obesity deteriorates axial malalignment, gait and mobility, which further increases weight.

Influence of visceral adipose tissue on hypercoagulability, chronic inflammation and insulin resistance

The relationship between obesity and the clinical pictures described above can be explained by mechanical mechanisms (increase of intra-abdominal, intertriginous and subsequently venous pressure) and those that emphasize the role of chronic inflammation and metabolic changes associated with obesity. These mechanisms are not mutually exclusive, but rather complement each other.

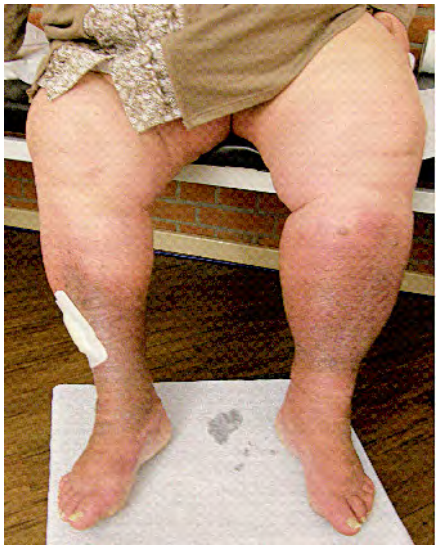


Fig. 1 Obesity-associated lymphoedema with secondary functional venous insufficiency. BMI 61 kg/m^2 (162cm, BMI 61. WHtR 0.88). Hyperpigmentation, dermatoliposclerosis, ulcus cruris on the right 0.5x0.5 cm, lymphorrhoea; diabetes mell. type II, art. hypertension.

Visceral obesity, thrombosis and secondary venous insufficiency

Willenberg and colleagues observed an enlarged diameter of the femoral vein and a deterioration of venous flow parameters in obese patients. They saw this as a confirmation that abdominal adipose tissue could mechanically increase the risk of venous thromboembolism and CVI by increasing intra-abdominal pressure (34). Darvall et al., on the other hand, described in a review that visceral obesity in particular is associated with an increased incidence and prevalence of arterial and venous thromboembolism (35). Visceral adipose tissue is not only an energy store, but also a production site for numerous hormones and cytokines that influence the glucose and lipid metabolism and clotting (▶ Tab. 1). The secretion of leptin is increased by TNF-α and hyperinsulinemia. Leptin promotes platelet aggregation, enhances the synthesis of CRP via activation of the IL-6 receptors and thus acts proinflammatory. Adiponectin is decreased in insulin resistance and obesity. High levels have an anti-inflammatory effect: CRP, TNF-α, IL-6, IL-8 and Plasminogen-Activator-Inhibitor-1 (PAI-1) decrease. Increasing levels are associated with decreasing insulin resistance and improvement of cardiovascular risk factors.

Overall, abdominal obesity increases the risk of thrombosis through the increased activity of the coagulation cascade, decreased activity of the fibrinolytic cascade, increased inflammatory processes, elevated oxidative stress and endothelial dysfunction. This is further accompanied by disorders of lipid metabolism and glucose tolerance in the context of metabolic syndrome (insulin resistance, increased triglycerides, low HDL), which also have proinflammatory effects and enhance endothelial dysfunction. These thrombogenic risk factors can invariably be improved by weight reduction (35). In their meta-analysis, Ageno et al. also concluded that visceral adipose tissue, as an endocrine organ, is responsible for chronic inflammation and thus for a thrombogenic condition that increases the risk of venous thromboembolism (36). Chronic inflammation increases fibrinogen, tissue factor (factor III) and factor VII, activating thereby the coagulation cascade. Moreover, patients with visceral obesity were often found to exhibit elevated levels of PAI-1 and low levels of tissue-specific plasminogen activator (t-PA), which is released from endothelial cells of vascular walls and acts as an endogenous activator of fibrinolysis by converting plasminogen directly into plasmin. The PAI-1 level correlates positively with the BMI and with the plasma insulin and triglyceride levels. If insulin levels are lowered by fasting or metformin, PAI-1 (37) also decreases, suggesting that hyperinsulinemia increases the hepatic synthesis of PAI-1 and thus contributes to a hypofibrinolytic condition (38).

