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Review

Rare adipose disorders (RADs) masquerading as obesity

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Rare adipose disorders (RADs) including multiple symmetric lipomatosis (MSL), lipedema and Dercum's disease (DD) may be misdiagnosed as obesity. Lifestyle changes, such as reduced caloric intake and increased physical activity are standard care for obesity. Although lifestyle changes and bariatric surgery work effectively for the obesity component of RADs, these treatments do not routinely reduce the abnormal subcutaneous adipose tissue (SAT) of RADs. RAD SAT likely results from the growth of a brown stem cell population with secondary lymphatic dysfunction in MSL, or by primary vascular and lymphatic dysfunction in lipedema and DD. People with RADs do not lose SAT from caloric limitation and increased energy expenditure alone. In order to improve recognition of RADs apart from obesity, the diagnostic criteria, histology and pathophysiology of RADs are presented and contrasted to familial partial lipodystrophies, acquired partial lipodystrophies and obesity with which they may be confused. Treatment recommendations focus on evidence-based data and include lymphatic decongestive therapy, medications and supplements that support loss of RAD SAT. Associated RAD conditions including depression, anxiety and pain will improve as healthcare providers learn to identify and adopt alternative treatment regimens for the abnormal SAT component of RADs. Effective dietary and exercise regimens are needed in RAD populations to improve quality of life and construct advanced treatment regimens for future generations.

Keywords: adiposis dolorosa; Dercum's disease; lipedema; multiple symmetric lipomatosis; familial multiple lipomatosis; familial partial lipodystrophy; lymph; lymphatics

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Introduction

Lifestyle-induced obesity in children and adults has reached epidemic proportions worldwide. In the United States (US), a third of adults aged 20 years and over are overweight, a third are obese, and over five percent are extremely obese[1]. The National Health and Nutrition Examination Survey and Pediatric Nutrition Surveillance System reported a tripling of the prevalence of obesity among US school-age children and adolescents over the past three decades[2]. Numerous published studies validate the weight loss efficacy of lifestyle changes that include decreased amounts and types of food, and improved exercise regimens. Medications used for the treatment of obesity are severely limited[3, 4]. Bariatric surgery has been exceptional in its ability to induce weight loss and resolve the co-morbidities of obesity, though complications rates can be high[5], many people are still obese by body mass index (BMI) after Roux-en-Y gastric bypass (RYGB)[6], and weight regain occurs[7, 8].

This review aims to demonstrate lymphatic dysfunction as a component of rare adipose disorders (RADs) that increases the amount and alters the location of subcutaneous adipose tissue (SAT) while resisting fat loss after lifestyle changes or bariatric surgery. Lipodystrophies are also discussed as they may be confused with rare adipose disorders (RADs).

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Non-lifestyle causes of obesity

Lipodystrophies

Lipodystrophies or fat redistribution syndromes involve a primary lack or loss of SAT; however, increased SAT in other areas can be confused with lifestyle-induced obesity. Human immunodeficiency virus (HIV)-associated lipodystrophy, is well-known, but familial partial lipodystrophies are rare and therefore less well known, and can go undiagnosed for years or are never recognized. Acquired partial lipodystrophy, also rare, with a progressive and symmetrical lipoatrophy of SAT starting from the face and spreading to the upper part of the body, sparing the legs, can be confused with the RAD, lipedema, due to a disproportion between upper and lower body SAT (see below).

Acquired lipodystrophies

Human immunodeficiency virus (HIV)-associated lipodystrophy

HIV-and highly active antiretroviral treatment (HAART)-associated lipodystrophy includes loss of SAT from the face,

buttocks, arms, and legs. In men with lipodystrophy, SAT can be increased on the abdomen and chest (gynecomastia), and a dorsocervical fat pad or "buffalo hump" is common[9, 10]. The SAT in the dorsocervical fat pad is thought to be identical to the SAT in multiple symmetric lipomatosis (MSL), one of the RADs (see below). Upper body fat, including parotid hypertrophy, circumferential enlargement of the neck and a dorsocervical fat pad are associated with insulin resistance in HIV+ men[11–13] as is intermuscular fat and SAT on the legs in HIV+ women[14]. Large breasts are part of HIV lipodystrophy in Black women and other non-Caucasian ethnicities[15]. Women with HIV may also develop increased SAT on the upper part of the arm out of context with the usual lipoatrophy in this area in HIV+ men suggesting an estrogen and/or progesterone component to location of the SAT. This upper arm SAT looks visually similar to the SAT in women with the RAD, MSL (see below and Figure 1). In addition to excision of excess SAT as treatment for lipodystrophy[16], tesamorelin, a synthetic analogue of human growth hormone-releasing hormone, is FDA-approved for the reduction of excess visceral adipose tissue in HIV-infected patients with lipodystrophy. Visceral adipose tissue was reduced up to 18% during active use of tesamorelin[17]. The glucagon-like peptide-1 agonist, exenetide, also improved the HIV- and treatment-induced obesity through weight loss in a single case[18].

Acquired partial lipodystrophy (APL; BARRAQUER-SIMONS syndrome)

Acquired partial lipodystrophy is characterized by a regional loss of SAT primarily in children and adolescents starting at the face and extending to the waist, sparing the legs; in fact SAT may be increased on the legs[19]. Because of the higher amount of SAT in the legs compared to the upper body, APL could be confused with the RAD, lipedema (Figure 2). In lipedema, there is increased fat on the legs but the fat of the upper body is normal or increased (see below). APL is thought to be autoimmune occurring after a febrile (viral) illness[20] with

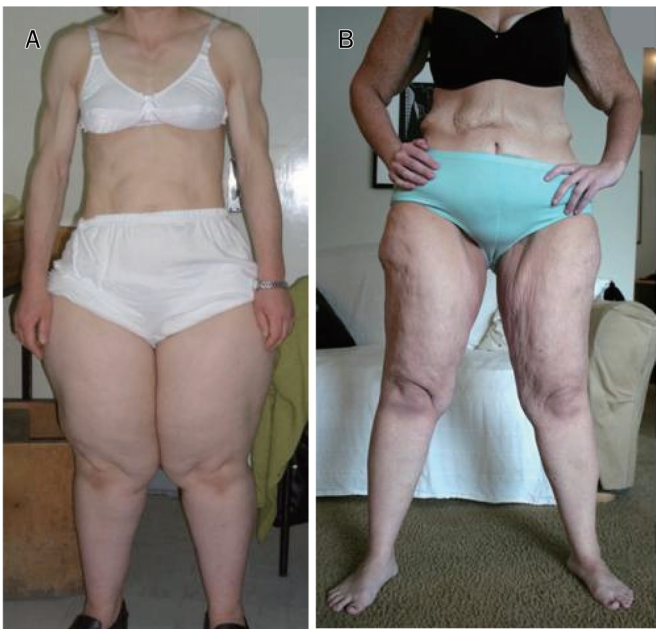

Figure 2. Acquired partial lipodystrophy and lipedema. A, a 37 year old woman with acquired partial lipodystrophy. C3 level<16.1 mg/dL (normal range: 90-180) and C4 level 23.11 mg/dL (normal range: 10-40). Note the loss of SAT from the upper body to the waist but obesity of the hips and legs (photo by Dr Alper GURLEK). B, a woman with lipedema stage II and a previous history of obesity with a 100 kg weight loss; note redundant skin on arms and abdomen from weight loss of non-RAD fat; note also lipedema in legs.

