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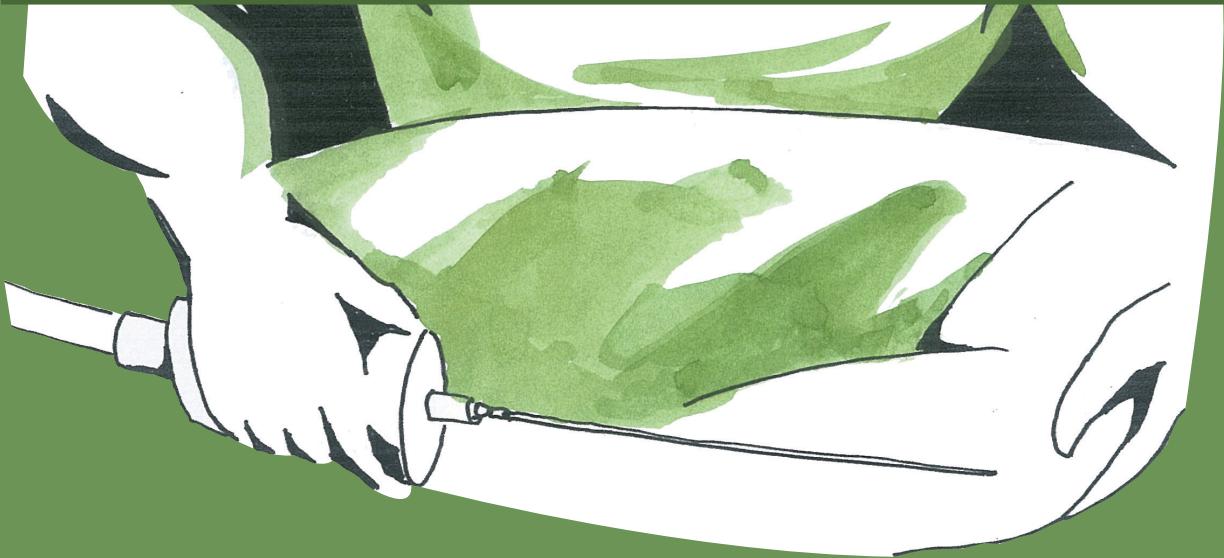
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Liposuction in Dercum's disease

Clinical studies regarding Dercum's disease and the effect of liposuction

Emma Hansson, MD, MA



Department of Plastic and Reconstructive Surgery
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Lund University, 2011

Liposuction in Dercum's Disease

*Clinical Studies Regarding Dercum's Disease and the Effect
of Liposuction*



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Abstract <p>Dercum's disease is a rare condition characterised by obesity, chronic pain (>3 months) in the adipose tissue and a number of diffuse associated symptoms. The experienced pains are often disabling and resistant to most tried treatments.</p> <p>The aims of this study were to investigate the effect of liposuction on thermal and sensory sensation, to examine the effect of liposuction on the pain experienced by patients, to examine neuropeptide levels in cerebrospinal fluid and plasma, and to investigate the inflammatory signs in adipose tissue of patients with Dercum's disease.</p> <p>A total of 111 patients with Dercum's disease were recruited to the study. The first 53 patients were operated on with liposuction and the following 58 patients were un-operated controls. In addition, 41 healthy obese women and 11 normal weight healthy women were recruited as different control groups. The patients and controls were followed for five years. Not all groups were included in every study.</p> <p>In study I, vibratory and thermal thresholds were determined. The results showed that there were only small differences in sensation postoperatively and none of these were statistically significant. In study II, pain was measured with VAS, NWC and PPT. The study indicated that liposuction might alleviate pain in patients with Dercum's disease. However, it is difficult to determine whether the effect was due to the actual surgery or to other factors. In paper III, neuropeptides were measured. The results showed that altered levels of neuropeptides cannot clearly be demonstrated in Dercum's disease. In paper IV, adipose tissue biopsies were examined. The results revealed that there was an inflammatory response in the adipose tissue of patients with Dercum's disease. However, the response was not more pronounced than in healthy obese controls.</p> <p>Collectively, we demonstrated that liposuction cannot yet be recommended as the standard treatment for Dercum's disease. Furthermore, we showed that the aetiology of the disease might not be inflammatory.</p>		
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Liposuction in Dercum's Disease

Clinical Studies Regarding Dercum's Disease
and the Effect of Liposuction

Emma Hansson



LUND UNIVERSITY
Faculty of Medicine

Malmö 2011

© Emma Hansson, MD, MA

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To my parents Ingrid and Jan.