There is much to suggest that in addition to the mechanical factors described above, chronic inflammatory and prothrombotic processes caused by visceral obesity also play a role in skin changes in the context of secondary venous insufficiency up to hydrostatic ulcers, since these increase, among other things, capillary per-

Tab. 1 Metabolic and inflammatory markers and cytokines

Marker, site of formation	
Adiponectin Peptide hormone, fat cells; antiatherogenic, antiinflammatory	**Low values associated with:** visceral obesity (suppresses secretion) insulin resistance and hyperinsulinemia dyslipidaemia (high triglycerides, low HDL) inflammation stress increased risk of type 2 diabetes mellitus, CHD
Intact proinsulin Precursor of insulin pancreatic -cells	**High values associated with:** advanced dysfunction of β cells prediabetes increased cardiovascular risk (stimulates PAI-I, blocks fibrinolysis) further weight gain
Leptin Proteohormone, adipocytes regulation of body weight	**High values associated with:** leptin resistance visceral obesity hyperinsulinemia, β-cell dysfunction, high triglycerides, low HDL inflammation
hs-CRP acute-phase protein liver, vascular muscle cells	**High values associated with:** chronic inflammation insulin resistance, increased risk of type II diabetes hypertension, metabolic syndrome increased risk of vascular events
Plasminogen Activator Inhibitor-1 (PAI-1) especially visceral adipose tissue	**High values associated with:** visceral obesity inflammation and oxidative stress
Inhibition of fibrinolysis	Increased risk of thromboembolic events, atherosclerosis insulin resistance, metabolic syndrome, type II diabetes mellitus
Inflammatory cytokines: IL-6, IL-8, TNF-α visceral adipose tissue stimulation of inflammatory processes	**High values associated with:** chronic inflammation visceral obesity insulin resistance, type II diabetes mellitus vascular events

meability, extravasation and consecutively the lymphatic burden (24).

Obesity, chronic inflammation and lymphoedema

Obesity and metabolic syndrome are associated with elevated levels of proinflammatory cytokines, detected not only systemically, but also in adipose tissue, in the liver and in skeletal muscle. Numerous studies have shown that an increase of proinflammatory cytokines such as TNF-α, IL-6, and MCP-1 (macrophage chemotactic protein 1) leads to insulin resistance in adipose tissue, increased lipolysis and fatty liver (39). In a mouse model, Karaman et al. showed that the VEGFR-3 receptor and its ligands VEGF-C and D, which are important for lymphangiogenesis, not only play a role in inflammation of adipose tissue and the development of metabolic syndrome, but are also of importance for the development of obesity-associated lymphoedema (39, 40). This influence is mediated by macrophages, which, along with T cells, play a major role in the obesity-associated inflammatory response (41).

It has long been known that the expansion of adipose tissue requires increased neoangiogenesis. Various studies have reported elevated serum levels of VEGF-A, C and D in overweight and obese patients as compared to lean individuals (42, 43). Interestingly, gender differences were also observed in this context. A higher increase of VEGF-C and D as well as of angiopoietin 2 was observed among overweight women compared to overweight men.