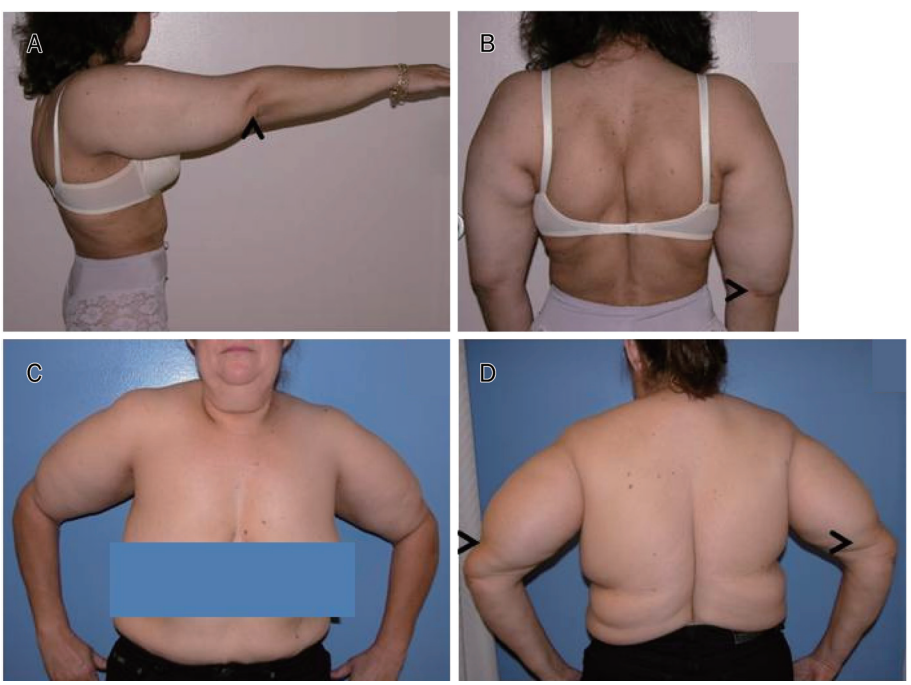

Figure 1. Multiple symmetric lipomatosis with or without HIV infection. A and B, non-HIV-related MSL Type II; note increased upper arm size and increased fat on back. Not shown is increased fat in the labia majora. C and D, increased arm and back fat, respectively in HIV-and HAART-induced MSL Type II. Arrows point to end of MSL fat on the upper arm. Normal labia majora (not shown).

low levels of complement factor 3 (C3) and the presence of a circulating autoantibody called complement 3-nephritic factor. Treatment with the thiazolidinedione, rosiglitazone, improved levels of C3 and increased SAT in a participant with APL[21].

Familial partial lipodystrophies (FPLD)

FPLD Type 1: FPLD1, also known as Köbberling lipodystrophy, is a lesser known partial lipodystrophy primarily found in women causing a lipodystrophy of the arms, legs, and sometimes breasts, with an increase in fat on the abdomen and remainder of the trunk[22]. The prevalence of FPLD1 and any genetic mutation remains unknown. There are no blood or urine biomarkers for FPLD1. FPLD1 may go unrecognized if the practitioner does not recognize the lipodystrophy; finding a ledge where SAT ends on the buttocks can help in the diagnosis. Diabetes and hypertriglyceridemia are highly prevalent in FPLD1 while acanthosis nigricans is minimal. Treatment is restricted to usual care of obesity-associated co-morbidities, although, RYGBP should be considered as it improved weight and co-morbidities in a case of FPLD1[23].

FPLD Type 2: The best studied FPLD is Type 2 (FPLD2), also known as Dunnigan lipodystrophy. In FPLD2, SAT is lost around the time of puberty from the legs, arms, buttocks, abdomen and chest; areas of remaining SAT deposits are on the back, face and chin, giving a Cushingoid appearance; fat is increased in the labia majora in women[24]; this finding also occurs in women with MSL (Figure 1). Mutations in the lamin A and C gene, LMNA, cause FPLD2[25]. People with FPLD2 have all the co-morbidities associated with obesity. Leptin levels can be very low in lipodystrophies and leptin treatment has shown benefit but remains investigational[26]. RYGB has also shown benefit in reducing the co-morbidities associated with FPLD2[27].

FPLD Type 3: Mutations in the peroxisome proliferator-activated receptor gamma (PPARG) gene can cause partial lipodystrophy with abdominal obesity[28] known as FPLD3[29]; people with FPLD3 may look very similar to FPLD2. Treatment with thiazolidinediones may be useful in people with PPARG gene mutations[30] and other cases of FPLD without identified gene mutations[31].

Additional lipodystrophies and single cases of additional types of FPLD have been well reviewed[19].

RADs

Multiple Symmetric Lipomatosis (Madelung's disease/syndrome; Launois Bensaude syndrome)

Multiple symmetric lipomatosis (MSL) is a rare syndrome (Table 1) originally described in 1846[32], characterized by the painless, symmetrical accumulation of abnormal tumor-like SAT. The first systematic treatise was by the German surgeon Dr Otto Madelung who collected 30 cases and reported an additional 3 cases in 1888 under the name "Fetthals" or fat neck[33], but the French Physicians Drs Pierre-Emile LAUNOIS and Raoul BENSAUDE gave prominence to and caused recognition of MSL by publishing a detailed account of 65 cases in 1898[34]. There are many synonyms for MSL including benign symmetric lipomatosis but this disorder is anything but benign, arguing against its use. Over 300 adult cases are reported in the literature with an age range of 20–71 years. The early literature on MSL was dominated by research on alcoholic men with a reported incidence of 1/25 000 in the Italian population[35]. Non-alcoholics and women are also affected[36–38]; two cases have been reported in children[39, 40].

Table 1. Identifying codes or numbers for SAT Disorders.

Code or number	SAT disorder		
	MSL	DD	Lipedema
OMIM	151800	103200	614103
Listed by NORD	Yes	Yes	No
NLM MESH ID	D008069	D000274	NA*
ICD-9/10	272.8/E88.8	NA/E88.2	NA
Alternative ICD-9/10	NA	338.4/G89.4 Chronic pain syndrome	457.1/189.0 Lymphedema, not elsewhere classified
Orphanet number	2398	36397	77243

ICD=International Classification of Diseases; MESH=medical subject headings; NLM=national Library of Medicine; NORD=National Organization of Rare Disease; OMIM=Online Mendelian Inheritance in Man®; *Application for a MESH code submitted

Diagnosis

Identification of MSL is by history and clinical exam. There are no blood or urine biomarkers for MSL and the gene(s) remains unknown in a majority of cases. Individuals with MSL have increased SAT, either as discrete non-encapsulated lipomas or as a confluent increase in SAT in a symmetrical distribution on the neck, the back, the chest, the upper arms, or on the thighs; MSL usually spares the distal limbs[41] but not in many women with MSL where the altered fat may be global[42] (Figure 3). Because the appearance and location of SAT in MSL can vary, MSL has been divided into three types:

Clinical types of MSL[37, 43]

Type I, head and/or neck with extension down the back, or only on the back: In rare cases, MSL SAT can invade the lingual muscles of the tongue[44, 45], or the vocal cords and compress the recurrent laryngeal nerve causing hoarseness[46], or increase periorbital fat[47]. Tracheal or esophageal compression and the superior vena cava syndrome can be found in 15%–20% of patients[48]. The presence of a dorsocervical fat pad (buffalo hump) can be found both in MSL[41, 49, 50] and HIV-associated lipodystrophy[9, 10, 51, 52]; it has been proposed that the fat in these two disorders arises from brown adipose tissue located in that area[53].