“*Poca favilla gran fiamma seconda*”

(*A mighty flame follows a tiny spark*)

The Divine Comedy, Paradiso, Canto I:34

Dante Alighieri (1265-1321)

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Abbreviations

ACA	anticardiolipin antibodies
AD	adiposis dolorosa. Synonym of Dercum's disease
ANA	anticardiolipin antibodies
ANCA	anti-neutrophil cytoplasmic antibody
β-END	β-endorphin
BMI	body mass index
cANCA	cytoplasmic anti-neutrophil cytoplasmic antibody
CD4	cluster of differentiation 4
CDT	cold detection threshold
CGRP	calcitonin gene-related peptide
CNS	central nervous system
CSF	cerebrospinal fluid
DD	Dercum's disease
DNA	deoxyribonucleic acid
DYN	dynorphin
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalography
ENK	enkephalin
EP	endorphin
ESR	erythrocyte sedimentation rate
HLA	human leukocyte antigen
IL	interleukin
LI	like immunoreactivity
MCP	monocyte chemotactic protein
m-ENK	met-enkephalin
MIP	macrophage inflammatory protein
MNG	multi-nucleated giant cells
MPQ	McGill Pain Questionnaire
NPY	neuropeptide Y

MSH	immunoreactive melanocyte-stimulation hormone
n	number of subjects
NPY	neuropeptide Y
NSAID	non-steroidal anti-inflammatory drug
NWC	number of words chosen
P	plasma
pANCA	perinuclear anti-neutrophil cytoplasmic antibody
PPT	pain pressure threshold
RF	rheumatic factor
SD	standard deviation
SF-MPQ	short form McGill Pain Questionnaire
SFS	Svensk förfatningssamling. The Swedish Code of Statutes
SOM	somatostatin
SP	substance P
SPSS	Statistical Package for the Social Sciences
T-cell	thymus lymphocyte
TNF- α	tumour necrosis factor- α
tRNA	transfer ribonucleic acid
VAS	visual analogue scale
VDT	vibration disappearance threshold
WDT	warmth detection threshold
VIP	vasoactive intestinal peptide
VPT	vibration perception threshold
γ_2 -MSH	γ_2 -melanocyte-stimulating hormone

List of Papers

The thesis is based on the following papers, which are referred to in the text by their roman numerals:

- I.** Hansson E, Svensson H, Rosén I, Brorson H. Thermal and vibratory thresholds do not differ after liposuction in patients with Dercum's disease. *J Plastic Surg Hand Surg.* 2011;45:72-76.
- II.** Hansson E, Svensson H, Brorson, H. Liposuction may reduce pain in Dercum's disease. *Pain Med.* 2011;12:942-952.
- III.** Hansson E, Manjer J, Svensson H, Åberg M, Fagher B, Ekman R, Brorson H. Neuropeptide alterations in Dercum's disease. *[Submitted for publication].*
- IV.** Hansson E, Svensson H, Stenram U, Brorson, H. Adipose tissue histology in Dercum's disease. *[Submitted for publication].*

The papers have been reprinted with kind permission from *Informa Healthcare* (I) and *Pain Medicine* (II).

Thesis at a glance

I. Sensitivity after liposuction in Dercum's disease

How does liposuction affect thermal and vibratory sensation in patients with Dercum's disease?

Patients: 39 women with Dercum's disease. The patients were followed for 1 year.

Methods: Vibratory and thermal thresholds were determined preoperatively, and three and 12 months after liposuction by the method of limits.

Conclusion: There were only small differences in sensation postoperatively, as compared with preoperatively, and none of these was statistically significant.

II. The effect of liposuction on pain in Dercum's disease

How does liposuction affect the pain experienced by patients with Dercum's disease?

Patients: 111 women with Dercum's disease and 41 healthy obese female controls. The patients were followed for 5 years.

Methods: The first consecutive 53 patients were operated on with liposuction and the following 58 patients with Dercum's disease were recruited as controls. Pain (VAS, NWC and PPT) was measured preoperatively and 3 months and 1, 2, 3 and 5 years after liposuction in all three groups.

Conclusion: Liposuction might alleviate pain in patients with Dercum's disease for a period of at least 5 years. However, it is

difficult to determine whether the effect is due to the actual surgery or to other factors.

III. Neuropeptides in Dercum's disease

Do patients with Dercum's disease have abnormal concentrations of neuropeptides in cerebrospinal fluid and plasma?

Patients: 53 women with Dercum's disease and 41 healthy obese female controls.

Methods: Neuropeptides were measured in cerebrospinal fluid and in plasma with radioimmunoassay. Examined neuropeptides were SP, NPY, β -END, CGRP, m-ENK, VIP, SOM, γ_2 -MSH, and DYN.

Conclusion: Altered levels of neuropeptides that have previously been seen in different pain conditions cannot clearly be demonstrated in Dercum's disease.