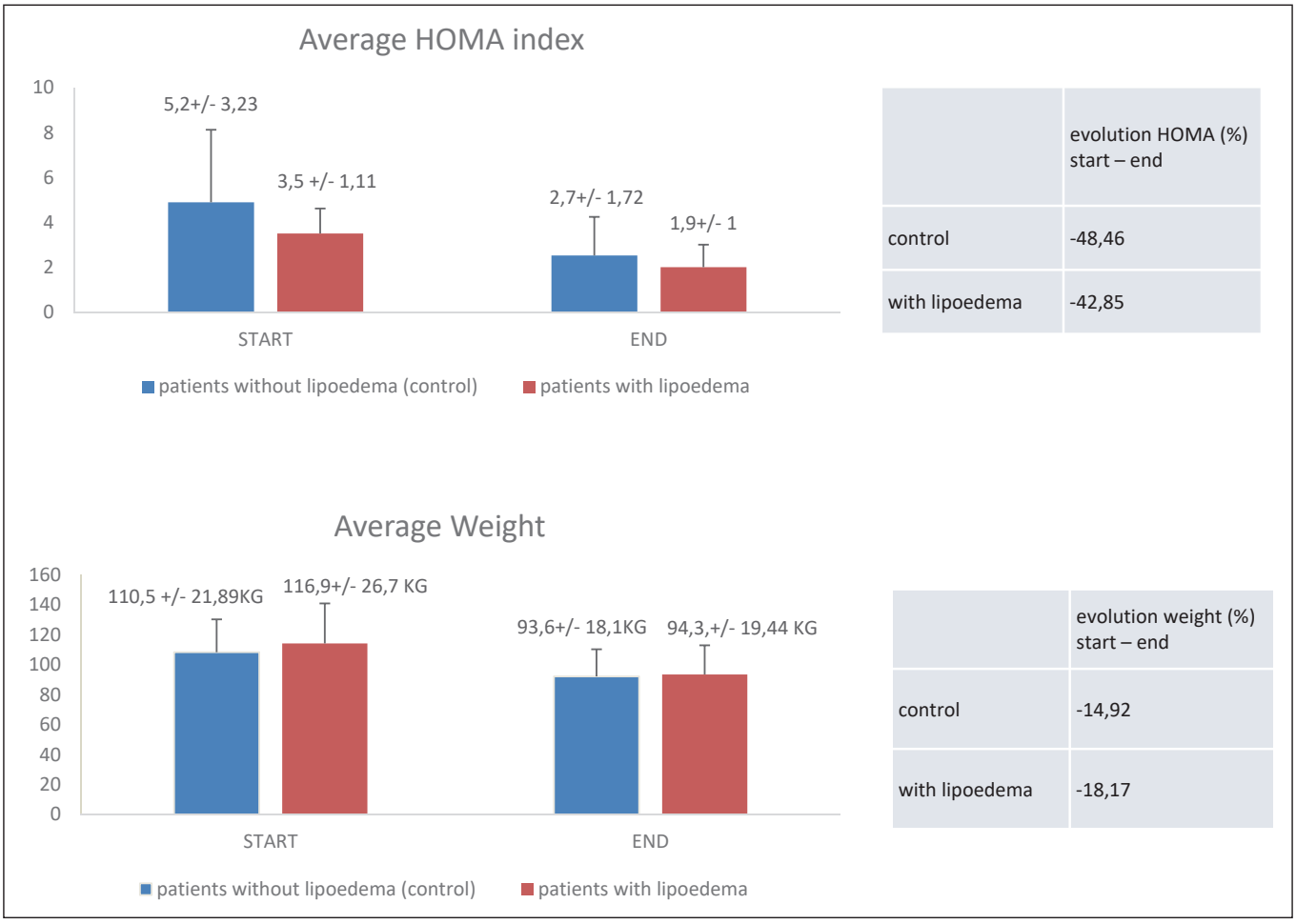
VEGF-A mainly stimulates the proliferation and migration of vascular endothelial cells. Overexpression of VEGF-A in transgenic mice resulted in an increased number and size of blood vessels. However, these mice were also protected from developing a high-fat-diet-induced obesity and from insulin resistance (44). In this respect, enhanced levels of VEGF-A appear to be an immune response to counter adipose tissue hypoxia and to regulate hypoxia-related inflammatory processes.

The obesity-enhanced expression of VEGF-C, the most important growth factor for lymphangiogenesis, appears, however, to result in a lymphatic dysfunction. This finding is supported by the observation that a blockade of the VEGFR-3 ligand VEGF-C in the mouse model leads to a reduction of oedema formation as well as to a significant improvement of insulin sensitivity and decreased hepatic steatosis (39).

Elevated levels of VEGF-C mRNA were observed in mouse adipose tissue in both genetically and diet-induced obesity, suggesting that inflamed adipose tissue itself is one of the sources of the elevated VEGF-C levels (39, 40). Obesity leads to increased migration of M1-polarized macrophages into adipose tissue. A feature of these M1 macrophages is, in addition to the release of proinflammatory cytokines, the enhanced expression of VEGFR-3.

Initially, VEGFR-3 stimulates lymphangiogenesis. However, several research groups have shown that obesity leads to reduced lymphatic flow and to a reduced uptake of lymphatic fluid into the lymph nodes. This seems to be caused by immature, increasingly permeable ("leaky") lymphatic vessels (45, 46). In addition, the release of inducible nitric oxide synthase (iNOS) by macrophages leads to a dilatation of the lymphatic vessels and a concomitant decrease in contraction intensity. Finally, the frequency of contraction of the lymph collectors is also reduced (45, 46).