Type II body: Includes the shoulder girdle, the upper arms, the thorax, the back, the abdomen and upper buttocks. In one case, fat grew around the testicles in the scrotum and was contiguous with MSL tissue in the perineum and the root of the penis[54]. Also rare is growth of the MSL fat on the hands[55].

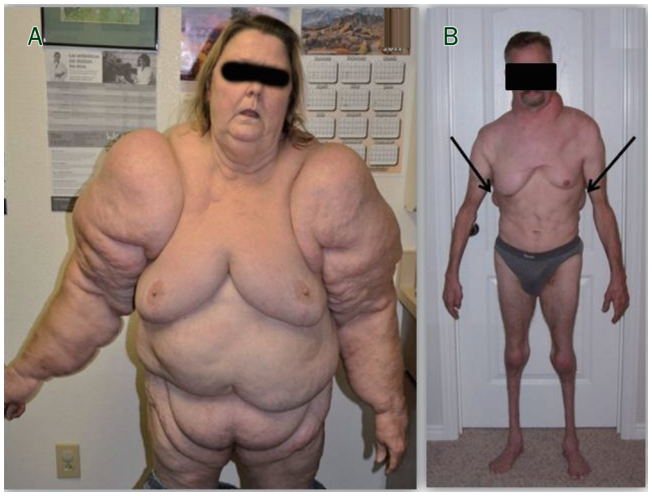

Figure 3. Whole body MSL and MSL-associated lipodystrophy. While MSL is noted to spare the forearms (see text), the entire body can be clearly affected. A, 60 year old woman with a history of alcohol dependence with global MSL SAT; note prevalent SAT on the forearms (photo by Dr Andy COREN). This type of MSL may be easily confused with global obesity or lipedema stage III. B, 50 year old man with MSL Types I and II with associated muscle and normal fat atrophy (also note the increased back MSL SAT; arrows); this type of MSL may be confused with partial lipodystrophy.

Many individuals have a combination of Types II and III. While the MSL fat grows, normal fat and muscle can undergo wasting which can be confused with a partial lipodystrophy (Figure 3).

Type III, thigh (female type): Rarest type. MSL type III is clinically similar to and may be instead, the RAD, lipedema (see below). Women tend to have Type II and III MSL with widespread altered SAT[41].

MSL inheritance

MSL is thought to be inherited through mitochondrial mutations in a few familial cases including multiple deletions of mitochondrial DNA, and the myoclonus epilepsy and ragged-red fibers (MERRF) tRNA(Lys) A>G(8344) mutation[56, 57]. Klopstock *et al* found mitochondrial mutations in only 2 of 12 patients studied[50]. Chalk *et al* found no mitochondrial pathology or mutations in four siblings with MSL with a pattern favoring autosomal recessive[58]. The phenotype of MSL may require a combined effect of alcohol (or other insult) and a currently unknown genetic mutation.

Histology of MSL fat

Individual fat cells have been described as smaller than normal[38, 49, 59] or normal sized[38]. MSL SAT is thought to be derived from brown adipose tissue (BAT) or as white adipose tissue (WAT) that transdifferentiates into BAT[49, 60, 61]. Ultrastructurally, brown adipocytes have numerous large mitochondria packed with cristae. Under light microscopy, brown adipocytes have cytoplasmic lipids arranged as numerous small droplets (multilocularity), while white adipocytes have cytoplasmic lipids arranged in a unique vacuole (unilocularity). In BAT, the metabolic reactions of mitochondria are uncoupled from ATP synthesis by uncoupling protein (UCP)-1 so that energy produced is released as heat[62]. Infants and even adolescents have a substantial amount of BAT, especially between the shoulder blades. BAT persists throughout adulthood in the perirenal, omental, mesenteric, pericardial, intercostal, axillary, cervical, and interscapular fat, embedded within WAT[63, 64] with an approximated ratio of 1 brown adipocyte for every 200 white adipocytes[65, 66].

By light microscopy, adipocytes in MSL SAT are monovacuolar[67, 68] or multivacuolar[69]. By electron microscopy of long-term primary cultures from the stromal vascular fraction (SVF), containing stem and immune cells, cells were polymorphic with thin microfilaments suggestive of elevated metabolic activity[69], were multivacuolar, and had large mitochondria packed with cristae suggesting a more BAT phenotype in MSL[60, 68].

Physiology of MSL SAT

MSL SAT may arise from a stem cell population either destined to form BAT, or WAT that transdifferentiates to BAT; in either case, UCP-1 levels help track BAT features. SAT cells from subjects with MSL express UCP-1 suggesting its origin as BAT[61, 70], but this is not substantiated in all cases[71]. Adrenergic receptors (AR) that respond to sympathetic input, such as the three subtypes of β-AR, β_1-, β_2- and β_3-, promote lipolysis and energy expenditure. Cells isolated from the MSL SVF did not increase UCP-1 in response to noradrenaline even though MSL cells express all three β-AR[61]. Resting energy expenditure (REE) may be expected to be higher in MSL with BAT; indeed REE when normalized to fat free mass was mildly higher in MSL subjects than normal, suggestive of energy uncoupling and heat generation[72], however, REE in other subjects with MSL was within normal limits[38]. In MSL cell culture, catecholamines did not increase lipolysis, expression of inducible nitric oxide synthase (iNOS) or PPARγ coactivator-1α (PGC-1α), a coregulator of nuclear receptors that control metabolic pathways in BAT[61, 73–75]. Two other groups found a normally reactive adenylate cyclase system and a normal number of a- and β-adrenergic receptors in MSL SAT[76, 77]. Cytokine and adipokine levels in MSL are also mixed[37, 61]. While the multilocularity of MSL SAT is suggestive of BAT, more data in a larger number of subjects of well characterized participants are needed to substantiate the cell type of origin and functionality of pathways.

The increase in MSL fat is extensive and deforming, compressing tissue structures and vessels. Early, MSL SAT is watery but later becomes fibrotic and scars easily[78]. Similarly in obesity, excess fat physically impedes lymph collection and flow, protein-rich lymphatic fluid collects in SAT, resulting in lymphedema and tissue hypoxia[79]. SAT also grows in the presence of lymphedema[80]. Further accumulation of fluid in the setting of decreased oxygen tension leads to fibrosis[81]. Interestingly, ischemia activates the growth of adipose-

derived progenitor cells[82]. Congestion of lymph nodes by other means, such as lymphoma in the neck, induces fat growth similar to MSL[83]. Increased volumes of SAT in MSL, like obesity, may therefore be sufficient to externally compress vasculature and lymphatics inducing further growth of SAT as seen in other localized fat collections[84]. Impedance of lymph flow into lymph collectors is a local effect and does not affect flow in larger lymph trunks, therefore the role of lymphoscintigraphy in MSL is questionable[85].