IV. Adipose tissue inflammation in Dercum's disease

Do patients with Dercum's disease have inflammatory signs in the adipose tissue?

Patients: 53 women with Dercum's disease and 41 healthy obese female controls and 11 normal weight healthy female controls as two different control groups.

Methods: Adipose tissue biopsies were obtained by surgical biopsy in all the patients and controls. The slides were examined by the same pathologist in a blinded manner and given an inflammatory score.

Conclusion: There is an inflammatory response in the adipose tissue in Dercum's disease. However, the response is not more pronounced than in healthy obese controls. This contradicts inflammation as the aetiology of Dercum's disease.

Introduction and Background

Dercum's disease

Francis Xavier Dercum (1856-1931)

Francis Xavier Dercum (Figure 1) was born on 10 August 1856 in Philadelphia, USA. He eventually embarked on his medical studies on the University of Pennsylvania and was awarded his medical degree in 1877. After graduation he was appointed demonstrator in histology and physiology at the university [1].



Figure 1. Francis Xavier Dercum. [Courtesy of University of Pennsylvania].

Dercum had an inborn interest in natural history and as a young man joined the Academy of Natural Sciences. In fact, his first scientific publications were not in medicine but in biology, on the nervous system of fish [2]. He eventually earned his PhD in medicine and became a pathologist and studied lesions of the nervous system [3] in the State Hospital for the Insane at Norristown.

In 1884, Dercum was appointed chief of the Nervous Clinic at the Hospital of the University of Pennsylvania and founded the Philadelphia Neurological Society. His research led to the publication of many papers and books, including works on the morphology and physiology of the epileptic brain and on clinical neurology. In 1888, he published his first article on adiposis dolorosa [4], and in 1885 he edited *A Text Book of Nervous Disease by American Authors*, the first American book on nervous diseases written by multiple authors [5].

In 1886, Dercum was appointed President of the American Neurological Association, and was elected to membership of foreign neurological societies in Paris, London, and Budapest [5].

In 1893, Dercum was made clinical professor of neurology at the Thomas Jefferson University [2] and in 1900, when the department of nervous and mental disease was established, Dercum was appointed head of the department and professor, a position he held until he retired in 1925 [5].

Dercum died of heart disease on April 23, 1931, as he was presiding over the two hundred and fortieth annual meeting of the American Philosophical Society, of which he had been elected president in 1927 [5].

History

The first case of Dercum's disease was described by Dercum at the meeting of the American Neurological Association held in September 1888. The case was later published in *The University Medical Magazine* [4] (Figure 2).

A SUBCUTANEOUS CONNECTIVE TISSUE DYSTROPHY
OF THE ARMS AND BACK, ASSOCIATED WITH
SYMPTOMS RESEMBLING MYXEDEMA.

By F. X. DERCUM, M. D.,
Instructor in Nervous Diseases, University of Pennsylvania.

Figure 2. Dercum's original publication on Dercum's disease. *The University Medical Magazine*, 1888, p. 1 [4]. Article in the public domain. [Reprinted with permission from University of Pennsylvania].

However, the first probable case of the disease was recorded by an Egyptian artist as early as 1500 B.C. The person affected was the fat Queen of Punt (Figure 3). Deir-el-Bahri's famous relief of her, exhibiting the characteristic adipose tissue masses of Dercum's disease, can be seen in the Cairo Museum, Egypt [6].



Figure 3. Drawing of the Cairo Museum relief of the queen of Punt (Leroy Smith, Jr.). *American Practitioner and Digest of Treatment*, 1951, p. 338 [6]. Copyright: Lippincott Williams & Wilkins. [Reprinted with permission].

In the case report from 1888, Dercum emphasised that the patient was affected by accumulations of painful fat across the trunk and arms, and symptoms similar to the ones seen in myxoedema (Figure 4).

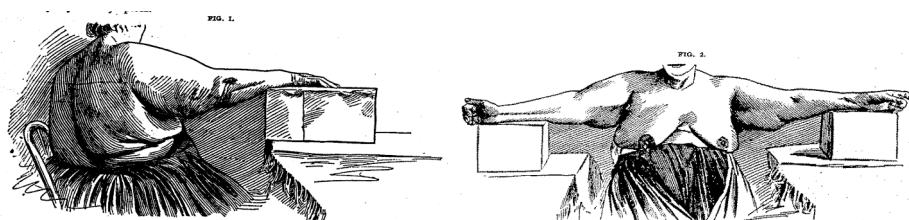


Figure 4. Illustrations of the first patient with Dercum's disease. From Dercum's original publication published in *The University Medical Magazine*, 1888, pp. 2-3 [4]. Article in the public domain. [Reprinted with permission from University of Pennsylvania].