This results in lymphatic stasis. In the long term, as with other secondary lymp-



	evolution HOMA (%) start – end
control	-48,46
with lipoedema	-42,85

	evolution weight (%) start – end
control	-14,92
with lipoedema	-18,17

Fig. 2 Average HOMA index and weight before and after nutritional therapy. Female lipoedema patients had a higher starting weight along with a lower HOMA index.

hoedemas, this leads – at least in subcutaneous adipose tissue – to an M2 macrophage shift and to a TH2-dominated inflammatory response, which is responsible for further lymphoedema-associated, local adipose tissue formation, fibrosis of the surrounding tissue and sclerosis of the lymphatic vessels (47). A vicious circle develops.

Obesity and lipoedema – inflammation, insulin and oestradiol

Although the pathogenesis of lipoedema is still largely unknown, there is much to suggest the involvement of inflammatory processes in addition to hormonal factors. It is not clear whether and in what way these are the primary cause or the consequence of other physical changes such as obesity or hormonal imbalances. It has long been known that obesity worsens symptoms in patients with a verified diagnosis of lipoedema (48, 49). However, there are also disease progressions, in which an asymptomatic lipohypertrophy only develops into a symptomatic lipoedema in the course of life, usually in a phase of marked weight gain. In both cases, this development may be reversible after weight loss and change in diet (50). It is understandable that in lipoedema too, the vicious circle of obesity and gradually increasing hyperinsulinemia not only leads to a further increase in adipose tissue, but also to the described proinflammatory and oedema-promoting effects of the visceral adipose tissue. In our own investigations, it is striking that insulin resistance in a population of obese lipoedema patients is less pronounced than in a control group of obese patients without lipoedema, despite a higher average weight, with this difference disappearing with increasing abdominal obesity (▶ Fig. 2) (51).

In addition, insulin directly stimulates the aromatase activity in adipose tissue and thus the conversion of androstenedione and testosterone to estrone and estradiol (52). It also reduces the sex hormone-binding globulin (SHBG) and thus further increases free estradiol (53, 54). Hyperinsulinemia thus promotes a shift in the hormonal balance between estradiol and progesterone in favour of estradiol, which in turn has pro-inflammatory, oedema-enhancing and lipogenic effects. The role of adipose tissue as an alternative site of estra-