Conditions associated with MSL

Alcohol-induced liver disease is common in MSL. Hyperlipidemia, hyperuricemia, hypothyroidism, and diabetes mellitus have been reported but are not consistent amongst those affected[86, 87]. People with MSL I or II should be tested for sleep apnea[87]. Cancerous transformation of the SAT is uncommon; development of myxoid liposarcoma was reported in one case[88]. Slowly progressive axonal sensory and autonomic peripheral neuropathies have been reported to occur after the development of MSL fat and impairment of autonomic function has been suggested as a cause of sudden death[86, 89]. The neuropathology is a distal axonal demyelination different from that associated with alcohol intake[58, 86, 90]; this impairment seems to be prevalently parasympathetic[48, 91]. In a ten year follow-up, ~10% of 31 patients died from sudden death due to autonomic neuropathy[36]. Surgical placement of a cardiac pacemaker may be needed.

MSL treatment recommendations

Primary recommendations

1) Alcohol abstinence: Abstinence from alcohol may arrest further progression of the MSL SAT but does not cause regression of the SAT deformities[92].

2) Lymphatic decongestive therapy (LDT): Includes manual lymphatic drainage (MLD), wrapping of the limbs, compression garments, exercise such as pool therapy and other non-impact exercise (so as to avoid lactic acid accumulation in tissue due to poor lymph flow), dietary recommendations, and skin care. Manual lymphatic drainage works well to reduce MSL SAT before fibrosis[93].

3) Surgery: Surgical resection and liposuction provide the only means of dramatically decreasing the MSL SAT[94–97]. In a majority of cases of MSL Type II and III, resection or liposuction of the lipomatosis is considered cosmetic and insurance companies are reluctant to cover this procedure[98]. Unfortunately, the fat usually penetrates and surrounds deeper structures such as muscle and bone, making total excision of the abnormal tissue difficult[92]; the lipomatosis can, therefore, recur after liposuction or excision[87, 99, 100]; in three of eleven patients in one series[101].

Additional considerations for MSL treatment

4) β_2-Adrenergic Agonist: After demonstrating an intact lipolytic response of the MSL fat to catecholamines, an oral β_2-AR specific drug, salbutamol, 15 mg per day in divided doses, reversed the rapid accumulation of the MSL fat and increased REE in a man with MSL, but was effective only during active use[102].

5) Fibric acid: A man with MSL Type II with a past history of hypertriglyceridemia was treated with fenofibrate 200mg daily. The circumference of his abdomen decreased 119 cm (46.9 in) to 108 cm (42.7 in) within a year. Fibric acids are PPARα agonists. Activation of the PPARα receptor may suppress expression of proteins involved in the architecture of BAT, thereby maintaining BAT in a quiescent state[103].

6) Growth hormone: Growth hormone (GH) treatment has been suggested in the community of individuals with MSL as a treatment option (personal communication) but GH levels were normal in one subject with MSL during a glucose tolerance test[49] and in three other subjects[104] suggesting a normal GH axis. Testing for GH deficiency should be undertaken and replacement considered only for those deficient in this hormone.

7) Lifestyle: Lifestyle improvements provide no resolution of the MSL SAT[105].

8) Local SAT injections: Corticosteroid injections have been suggested as treatment for lipomatosis such as MSL SAT[106] but there are a number of cases demonstrating the development of lipomatosis after steroid use[107, 108]. Local injection with thyroxine[107], enoxaparin[109], deoxycholate[110], and phosphatidylcholine[78] have also been proposed for treatment of lipomas but the latter require multiple injections and use of thyroxine injections in the presence of autonomic dysfunction would be dangerous. In addition, the extent of the SAT in MSL does not allow for single site injections, limiting these treatments to lipomas.

Lipedema (lipoedema; lipalgia; adiposis dolorosa; lipomatosis dolorosa of the legs; lipohypertrophy dolorosa; painful column leg)

Lipedema is generally unknown to medical providers, is easily confused as obesity, does not have a MESH term in the National Library of Medicine, and does not have an International Classification of Diseases (ICD) code; it does have an Online Mendelian Inheritance in Man code, and is recognized by Orphanet (a European website providing information about orphan drugs and rare diseases (Table 1). Drs Allen and Hines Jr from the Mayo clinic labeled this condition as lipedema in 1940[111]. Outside the US, lipedema is known as "lipoedema", meaning edema of the fat. This disorder is likely very common but underdiagnosed.

Diagnosis

The diagnosis of lipedema is made clinically by history, visual inspection and physical exam as extensive deposition of SAT between the iliac crest and the malleoli and approximately 30% of the time, on the arm[42]. When the fat is palpated, it will be tender and feel like round peas in a plastic bag or a "beanie baby"[111, 112]. Larger nodules, lumps, lipomas or angiolipomas may also be found in the SAT. There are no blood or urine biomarkers for lipedema and the gene(s) is unknown. The skin and SAT is thicker in lipedema compared

to healthy controls and muscle mass is not edematous as it is in lymphedema[113]. The skin is also less elastic and striae are common in lipedema.

In 1951, Wold, Hines and Allen analyzed 119 cases and provided the diagnostic criteria for lipedema[114]:

1) Almost exclusive occurrence in women developing by the third decade of life. Prevalence within the population remains grossly under diagnosed[115]. According to an epidemiologic study by Földi E and Földi M[116], lipedema affects 11% of the female population. At least seven cases have been reported in men with testosterone or GH deficiency, or liver disease[114, 115, 117].

2) Bilateral and symmetrical nature with minimal involvement of the feet, resulting in an ''inverse shouldering'' or ''bracelet" effect at the ankle

3) Minimal pitting edema (non-pitting edema is present)

4) Pain, tenderness, and easy bruising

5) Persistent enlargement despite elevation of the extremities or weight loss

6) Increased vascular fragility; easy bruising

Often women note that the lipedema appears or is exacerbated at the time of puberty, pregnancy[118] or menopause suggesting an estrogen component; that few men have this condition except those with hypogonadism or hyperestrogenemia supports this hypothesis.

There are five types of lipedema[119]

Type I: Pelvis, buttocks and hips (saddle bag phenomenon)

Type II: Buttocks to knees, with formation of folds of fat around the inner side of the knee

Type III: Buttocks to ankles

Type IV: Arms

Type V: Lower leg

There may be a mixture of lipedema types in one person, for example Type II and IV. Only the arms may be affected in 3% of lipedema cases (Type IV)[42]. The importance of knowing the different lipedema types is to improve recognition, and identification of differences *ie*, all people with lipedema do not look alike; treatment is similar amongst the types. In addition to types of lipedema, the lipedema progresses through stages; the progression varies greatly amongst those affected and there is no data suggesting everyone need progress through all stages.