The second case was described in 1890 by another Philadelphian neurologist, Frederick Henry [7]. Henry also emphasised the similarities with myxoedema. However, in 1892, Dercum published a report on the third and fourth cases. In this article, he separated Dercum's disease from myxoedema, and identified the two cardinal symptoms of the condition: obesity and painful adipose tissue. Based on the cardinal symptoms, he named the disease “adiposis dolorosa” and concluded:

Evidently the disease is not simple obesity. If so, how are we to dispose of the nervous elements present? Equally plain is it that we have not myxoedema to deal with. It would seem, that we have here to deal with a connective-tissue dystrophy, a fatty metamorphosis of various stages of completeness, occurring in separate regions, or at best unevenly distributed and associated with suggestive of an irregular and fugitive irritation of nerve-trunks – possibly a neuritis [8].

In the years that followed, a number of similar cases were reported in the USA. The first reported European patient affect by the condition was observed in 1895 by Ewald in Berlin [9].

In 1900, Giudiceandrea presented the first classification of the disease [9] and a year later Roux and Vitaut proposed four cardinal symptoms for Dercum's disease [10]. The cardinal symptoms are

described under *Symptoms and diagnostic criteria* (pp. 23-26). In 1930, Gram studied 60 patients, and based on his observations, he questioned whether Dercum's disease is a clinical entity or part of a triad composed of painful adipose tissue, knee arthritis and hypertension [11]. In 1937, Kling studied 112 patients with Dercum's disease and concluded that there is a juxta-articular form of the condition [12]. The aetiology of the disease is still unknown [13].

Thus far, more than 450 clinical cases have been described. The first attempt to treat the condition with liposuction was reported in 1987 [14].

Synonyms of the disease that can be found in the medical literature include adipositas dolorosa, adiposalgia, lipomatosis dolorosa, and adipose tissue rheumatism [15].

Classification

In 1900, Giudiceandrea [9] reported a patient and reviewed all the thus far published cases. Based on the results of the review, he proposed the following clinical classification of Dercum's disease:

- I. *Nodular type.* A form with painful lipomas, most commonly on the arms or the legs or on the back or thorax. Sometimes the lipomas occur on multiple locations and occasionally the lipomas form a confluent mass. The nodules are variable in size and painful on palpation.
- II. *Diffuse type.* A form with diffusely painful adipose tissue. The pain is symmetric.
- III. *Mixed type.* A form with diffusely painful adipose tissue and with painful nodular masses.

In 1901, Roux and Vitaut [10] modified the classification to the following:

- I. *Nodular type.* A form with intense pain in and around multiples lipomas.
- II. *Circumscribed diffuse type.* A form with painful folds of fats. The folds are often located on the inside of the knee and/or on the hips.
- III. *Generalised diffuse type.* A form with diffusely widespread painful adipose tissue. The most common location of the pain is the extremities and the trunk.

Another classification, Type I (juxta-articular), Type II (diffuse-generalised) and Type III (nodular), is sometimes mentioned [13, 16,

17]. However, we have not been able to establish who made this classification and when it was compiled. The first time the term juxta-articular Dercum's disease was used was in 1937 by Kling [12]. Since then, three cases of juxta-articular Dercum's disease in association with seropositive rheumatoid arthritis have been reported [18, 19], and Weinberger et al [19] have speculated on whether juxta-articular Dercum's disease could actually be an extra-articular manifestation of rheumatoid arthritis. Furthermore, Kling has come up with the theory that adipose tissue deposits around the knees might interfere with the blood supply, by pressure on the joint, and result in the development of painful osteo-arthritis [12]. In brief, it is unclear whether the juxta-articular form of Dercum's disease exists, or if painful localised fat around the joints simply should be designated as the circumscribed diffuse form.

Epidemiology

Dercum's disease most commonly appears between the ages of 35 and 50 years of age [20, 21]. It is five [21] to thirty times [22] more common in women than in men and, originally, Dercum proposed that the condition mainly affects postmenopausal women. However, a recent survey has revealed that 85.7 percent of the included patients developed Dercum's disease before menopause [21]. The prevalence of Dercum's disease has not yet been exactly established.

Symptoms and diagnostic criteria

The main symptoms of Dercum's disease are obesity and painful adipose tissue [8]. The most common locations for painful fat and for lipomas are the extremities, the trunk, the pelvic area, and the buttocks. When palpable lipomas exist they vary in size and firmness [21]. The pain is most commonly described by patients as burning or aching. It can vary from hyperalgesia in the subcutaneous fatty tissue [13] and discomfort on palpation to paroxysmal spontaneous attacks

of pain. The onset of the condition may be abrupt or indolent [21]. The natural history of Dercum's disease has not been studied [13].