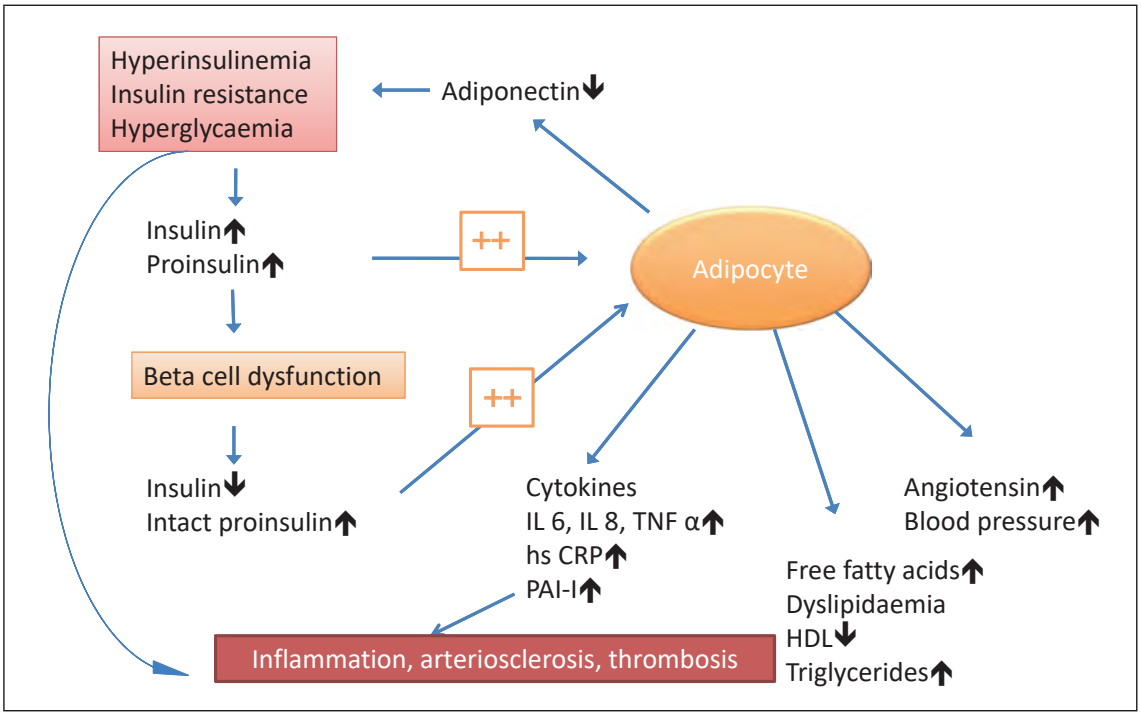


Fig. 3 Relationships between adipogenesis, insulin resistance and inflammation (modified according to Pfützner 2005).

diol production thus enhances the physiologically present estradiol dominance in the pre- or perimenopausal phase and thus contributes to the late manifestation of lipoedema in this phase of life (51).

Reducing hyperinsulinemia, fighting inflammation

Hyperinsulinemia increases adipogenesis and reduces lipolysis, leading thereby to an increase of visceral adipose tissue and thus to a formation of proinflammatory and coagulation-activating hormones and cytokines. The formation of oedema increases, on the one hand, as a result of the inflammatory-mediated increase of capillary permeability and the increased retention of water and sodium and, on the other hand, as a result of the insulin-mediated increase of estradiol.

Therapeutic options should therefore target primarily the reduction of hyperinsulinemia and the resolution of insulin resistance as well as fighting chronic inflammation (▶ Fig. 3; ▶ Tab. 2)

In cases of low to moderate insulin resistance, insulin sensitivity can be improved solely by changes in dietary habits and lifestyle.

Increased physical activity, especially endurance training in the aerobic range, promotes fat burning and serves primarily to increase the insulin sensitivity of muscle cells, rather than to burn calories, the importance of which is anyway usually overestimated (55). In cases of severe obesity, the various forms of water exercises (Aqua Cycling, Aqua Jogging etc.) are particularly suitable to avoid excess strain of the joints.

In terms of nutrition, importance must be given, on the one hand, to its composition, as blood glucose and insulin peaks should be avoided in the context of a diet with low glycaemic load by abstaining from sugar and refined carbohydrates (56), but perhaps even more decisive is a reduction in the frequency of meals and abstaining from between-meal snacking. This is a radical turning away from the recommendation to eat many small, especially carbohydrate-dense meals. The awarding of the Nobel Prize in Medicine to Y. Ohsumi for his research on autophagy has once again brought the various forms of fasting and their effects on the metabolism into focus. Here an extension of the nocturnal fasting period or the introduction of individual fasting days (intermittent or periodic fasting) not only seem to favourably influence weight and insulin sensitivity, but would also appear to have anti-inflammatory effects (57–59).

This and a significant reduction of calorie intake can result in non-diabetic fasting blood glucose levels after eight weeks in 87% of patients, who have been suffering from diabetes for a short period of time, and in 50% of patients, who have had diabetes for a longer period of time, and can significantly improve blood pressure and blood lipids irrespective of the duration of the diabetes (60, 61). These results are therefore comparable to those after bariatric surgery, in which a rapid normalization of the metabolism is also achieved in type II diabetes, but which is neither possible nor desirable for all patients and is not without risks. In addition to the immediate risk of surgery, these include long-term malnutrition, osteoporosis, oesophagitis, dumping syndrome and blood sugar fluctuations in diabetes, increased suicide and accident rates compared to non-operated patients, increased drug use and a failure rate of up to 20% (62–64). Long-term follow-up care and supervision is imperative after both bariatric surgery and nutritional