There are three stages of lipedema (Figure 4)[112, 120]

Stage 1: Normal skin surface with enlarged hypodermis

Stage 2: Uneven skin with indentations in the fat[121]; larger mounds of tissue grow as unencapsulated masses, lipomas and angiolipomas

Stage 3: Large extrusions of tissue causing deformations especially on the thighs and around the knees

Stage 4: Lipedema with lymphedema (lipolymphedema)

Progression to lipolymphedema can develop during stage II-III. The description and representative pictures of Type III MSL[41] are that of lipedema stage II[38]; no study has formerly differentiated these two SAT disorders. Synonyms for lipedema also include adiposis dolorosa, which is another name for the RAD, Dercum's disease (see below). However, according to Cornely, the trunk, hands and feet are not involved in lipedema "Thus, lipedema differs clearly from Dercum's disease"[122]. As lipedema progresses to lipolymphedema, the hands, feet, trunk and head develop excess SAT making this statement incorrect. Because lymphatic dysfunction is a part of Dercum's disease and many early cases of Dercum's disease are visually and descriptively lipedema (see below), the two SAT disorders are at a minimum, in the same spectrum. Lipedema may also be confused with APL, however, in APL there is a lack of SAT on the face and upper body while in lipedema, SAT is normal or increased in these areas (Figure 1).

Inheritance of lipedema

Inheritance has been noted up to 60% of people with lipedema[118, 123, 124] but is likely higher due to under diagnosis. In six families over three generations with lipedema, the inheritance pattern was autosomal dominant with incomplete

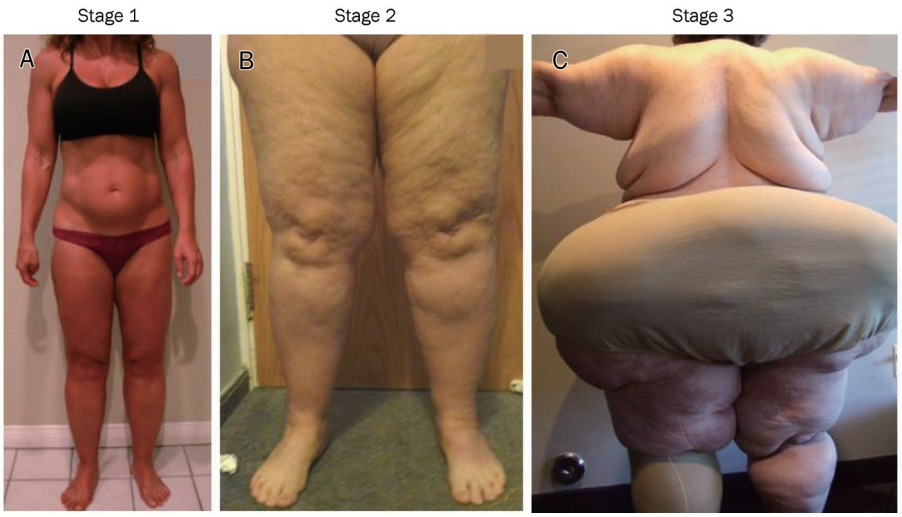

Figure 4. The three stages of lipedema. A, Stage I with little alteration of the skin surface. B, In stage 2, the surface of the skin takes on the appearance of a mattress with lipomas in the fat. C, In stage III lipedema, there are much larger fat extrusions.

penetrance[115].

Histology of lipedema SAT

The gross description of the fat in lipedema is similar to that of MSL with "free fluid fat" in biopsy specimens[125]. Histological exam is not unlike that found for cellulite with dilation of subdermal blood capillaries, perivascular cells, fibrosis of arterioles, fibrosis and dilation of venules, and hypertrophy and hyperplasia of adipocytes[126, 127]. Histochemical studies show adipocytes death and stem cell regeneration[128]. There are also increased numbers of blood vessels especially capillaries and prominent venules[116]. Large clusters of macrophages are found around multiple fat cells (not isolated crown-like structures[129]), surrounding blood vessels and forming oil cysts in lipedema SAT[116, 130]; macrophages may also be a prominent component of cellulite[131]. The histology of lipedema SAT can also appear as normal[125].

Physiology of lipedema SAT

The elasticity of the skin and fascia is decreased in lipedema[132] which in Stage III may progress to abnormally clumped elastic fibers or pseudoxanthoma[133]. The skin loses its role as an abutment for the skeletal muscle venous pump and the increased compliance of the SAT results in an increase in capillary compliance[116, 124]. The permeable capillaries release excess protein-rich fluid into the interstitium along with blood[42, 116, 134, 135]. The veno-arteriolar reflex in lipedema is also absent so that under orthostatic conditions (standing), there is limited vasoconstriction and increased net filtration driving edema[116]. Early on, lymphatic transport increases to accommodate the increased fluid flux from the capillaries[136, 137]. During this time, visualization of lymphatic vessels on a gross level by lymphoscintigraphy is normal[138, 139]. As lipedema progresses, microaneurysms appear in the lymphatics in the skin[139, 140] which eventually leak[125, 136]. It is during this time that hypertrophy and hyperplasia of fat cells accelerates[138] further altering the microlymphatic architecture and increasing venous congestion. The resultant edema increases hydrostatic pressure in the tissue and pain[123, 141].

As an example of what happens in SAT when lymph leaks, mutation of prospero homeoboxprotein 1, encoded by the PROX1 gene, causes leakage from lymphatics and resultant obesity in heterozygote mice[142]. Lymph placed on adipocytes in culture also induces robust growth; in essence, "lymph makes you fat"[143]. Although PROX1 mutations are not known to be associated with lipedema, it is clear that fat grows in response to lymph[80]. Eventually, the microlymphatics may become obliterated in lipedema[144] leading to backflow and an overall dynamic insufficiency of the lymphatic system[42]. The increased tissue pressure and lymphatic vessel leakage lead to the development of lipolymphedema[136, 145, 146]. While lymphedema does not usually develop with cellulite in women, the pathophysiology of cellulite development is similar to that in lipedema, and LDT (see treatments below) improves the cosmetic appearance of cellulite[147, 148]. Lipedema may therefore be an extreme form of cellulite.

Conditions associated with lipedema

Depression and anxiety are very common in people with lipedema for many reasons including the lengthy time to diagnosis, repeated counseling on diet and exercise by the healthcare community when neither is particularly effective and because of the massive and sometimes rapid body metamorphosis over a lifetime. In one clinic, women with lipedema were found to be more depressed than patients with paralysis[112]. Painful SAT is a chronic problem in lipedema[111, 114]. The excess tissue fluid weakens nearby structures leading to the development of joint pains; with progression of lipedema, arthritis develops[149]. Capillary fragility, ecchymosis, hematomas and venous varicosities are common[150]. The Kaposi-Stemmer sign is negative in lipedema (the skin cannot be pinched as a fold by the fingers) until the development of lipolymphedema. Idiopathic edema (IE) is similar to lipedema by description and has been identified in women with lipedema[116, 134]. Other changes in skin include dryness, fungal infections, cellulitis, and slow wound healing. Free fatty acids may be different in both blood and the lipedema SAT[125].