In 1901, Roux and Vitaut [10] proposed four cardinal symptoms of Dercum's disease:

1. Multiple, painful, fatty masses
2. Generalised obesity
3. Weakness and susceptibility to fatigue (asthenia)
4. Psychiatric manifestations, including emotional instability, depression, epilepsy, confusion, and dementia.

However, it can be discussed which symptoms are cardinal and which are associated. In fact, already in 1927, Labb   and Boulin [23] questioned whether the weakness and susceptibility to fatigue and psychiatric manifestations should be classified as cardinal symptoms. They argued that obesity *per se* can induce asthenia, and that it is unclear whether mental disturbances should be included as a cardinal symptom, as they have not been described in all cases of Dercum's disease [23]. Moreover, in 1910, Stern [24] remarked that the only two symptoms that are always present in the disease are obesity and painful adipose tissue. Furthermore, in 1930, Gram presented 69 cases of Dercum's disease and he did not note psychiatric manifestations in all of them [11].

In fact, the third cardinal symptom, weakness and fatigability, is frequently part of different psychiatric disorders, including depression [25]. Moreover, severe obesity is associated with sleeping disorders [26], which could contribute to the weakness and susceptibility to fatigue experienced by patients with Dercum's disease.

With regard to the fourth cardinal symptom, psychiatric manifestations, modern research has revealed that pain is a common symptom in depression [27]. Similarly, it has been demonstrated that there is a co-morbidity of chronic pain disease and psychiatric disorders. Post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and generalised anxiety disorder (GAD)

have been expressly described in a community sample of patients with fibromyalgia [28]. Furthermore, an association between BMI and anxiety and personality disorders has been seen [29]. Hence, the patients' pain as well as their obesity could contribute to psychiatric manifestations in Dercum's disease.

The four cardinal symptoms have sometimes been used as diagnostic criteria [30-37]. However, as it is unclear which symptoms are cardinal and which symptoms are associated in Dercum's disease, it is unclear which should be used as diagnostic criteria. In addition, there are no laboratory markers for the condition and laboratory tests for inflammatory and autoimmune disease are commonly negative [15, 16, 21, 38, 39]. Based on this, the following criteria for the diagnosis have been applied in the present study:

1. Generalised obesity
2. Chronic pain (>3 months) in the adipose tissue

The typical distribution of the pain is illustrated in Figure 5.

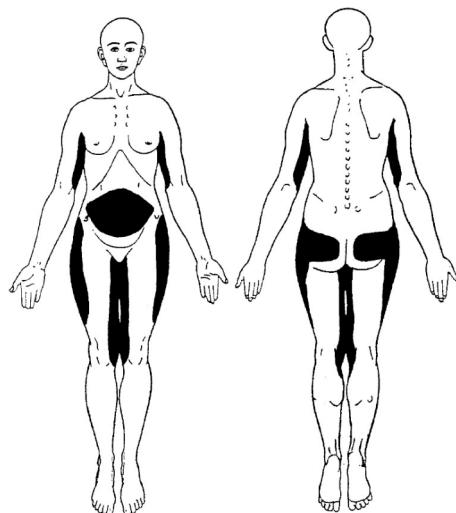


Figure 5. Typical pain distribution in Dercum's disease. Copyright: Håkan Brorson [Reprinted with permission]. The figure has previously been published in *Läkartidningen* [13].

Regarding the associated symptoms in Dercum's disease, only case reports have been published. No study involving medical examinations has been performed in a larger group of patients. However, Herbst and Asare-Bediako have performed a questionnaire including 110 patients with Dercum's disease. The symptoms the patients stated are summarised in Figure 6.