Tab. 2 Therapy recommendations for insulin resistance and inflammation

Laboratory marker	Lifestyle recommendations	Dietary recommendations	Recommendations on nutritional supplements
Inflammation markers: • hs-CRP • IL 6, IL8 • TNF- α Metabolic markers: • HOMA-IR • Adiponectin • Proinsulin	Elimination/treatment of inflammatory diseases Increase of insulin sensitivity by: • More exercise (especially aerobic) • Sufficient sleep • Stress reduction • Weight loss • Reduction of the number of meals • Intermittent fasting where appropriate • Ketogenic diet where appropriate	Avoiding: • Sugar, fructose, refined carbohydrates, trans fats, • Omega-6 rich oils • Preservatives and additives, processed meat products • Meat from intensive rearing • Wheat • Reduction of sweeteners Increasing healthy fats: • Omega-3 fatty acids (cold-water fish) • Olive oil, nuts and seeds, • Meat and dairy products (full fat) preferably from pasture raised animals • High fibre diet, lots of fresh vegetables, moderate amount of fruit (preferably berries)	• Fish oil • Vitamins D, C, B If required: • Zinc, magnesium, chromium, selenium • Green tea extract (EGCG) • Resveratrol • Curcumin • Garlic, ginger • Rosemary, basil • Gymnema silvestre Hormones: • If necessary, DHEA (if decreased) • If necessary, progesterone (transdermal)

therapy; only then are satisfactory long-term results possible (65).

Numerous studies have already demonstrated a reduction in inflammatory parameters and cardiovascular risk factors associated with a ketogenic diet (very low carb ketogenic diet (VLCKD) (66–68); favourable effects are also evident in neurodegenerative diseases (69, 70). The reduction in carbohydrate intake below the individual ketogenic threshold normalizes glucose and insulin at low levels. The secretion of proinflammatory enzymes (Interleukins 6 and 8, TNF-α) is reduced, diuresis and natriuresis are increased and the blood concentration of arachidonic acid and omega-6 fatty acids decreases. Beta-hydroxybutyrate has a direct anti-inflammatory effect in that it blocks a part of the immune system involved in various inflammatory diseases (71). In contrast to the extremely high-fat, ketogenic diet in other diseases, in which a weight loss is undesirable (epilepsy, tumours), a calorie deficit can be induced in overweight individuals by a low to moderate fat intake, since the formation of ketones takes place via lipolysis. In this context, attention should be paid to the quality of the dietary fats: Desirable is the highest possible share of anti-inflammatory omega-3 fatty acids from plant and marine origins and the lowest possible share of proinflammatory omega-6 fatty acids. In contrast to industrial trans fats, the natural trans fats contained in dairy products were found to have positive effects on HDL, inflammatory markers and vascular health. Because of their higher content of omega-3 fatty acids and conju-

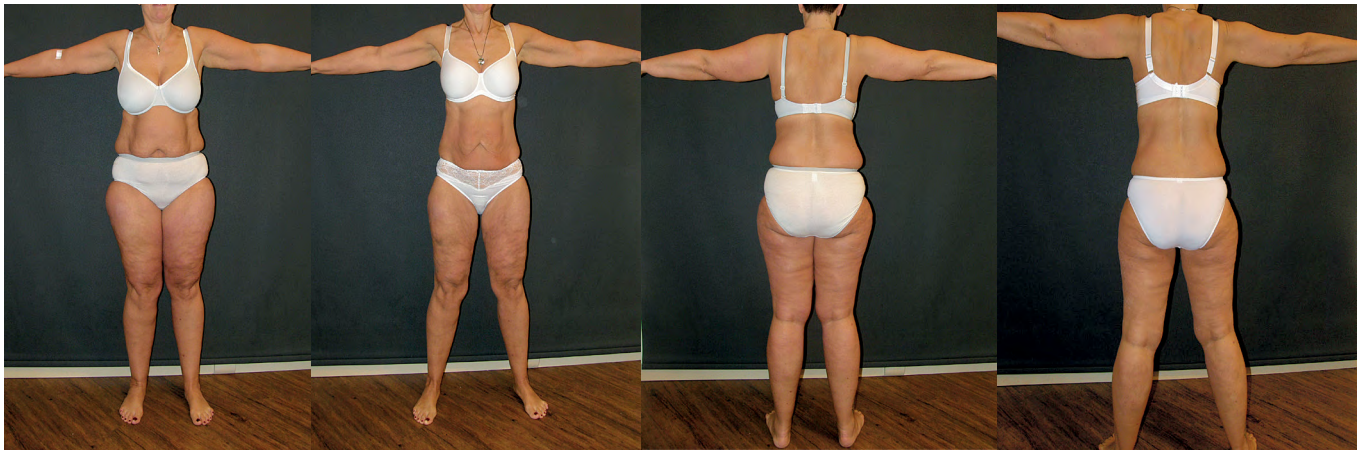


Fig. 4 Lipoedema case study: Grade I obesity (BMI 31.1), 91.2kg; WHtR 0.55; lipoedema of the arms (Stage I) and legs (Stage II); contact sensitivity, spontaneous pain, 3–4 Ibu 400/day; retired early „because of her legs and the pain"; rheumatology and muscle biopsy without pathological findings; HOMA-IR 1.3; CRP 2.3; right photos: ketogenic diet, omega 3 supplementation; weight loss 19 kg in 3 months. Free of complaints, no more pain medication; practices sports again