Lipedema treatments recommendations

Primary recommendations

1) Lymphatic Decongestive therapy (LDT) is the standard of care for lipedema. Includes manual lymphatic drainage (MLD), wrapping of the limbs, compression garments, movement therapy, dietary recommendations, and skin care. LDT has been shown to improve skin elasticity, restore the veno-arteriolar reflex, increase pre-lymph drainage and lymph transport in lymphatic vessels[116, 151], and reduce capillary fragility in lipedema[152]. Intermittent pneumatic compression may not improve limb size over MLD alone[153] but may be effective alone when MLD is not available[154]. Compression is most effective when tissue edema is present[155] as in its absence, it has little effect[156]. That compression was effective in lipedema was noted by Hines in a woman with lipedema whose fat and edema were absent under the area covered by her "high-topped shoes"[157].

2) Exercise: Aqua lymphatic therapy (pool hydrotherapy) significantly reduces limb volume in lymphedema[158]. In addition to improving strength and bone mineral density, whole body vibration (WBV) improves peripheral circulation[159, 160] and increases lymph flow, raising the threshold level for edema formation in the legs[161]. During WBV, the user simply stands (or stretches/exercises) on a platform for 10-15 min. making this a very accessible exercise modality.

3) Pain Control: Must be individually optimized; liposuction improves pain (see below).

4) Psychological support: Many women with lipedema are left on their own to find their diagnosis, convince their healthcare providers about lipedema and then seek treatment, all complicated by depression, anxiety and eating disorders; counseling and support during treatment are necessary when any of these are present[116]. Counseling reduces anxiety by 50% in people with secondary lymphedema[162].

5) Surgery: Liposuction works effectively for lipedema to

reduce SAT and pain[122, 163, 164]. In patients who have lipolymphedema, it may be prudent to undergo lymphoscintigraphy to confirm the absence of large lymph vessel damage before pursuing liposuction[116]. Bariatric surgery is ineffective in uncomplicated lipedema (without obesity or lymphedema)[165, 166] but effective in lipedema and lymphedema associated with obesity as long as LDT is performed before and after bariatric surgery[167].

Additional considerations for lipedema treatment

6) Beta-adrenergic agonist: Modeling treatment after capillary leak syndrome, terbutaline sulfate, 5 mg five times daily, and theophylline, 200 mg twice daily, were given to a woman with lipedema (called lymphedema in the paper) and after 10 months a weight loss of 20 kg was noted. Cessation or lowering the medication allowed weight regain[168].

7) Corticosteroids: Corticosteroids produce a fast reduction in swelling and pain but increase the risk of infection, capillary fragility and SAT growth. A series of corticosteroid joint injections is usually well-tolerated without exacerbation of lipedema.

8) Diuretics: Diuretics can quickly deplete lymphedema fluid but concentrate protein in edematous tissue promoting fibrosclerosis[169]. Use of diuretics in lipedema before lymphedema may result in the development of pseudo Barrter's syndrome characterized by hypokalemic-hypochloremic alkalosis, hyperactivity of the renin-angiotensin-aldosterone system and elevation of atrial natriuretic peptide[116, 170].

9) Flavonoids: Daflon is a flavonoid that has been used to treat lymphedema[171-173]; it may be expensive and is unlikely available by prescription. Other flavonoids such as those for venous disease[174] have not been formerly tested in lipedema participants. The International Society of Lymphology does not endorse the use of flavonoids as a substitute for LDT.

10) Lifestyle: Obesity can occur along with lipedema especially in Stage III when the lipedema limits movement, but can also occur when movement is limited by pain in earlier stages; lifestyle improvements should always be considered but are not the cause of lipedema[175]. Lipedema SAT is unaffected by caloric restriction alone[175].

11) Selenium: Sodium selenite (selenium) has proven effective for reduction of secondary lymphedema[169, 176–181]. The US National Research Council has defined the individual maximum safe dietary intake for selenium as 600 μg daily and the no adverse effect level as 800 μg daily.

12) Shock wave therapy: One report suggests that shock wave therapy functions similarly to LDT in reducing oxidative stress of the tissues and in smoothing the dermis and hypodermis[182] which may be useful as part of a treatment plan and when lymphatics are still functioning.

Dercum's disease (adiposis dolorosa; Morbus Dercums)

Dercum's disease (DD) was recognized in 1892 as a clinical entity called "adiposis dolorosa", meaning painful fatty deposits, when Dr Francis X DERCUM from the University of Pennsylvania published on three cases[183]. This sentinel publication was preceded by a report of a single case in 1888[184] and followed by the published autopsy of that case[185]. Numerous case studies, case series and descriptions of DD have been published with such a wide variety of locations for the fatty deposits, including misdiagnoses of obvious cases of lipedema, familial multiple lipomatosis and MSL[186] that, unless one is an expert in SAT disorders, it would be difficult to diagnose this often misunderstood syndrome. DD is currently considered to be a rare disorder (Table 1).

Diagnosis

Diagnosis of DD is made by history and physical exam. Dercum's disease occurs primarily in women with a ratio of females to males of 5-7:1[186–188]; the average age of development in one series was 35 years[188] but it has been reported to develop in children[188–191] and in adults up to age 80 years[186]. One in a 1,000 are affected in Sweden[187]. Many cases of peri- or post-menopausal women with DD have been reported suggesting a hormonal component to the development of DD[192]. In addition to painful SAT, there are many other signs and symptoms associated with DD so a lengthy review of systems is helpful (Table 2).

There are three types of DD[187, 193]:

Type I, juxta-articular (around the joint): Painful folds or nodular fat on the inside of the knees and/or on the hips; in rare cases only evident in the upper-arm fat (similar to Type IV lipedema).

Type II, diffuse, generalized type: Widespread pain from fatty tissue found anywhere from head to the soles of the feet.

Type III, nodular type: Intense pain in and around multiple "lipomas", sometimes in the absence of obesity.

Interestingly, the painful lumps of fat first noticed around joints in DD Type 1 occur in locations of lymph nodes, for example around the knee (popliteal nodes), the elbow (cubit nodes), hips and thighs (inguinal nodes), upper arm (axillary nodes) and supraclavicular. As Dr Kling reported in 112 cases of Type I DD, "Juxta-articular adiposis dolorosa is regarded as the initial and intermediate stage of generalized adiposis dolorosa"[194]. Dercum's disease Type I is therefore, the first stage of DD, and Type II a stage with more widespread dysfunction. Type I DD around the knees is visually consistent with Type IV and Type II lipedema Stages 2–3.

Type III DD is likely a variant of familial multiple lipomatosis (FML) in which men present mainly with lipomas and/or angiolipomas predominating on the lower and upper arms, the lower trunk and thighs and women present with lipomas, angiolipomas and obesity[188, 195]. Angiolipomas can be found in up to 30% of people with DD[188, 196]. The lipomas are generally not painful in FML except if they are growing or traumatized frequently, however, they are painful in DD Type 3. In a DD family, family members may have lipomas without pain[195]. Even if a person with FML has non-painful lipomas, at some point in time a lipoma can become painful, followed by generalized pain in all lipomas. Pack and Ariel[197] described this as lipoma dolorosa, distinct from DD. It is

unclear why the authors make this distinction as others ascribe the same pathological process to both FML and DD Type III, with pain in the latter due to "local conditions"[198]. The "local conditions" may be increased tissue tension from fluid accumulation. In two cases of DD Type III, pain was relieved after local hemorrhage[186]. The underlying pathophysiology of DD needs to be elucidated to further differentiate or group the three types of DD.