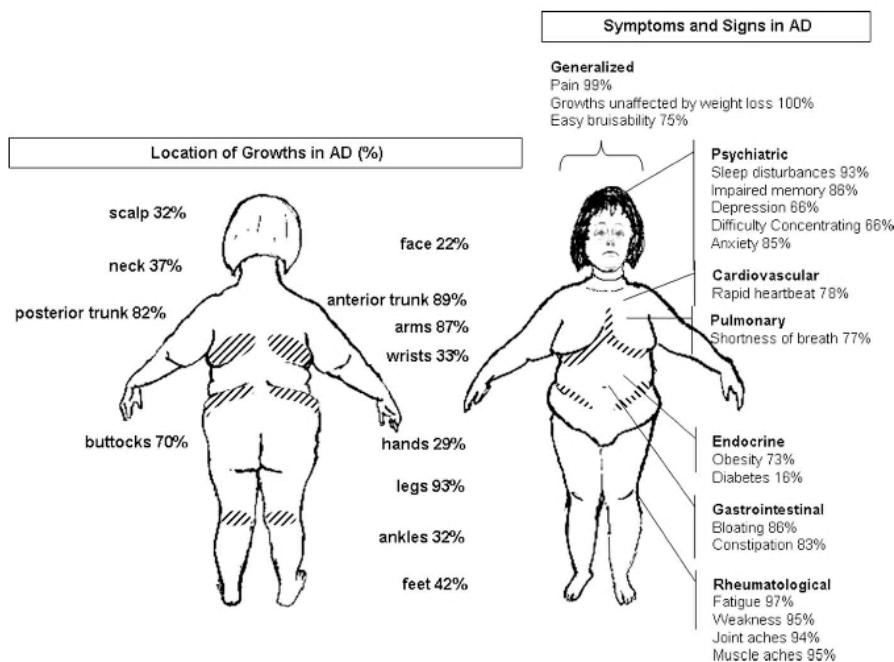


Figure 6. Cumulative symptoms and signs in 110 individuals with Dercum's disease according to a questionnaire performed by Herbst and Asare-Bediako. AD: Adiposis dolorosa, which is a synonym to Dercum's disease. *The Endocrinologist*, 2007 [21]. Copyright: Lippincott Williams & Wilkins. [Reprinted with permission].

Unusual signs and symptoms described

A number of other signs and symptoms have been described in patients with Dercum's disease. The reported cases are summarised below.

Haddad et al [40] reported a case of septic shock secondary to a steatocutaneous necrosis in a lipoma in a patient with Dercum's disease. The patient had a BMI of 46.4 and adipose tumours on the abdomen and on the thighs and arms. The lipomas on the thighs had a diameter of circa 30 cm. The necrosis, which was located on one of the thighs, had a diameter of 15 cm and was surrounded by an inflammatory zone of about 30 cm. The necrosis was treated with excision and the sepsis cured with antibiotics.

Kyllerman et al [41] described a family with painful lipomatosis interpreted as Dercum's disease. The affected subjects developed associated dysarthria, visual pursuit defects and progressive dystonia. Magnetic resonance imaging revealed bilateral increasing cystic lesions in the basal parts of the putamen. No genetic abnormalities could be detected in the subjects. The condition was interpreted as a Dercum's disease variant.

Rosenberg et al [42] reported a case of Dercum's disease with an unusual distribution of the fatty deposits. The adipose tissue infiltrated retroperitoneally, paravesically, and pararectally. The disease started with painful adipose tissue in the left lower extremity. Within a month the pain had spread to the right lower extremity as well. The same year a mass could be palpated along the right side of the rectum. Palpation of the mass produced the same pain in the legs as the patient had experienced spontaneously. An intravenous pyelography and a gravity cystogram revealed hydronephrosis bilaterally and a displaced urinary bladder. A barium enema revealed an elongated sigmoid colon displaced up-ward and to the left. Six months later, the adipose tissue pain had spread to both upper extremities. On examination, an irregular mass, extending from the symphysis pubica to the umbilicus, could be palpated. Neurologically, a positive Babinski sign was found on the left and sensation errors for vibration were noted at and below the iliac crest. During surgery, an adipose tissue tumour was found connected with the peritoneum. The tumour measured 15 by 10 cm and was adherent to the dome of the right wall of the bladder, the right lateral rectal wall, the right ureter and the retroperitoneal tissues. The histological examination revealed normal adipose tissue. The condition was

interpreted as Dercum's disease, where the adipose tissue compressed the urinary bladder, the ureter, the sigmoid colon and the sciatic nerve.

Trentin et al [43] published a case of Dercum's disease where the patient developed multiple painful adipose tissue lumps in the breasts. The authors concluded that Dercum's disease is a rare cause of mastalgia.

Reece et al. [44] noted a patient who developed painful fatty swellings around the neck. Later, a tender lump was excised from the back. The histological examination of the lump revealed normal adipose tissue. The diagnosis of Dercum's disease was based on the lump found on the back. However, in Dercum's disease, the head and neck are not affected [13, 45], even though this has recently been contradicted by the findings of Herbst et al [21]. Reece et al. do not comment on whether they have excluded Madelung's disease [44].

Szypula et al [38] described a case of Dercum's disease that was affected with severe hypercholesterolemia and advanced atherosclerosis at the age of 51. However, it is unclear whether there is a link between the conditions or if they merely represent a coexistence of two separate disorders.

Margherita [46] reported a pathological fracture in a patient with Dercum's disease. However, the origin of the pathological fracture was unclear (cf. *Trauma induced Dercum's disease*, pp. 39-40).

In brief, it is unclear whether the complications described in Dercum's disease are caused by the condition, or if the occurrence of them is merely coincidental.