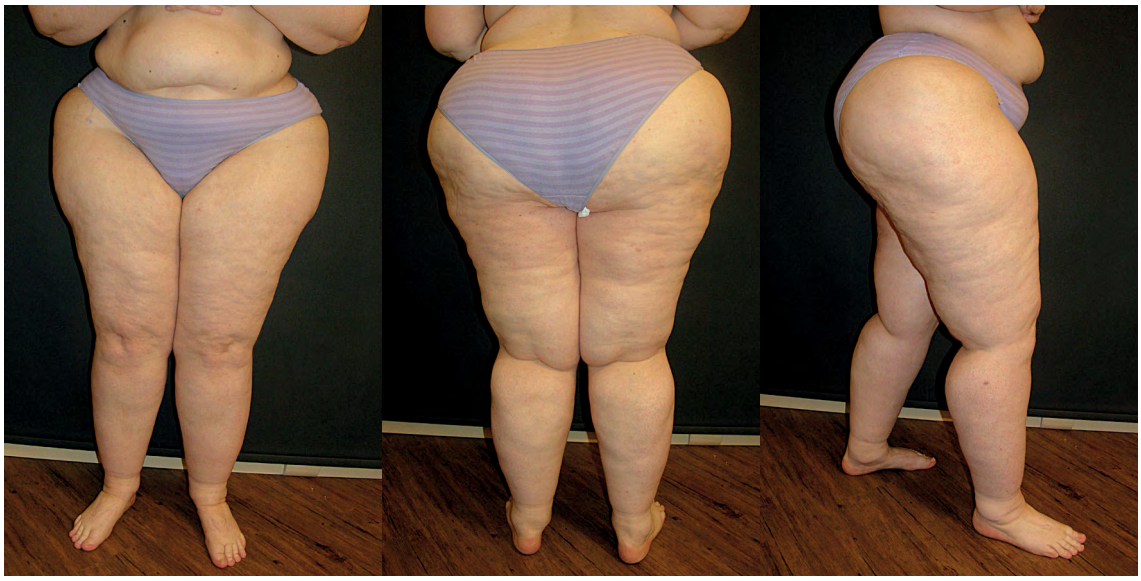


Fig. 5
Lipoedema case study: Lipoedema stage II; weight 141 kg; 178cm; BMI 44.5; ketogenic, high-protein diet; symptom improvement already after 1 week (subjectively and objectively by lymph therapist)

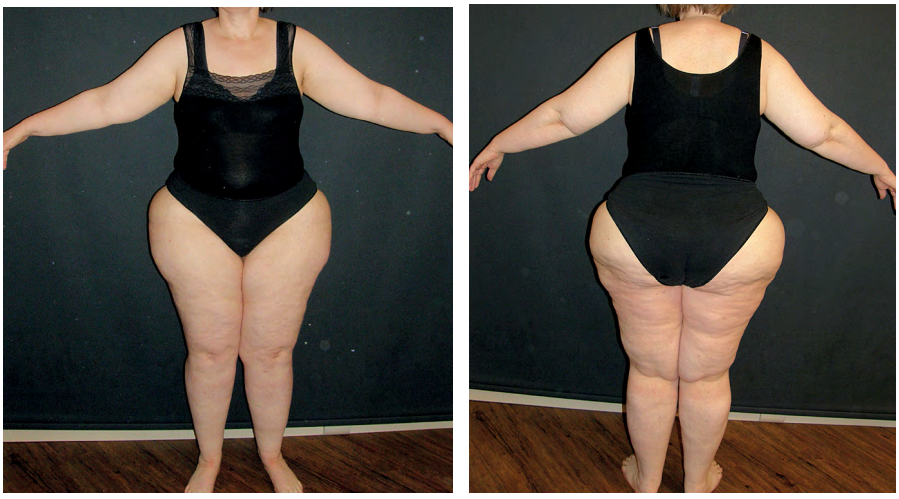


Fig. 6 Lipoedema case study: Weight loss; 104kg (-36.5 kg), Circumference reduction of 10–18cm: Still massive lipohypertrophy. No complaints, lymphoedema no longer present.

gated linoleic acid, full-fat, pasture raised dairy products are recommended (72).