DD inheritance: Thought to be autosomal domin-ant[188, 195, 199, 200]. In two families, females were more affected than males suggesting a sex-specific influence on the expression of the DD phenotype[195].

Histology of DD

Some of the unilocular adipocytes are extremely large in DD SAT compared to weight matched controls[187]. Dr Dercum and others found an infiltration of nerves (neuritis)[185, 201] but this has not been substantiated. Increased connective tissue around nerves, blood vessels and as thickened septae has been noted[185, 202, 203]. Perivascular cells[203], giant cells[204], and granulomas suggestive of a foreign body reaction are apparent in some areas[205]. The histology of DD SAT can also appear normal[194, 206–209].

Physiology of DD

The physiology of DD is unknown and many etiologies have been advanced. These include thyroid dysfunction[185], pituitary dysfunction, polyglandular disease, infection, neuritis, alcohol, trauma, a defect in the synthesis of long chain fatty acids[205], lower resting energy expenditure[202], and altered responses to norepinephrine and insulin.[210] Ballet may have been closest to the actual etiology when he stated that it is a "chronic intoxication of endogenous origin"[211]. The evidence currently points to an underlying vascular and lymphatic dysfunction in DD Types I/ II similar to lipedema (Birgher Fagher, personal communication) for the following reasons:

1) Vascular dysfunction as hematemesis[212, 213], epistaxis[213, 214], hemaochezia[212], heavy menses[215, 216], varicose veins[194], and altered vasoconstrictor responses[217] is common in both lipedema and DD. Perivascular infiltration of immune cells have been found in DD tissue[218] suggesting damage to or repair of blood vessels, and brain vasculitis in DD has been reported[219].

2) LDT has been reported to be beneficial in DD[220] as in lipedema.

3) Multiple lipomas can develop in lipedema as in DD[221].

4) Fibrosis secondary to lymphedema[222] is common in lipedema[112] and DD[202].

5) In the presence of lymphatic and vascular dysfunction in lipedema, the fat is painful[112], similar to DD.

6) In the German literature, lipedema is known as adiposis dolorosa, another name for DD[118].

7) Original descriptions of DD match descriptions of lipedema. For example, Spiller described a woman with painful fat as follows: "The obesity was marked over the thighs, calves, abdomen, nates (buttocks), and back. It was also very great in the arms, less marked in the forearms, and absent in the feet and hands"[223]. Dr Collins noted that "The fatty accumulations have not been noticed in the hands, face or feet, and frequently the contrast between the feet which preserve their normal outline and contour and the legs, when the latter are involved, is most striking"[214]. These cases are similar to lipedema in terms of the pattern of painful fat (less likely early on in the hands, feet, face, and forearms) and the latter case describes well the distinct "bracelet" of fat seen at the base of the leg above the foot that is classic in lipedema[112]. The published photographs of the columnar legs with the cuff of fat above the foot, or the mass of tender fat inferomedial to the knee, and the enlarged upper arms in DD are consistent with lipedema[112, 183, 184, 224, 225].

8) The nodular "beans in a bag" feel of the fat in lipedema is the same as in DD Types 1 and 2[188, 226].

9) Dr Dercum described DD as a disorder of the "haemolymph system"[227] though the importance of these structures in humans is unclear. Hemolymph nodes are structures resembling a lymph node, but which can have blood in the sinuses; erythrocytes enter the hemolymph nodes through afferent lymphatics[228]. There are few reports on the function of hemolymph glands in humans.

10) Dr Mills reported "In one case studied carefully with Dr Dercum, there was a general disease of the lymphatic system"[229].

The data suggest that the vascular and lymph system are dysfunctional in both lipedema and DD, that pre-lymph remains in the tissue longer, inducing fat growth and the characteristic beans in a bag feel to the fat. In both lipedema and DD there is a hereditary component[195, 199]. Also in both cases, estrogen and/or progesterone likely play a role resulting in the predominance of women with lipedema and/or DD; lipedema is known to occur with the onset puberty and pregnancy, and DD with menopause, both times of changing hormone levels. In DD, a more widespread insult to the vascular and lymphatic system may occur compared to lipedema. Many of the early reported cases of DD had syphilis[213, 216, 230], well known to affect the lymph nodes, consumed alcohol[214, 231] which acutely increases mesenteric lymphatic pumping but decreases lymphatic myogenic tone[232], or had antecedent trauma which may have affected lymphatic function[207, 213, 233]. Many patients with DD Type I or II noticed their first painful area of fat after a viral flu, severe pneumonia or trauma[188, 213, 234]. Data are needed on lymphatic function in DD to confirm these hypotheses.

Conditions associated with DD

In addition to the two cardinal symptoms of fatty deposits and pain proposed by Dercum[184], Vitaut added the third cardinal symptom of DD, asthenia (abnormal physical weakness or lack of energy)[193]. Accessory symptoms in DD are found in the psychiatric, motor, sensory and sympathetic nervous systems[186] as well as the pulmonary, endocrine, gastrointestinal and rheumatological systems[187, 188, 235] (Table 2).

Thyroid dysfunction has been suggested as one etiology of

Table 2. Cardial and accessory signs and symptoms of Dercum's disease with checkbox.

Cardial Signs/Symptoms	Details	√
Fat deposits	Nodules (lipomas) in fat ranging in size from rice grains to a fist or larger	
Pain in fat deposits for at least 3 months	Pain exacerbated by stress, strenuous exercise, trauma, changes in weather, or other; pain can be spontaneous or on palpation; may wax and wane or move around	
Fatigue (asthenia)	Exacerbated by activities of daily living or exercise	
≥2 accessory symptoms		
Cognitive change(s)	Memory difficulties; difficulty forming thoughts; "brain fog"	
Weight gain	Difficult to lose fatty deposits with lifestyle changes	
Vascular involvement	Visible vascularity near lipomas; telangiectasias; multiple cherry angiomas, multiple petechiae; easy bruising; flushing; hematuria of unknown etiology; heavy or prolonged menstrual bleeding; epistaxis	
SAT edema	Non-pitting	
Gastrointestinal complaints	Gastroesophageal reflux disease, irritable bowel syndrome, bloating, abdominal pain, early satiety	
Joint pain and/or stiffness	Increased in areas of fat deposits	
Muscle pain/stiffness	Especially on awakening or the day after physical activity	
Shortness of breath	In the presence of normal oxygen saturation or as part of the need for oxygen supplementation	
Tachycardia	Varies from palpitations to supraventricular tachycardia requiring beta-blockade	

DD. While a few cases of DD benefited from thyroid treatment[216, 236] many cases of DD failed to improve[192, 215, 230, 237, 238] and DD generally continues to progress during adequate thyroid replacement[188]. Others have suggested multiple endocrine dysfunction as a cause for DD[201] (reviewed[186]) but ACTH and pituitary extract did not improve signs and symptoms associated with DD[192, 239] and hormone testing was normal in other cases[210, 240]. If hypercholesterolemia is present, severe and generalized vascular disease may be found[241].