Differential diagnoses

Many diagnoses have similar symptoms as the symptoms experienced in Dercum's disease. The diffuse types of Dercum's disease (type II and III) have traits in common with conditions with general pain (Table I). The nodular type of Dercum's disease (type I) has to be differentiated from conditions that may include lipomas that are sometimes painful (Table I).

Table I. Differential diagnoses of Dercum's disease

Differential diagnoses
<i>Diffuse type of Dercum's disease</i>
Fibromyalgia
Lipoedema
Panniculitis
Endocrine disorders
Lipodystrophy
Primary psychiatric conditions
<i>Nodular type of Dercum's disease</i>
Multiple symmetric lipomatosis (Madelungs disease)
Neurofibromatosis type I
Adipose tissue tumours
Multiple endocrine neoplasia I
Myoclonic epilepsy with red ragged fibres

The similarities and differences of these conditions and Dercum's disease are briefly presented below.

Fibromyalgia

Fibromyalgia is a condition with widespread muscle pain and a painful response to pressure on at least 11 out of 18 specific tender point sites. It is associated with a range of other symptoms, such as sleep disturbances, fatigue, cognitive disturbances, and depressive symptoms. The aetiology is unknown [47] and the demarcation from Dercum's disease is sometimes arbitrary.

Lipoedema

Lipoedema is characterised by bilateral, symmetric lower extremity enlargement due to subcutaneous deposition of adipose tissue. The patients experience pain on palpation. The condition affects women almost exclusively. Typically, the disorder develops insidiously after

puberty and progresses gradually. In contrast to patients with lymphoedema, the patients do not have any lymphatic dysfunction. However, patients with morbid obesity and longstanding lipoedema can develop a secondary mechanical insufficiency of the lymphatic system, producing a lipolymphoedema [48] due to associated difficulties with ambulation, which limits activation of the muscle pump in the lower extremities and subsequently leads to pitting edema due to inactivity [49].

Panniculitis

Panniculitis is a group of inflammatory conditions in which the principal focus is the subcutis. Panniculitis is classified according to which structure it affects: septal panniculitis denotes inflammation in the connective tissue septa, whereas lobular panniculitis refers to inflammation in the fat lobules. Panniculitis occurs with or without accompanying vasculitis.

Septal panniculitis without vasculitis (erythema nodosum) most commonly manifests itself as tender erythematous nodules on the lower extremity. As some nodules heal, others arise. Normally, all lesions heal without scarring within six weeks. Lobular panniculitis with vasculitis (erythema induratum, nodular vasculitis) presents itself with recurrent, tender, erythematous subcutaneous nodules on the lower extremity. The lesions frequently ulcerate, and they heal with atrophic scars. The condition may continue for several years.

A special form of panniculitis is Pfeifer-Weber-Christian disease (idiopathic relapsing febrile lobular non-suppurative panniculitis). It encompasses panniculitis, as well as fever and malaise due to systemic inflammation. It is most commonly idiopathic, but can be caused by systemic lupus erythematosus, α 1-antitrypsin deficiency, lymphoma, trauma, pancreatitis, and certain types of infections [50].

Endocrine disorders

A number of endocrine disorders can cause generalised pain in combination with obesity and psychiatric symptoms. For example, Cushing's syndrome (corticotropin-independent adrenal hyperfunction) is characterised by aching joints, as well as a gradual onset of obesity, typically located around the face ('moon face'), back ('buffalo hump'), and trunk. In addition, the majority of patients suffer from psychiatric manifestations, including irritability, emotional lability, and depression [51]. Another endocrine disorder encompassing weight gain [51] and pain in the extremities, is hypothyroidism [52]. The patients are also affected by psychiatric manifestations, comprising depression, memory loss and general slowing of mental processes. If myxoedema develops, oedemas of the face, hands and feet are added to the signs [51].

Lipodystrophies

Lipodystrophies are characterised by selective loss of body fat from different parts of the body. The adipose tissue loss can be limited, and result in well-demarcated subcutaneous areas, or extensive, leading to widespread absence of body fat [53]. There are different types of lipodystrophies, both congenital forms, such as Berardinelli-Seip syndrome, and acquired forms, such as Lawrence syndrome and Barraquer-Simons syndrome [54].

Primary psychiatric disorders

Patients with depression are often diagnosed with chronic pain conditions and vice versa [55]. Both disorders activate common neurocircuitries, for example, the hypothalamic-pituitary-adrenal axis, limbic and paralimbic structures, ascending and descending pain pathways [56], and it is therefore sometimes difficult to determine whether the pain disorder or the psychiatric condition is the primary diagnosis.