A qualitatively and quantitatively adequate protein intake, as is necessary for the protection of the lean mass and for saturation (73), can also be modified with regard to pro- or anti-inflammatory properties: fish, especially high-fat, cold-water fish such as herring, mackerel and wild salmon are recommended because of their content of omega-3 fatty acids. Meat from pasture raised livestock (lamb, cattle) or game contains more omega-3 fatty acids and significantly less arachidonic acid than pork and turkey or meat from industrially mass-farmed animals. A study of 37 patients with type II diabetes showed that a high-normal protein intake reduces liver fat content, liver enzymes, inflammatory parameters and insulin resistance (73). An amount of 1 to 1.2 grams of protein per kilogram of the normal weight is recommended, which is usually enough to protect lean mass (74) and, as the brain is good at using the ketones as an alternative energy source, but depends on glucose to about 15 to 20 %, to maintain the necessary gluconeogenesis. Insulin secretion increases only at a significantly higher protein intake (>2g/kg) due to increased gluconeogenesis.

For patients, ketosis has the immediate benefit of physical and mental well-being, as ketone bodies have a satiating effect (75–77) and are slightly mood enhancing.

In terms of weight loss and symptomatology, the ketogenic diet seems to be particularly effective for lipoedema (▶ Fig. 5, ▶ Fig. 6). It not only leads to weight loss and degradation of visceral fat, but also to a reduction of the alimentary, i.e. not exclusively lipoedema-related, subcutaneous adipose tissue at the extremities. According to our own investigations, typical symptoms such as sensation of tension, oedema, often tenderness to palpation as well, are improved in more than 80% of cases, so that a reduction of the therapeutic measures is often possible (50). Interestingly, even patients with normal weight often experience a relief of their complaints by avoiding refined carbohydrates and sugars. Hence, this improvement is not only a consequence of weight loss, but most likely of the anti-inflammatory and anti-oedematous effects of the metabolic readjustment as well.

Additional dietary recommendations

Even though they do not contain usable carbohydrates, sugar-free sweeteners should also be avoided or consumed in only small quantities, as they can also increase the insulin secretion via the sense of

taste (so-called „cephalic phase"), which subsequently leads to a drop of blood glucose (78–80). Damage to the healthy intestinal flora is discussed for some sweeteners (81, 82). In contrast, a study from Basel found significant advantages for the polyols erythrol and xylitol. Not only do they show no (erythrol) or only minor (xylitol) effects on plasma glucose and plasma insulin, but they also have a filling effect, as they slow down gastric emptying and increase secretion of the satiety hormones CCK and GLP-1 (83).

A pathologically altered intestinal flora contributes via the immune system to the development of low-threshold inflammation, insulin resistance and metabolic syndrome.

In addition, an altered microbiome can increase the energy intake by 10 to 15 percent, contributing thereby to obesity (84). To maintain a healthy intestinal flora, the diet should therefore be above all rich in soluble fibre (inulin, oligofructose, resistant starch, pectin, at least 30 g/day) and low in sugars (85, 86).

Conclusion

Various studies have shown that weight reduction can improve the skin changes in secondary venous insufficiency and reduce thrombogenic risk factors. Obesity-associated lymphoedema can regress completely and the symptoms of lipoedema decline significantly. Besides treatment of the respective acute or chronic symptoms by anticoagulation, compression, lymphatic drainage or wound therapy, the therapeutic efforts must also focus on the reduction of weight, especially of visceral obesity, through dietary changes and a modification of lifestyle, in order to achieve a long-term reduction of insulin resistance and the associated proinflammatory, oedema-enhancing and procoagulant effects of adipose tissue.

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Conflict of interest

The authors report no conflict of interest.

Ethical guidelines

No studies on humans or animals were performed for this manuscript.

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