DD treatment recommendations

Primary recommendations

1) Exercise: Similar to lipedema. Supporting the use of WBV as exercise in DD, WBV slowed the acquisition of fat in female rats[242] and improved pain and fatigue in women with fibromyalgia[243].

2) LDT: LDT[220] and "massage"[225] are known to be beneficial for DD Types I and II; recommendations are similar to lipedema (see above).

3) Pain control: Must be individually optimized; only published or important anecdotal reports are included here:

(a) Chemotherapy: A patient with DD had improved pain and growth of DD SAT slowed on methotrexate combined with infliximab[244]. One case had resolution of her lipomas and pain with paclitaxel and carboplatin (unpublished); once the paclitaxel was discontinued because of neuropathy, the pain and lumps returned.

(b) Cyclic Variations in Adaptive Conditioning (CVAC™): A novel therapy that reduces tissue fluid by variable patterning of different atmospheric pressures around a person sitting in an altitude simulator. Peri-corporal pressure patterns vary from sea level to four sequential altitude levels: 3200 m (10.5K ft), 4419 m (14.5K ft), 5638 m (18.5K ft), and 6858 m (22.5K ft). This 'body conditioning' reduced fluid and pain in 10 DD participants[245] and improved VO_2max in healthy men[246].

(c) Lidocaine: Intravenous (IV) lidocaine has been used with some success to treat the intractable pain associated with DD[217, 247–253]. Many individuals with DD obtain good local pain relief using lidocaine patches, cream, gel or EMLA[248, 254].

(d) Mexilitene: Mexilitene (an antiarrhythmic drug) has been used for the effective treatment of pain in DD[196].

(e) Pregabalin: LDT combined with pregabalin (an anticonvulsant drug used for neuropathic pain) has been used to treat the pain associated with DD[220].

4) Psychological support: See lipedema (above).

5) Surgery: Liposuction is one of the accepted methods of treatment for DD[196, 255–257] resulting in decreased pain[258, 259]. When asked specifically about liposuction in a series of 110 patients, 83 respondents (75.5%) reported having had liposuction; of these, 50.6% reported that the painful fat depots grew back[188]. Surgical resection and liposuction should be preceded by LDT and compression to support all vasculature and decrease the risk of seroma and hematoma formation. DD may be one reason why RYGBP without LDT failed to result in weight loss in a published case[260].

Additional recommendations

6) Aminoacetic acid (glycine) and prostigmine: In three women with DD, a diet consisting of 70 grams protein, 70 grams of fat and 100 grams carbohydrate or 1500 calories/day (specifics unavailable), 10 grams glycine and 45 mg prostigmine daily improved weight loss and energy[261]. If glycine binding in the central nervous system is antagonized, feeding in rats increased[262]; glycine may therefore be an appetite suppressant while prostigmine improves asthenia.

7) Corticosteroids (oral): Cortisone treatment has been shown to help with pain but with none of the other features of DD[263]; cortisone treatment can also induce DD[264]. A series of corticosteroid joint injections is usually well-tolerated without exacerbation of symptoms and signs in DD.

8) Hormonal testing: Testing for thyroid function and assessing a complete panel of pituitary hormones at least once after diagnosis of DD and when symptoms change is prudent so as not to miss accompanying hormonal dysfunction, which should be treated with usual methods. Adipose tissue is a very hormonally responsive tissue[265], so estrogen, progesterone and testosterone levels should be monitored regularly on any replacement regimen so as to regulate high and low levels and avoid wide fluctuations.

9) Lifestyle: While obesity is prominent in DD, the DD SAT is resistant to loss with lifestyle changes[261, 266] while normal SAT as part of obesity can be lost[261].

10) Oxygen therapy: Many people with DD feel short of breath[188]. This can progress on to the need for continuous oxygen therapy. It is unclear why the shortness of breath occurs but it is likely a combination of increased interstitial fluid moving cells away from their oxygen source and a weakened diaphragm. Pulmonary function testing should be performed on everyone with DD that has shortness of breath even if it serves simply as a baseline for future changes or symptoms. Similar to MSL, if a patient has increased thickened fat around the chest or neuropathy, DD patients with shortness of breath and/or edema should be evaluated for thoracic outlet syndrome, sleep apnea and/or autonomic dysfunction.

Co-morbidities associated with obesity in DD are treated as usual.

Conclusions

Obesity is very common and in the limited time allotted to patient care, it may be easy to misdiagnose a patient with a lipodystrophy or a RAD disorder as having simple obesity, and prescribe lifestyle changes only. The widespread increase in abnormal SAT in MSL, DD or lipedema Type II or III can easily masquerade as global obesity (Table 3). The loss of normal fat and muscle in MSL or the disproportion of fat in lipedema can also be confused with lipodystrophy; lipedema Type I is usually overlooked. Lifestyle changes and bariatric surgery work effectively for the obesity component of FPLD and RADs but not for the abnormal SAT tissue in RADs. The RAD SAT likely results from the growth of a brown stem cell population that secondarily compresses lymphatics and vessels (in MSL) or a primarily vascular and lymphatic dysfunction with secondary growth of SAT (in lipedema and DD), neither of which respond well to caloric limitation. Academic testing of various dietary regimens, mechanical treatments, surgery, medications, and supplements is needed for RADs. Understanding the genomics of the RADs is also important to help differentiate lipedema, MSL and DD especially in women where the three disorders can look so much alike, and to assess for RADs in obesity. Improved recognition of RADs may also prove that lipedema and DD are not RADs at all but common disorders and that understanding the underlying pathophysiology of RADs may improve our understanding of refractory obesity. Lymphatic drainage methods used for RADs should be considered in resistant obesity cases or before bariatric surgery, low to very low calorie diets or other methods that induce rapid weight loss requiring optimal lymphatic function.

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Conflicts of interest

This study was approved by the University of California, San

Table 3. Comparison of RAD characteristics.

Characteristic	MSL	RADs DD	Lipedema
Abnormal SAT location	Upper*	Global	Legs±Arms
Diet-resistant SAT	Yes	Yes	Yes
Lipomas	Common in males	Common	Large nodular fat masses
Time of SAT change	Adult	Child to adult	Puberty; by third decade
Painful SAT	Not usually	Yes	Yes
Sex predominance	Male	Female	Female
Lymphatic dysfunction	Secondary	Primary	Primary
Look-alike conditions	Obesity; HIV lipodystrophy	Obesity; FML	Obesity; APL
Associated conditions	Neuropathy	Autoimmune; diabetes	Lymphedema
Population frequency	Rare	Likely common	Likely common
Inheritance pattern	Autosomal dominant or recessive	Autosomal dominant; sex-specific influence	Autosomal dominant; incomplete penetrance
Known gene	tRNALys mutations uncommon	None	None
Known biomarkers	No	No	No
Alcohol association	Yes	No	No

* Can be global especially in women; APL=acquired partial lipodystrophy; FML=familial multiple lipomatosis; RAD=rare adipose disorder; SAT=subcutaneous adipose tissue

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