Multiple symmetric lipomatosis

Multiple symmetric lipomatosis is principally distinguished by large subcutaneous fatty masses distributed in a symmetrical fashion around the neck, shoulders, upper extremities, and trunk. Epidemiologically, the incidence of the disorder is highest in males. The majority of the patients are not obese. The lipomas are usually not experienced as painful [57]. Sometimes multiple lipomatosis is inherited in an autosomal-dominant way, and is then referred to as familial multiple lipomatosis. The condition can be associated with an A to G mutation at position A8344 of mitochondrial DNA [58].

An example of a localised acquired lipomatosis is Madelung's disease (Launois-Bensaude's syndrome). This disease consists of adipose tissue masses symmetrically distributed mainly in the head and neck region. The disease mostly affects men between the age of 30 and 60 [56] that are chronic alcohol abusers [59].

Neurofibromatosis type 1

Some patients with neurofibromatosis type 1 (von Recklinghausen's disease) develop subcutaneous neurofibromas that cause pain and neurological symptoms [60].

Adipose tissue tumours

Benign adipose tissue tumours (solitary/multiple) are subcutaneous tumours composed of well-differentiated adipocytes. There are a number of varieties of lipomas, some of which are frequently painful [51]. Angiolipomas are lipomas with extensive vascular proliferation [51], and are often multiple and painful [61]. Neural fibrolipomas are lipomas that surround and infiltrate nerve bundles. They most often occur in the hand and upper extremity and the patient usually experiences pain and diminished sensation in and around the mass [62]. Lipoblastomas/lipoblastomatosis affect infants and children almost exclusively before the age of 8 years. They are usually not painful [63]. Myolipomas (lipoleiomyoma) most commonly occur in

deep tissues in the abdomen, retroperitoneum and the abdominal walls, and rarely occur in the subcutaneous tissue. Histologically, the tumours are composed of adipose tissue and bundles of smooth muscle. They are usually not painful [64]. Chondroid lipomas occur in subcutaneous tissue or in deeper soft tissues, predominantly in the extremities, the trunk, and the head and neck region. They mainly affect female patients and are usually not painful [65]. Spindle cell/pleomorphic lipomas occur predominantly in subcutaneous tissue of the neck, shoulder or upper back, in mainly male patients. They are usually not painful [63]. Hibernomas are rare adipose tissue tumours of brown fat, occurring most frequently in the interscapular regions. They are usually not painful [63].

Cutaneous adipose tissue malignant neoplasms are exceptionally rare and are usually not experienced as painful. Such tumours include cutaneous angiolipoleiomyoma ('angiomylipoma'), adenolipoma of the skin, cutaneous spindle cell/pleomorphic lipomas, and liposarcomas [66].

Multiple endocrine neoplasia I

Patients with multiple endocrine neoplasia I (MEN 1) sometimes exhibit several subcutaneous tumours, including multiple lipomas, which are, however, not painful [67].

Myoclonic epilepsy with ragged red fibres

Myoclonic epilepsy with ragged red fibres (MERRF), an inherited disease of the mitochondria, is sometimes accompanied by multiple symmetric lipomatosis. The most common cause is a mutation in position 8344 of the tRNA gene of mitochondrial DNA [68].

Inheritance and genetics

The majority of the cases of Dercum's disease occur sporadically. We have found five reports on the inheritance of the disorder. The studies have suggested that Dercum's disease might be an autosomal dominant disorder with variable expression [20, 69-72]. A gender factor has been proposed as the affected women were markedly obese and experienced considerable pain, whereas the expression of the disease in the affected men was so mild that it would not have been noticed if a very thorough physical examination had not been performed [71]. The possible genetic heterogeneity could explain why the disease has been reported in females with a frequency that is up to 30 times greater than in males [22]. Furthermore, it has been suggested that Dercum's disease might actually be an extreme expression of familial multiple lipomas [41, 69]. This implies that many of the affected men could have had the diagnosis familial multiple lipomas instead of Dercum's disease, as their symptoms are so discreet [20].

In addition, studies have revealed that the A to G mutation at position A8344 of mitochondrial DNA, which is sometimes associated with familial multiple lipomas, cannot be detected in patients with Dercum's disease [41, 69]. Similarly, HLA (human leukocyte antigen) typing, which has been performed in a family of five patients affected by Dercum's disease [73], has not revealed any correlation between typical antigens and the presence of the condition.

Aetiology

The aetiology of Dercum's disease is unknown. However, a number of theories for the aetiology have been suggested. They are summarised below.

Endocrine dysfunction

Originally, Dercum [8] attributed the disease to an endocrine dysfunction, as he found atrophy of the thyroid gland. Similarly, Waldorp [74] proposed that the disease is caused by hypophyseal dysfunction. Furthermore, Winkelman and Eckel [75] reviewed 16 autopsies of patients affected with Dercum's disease and noted varying abnormalities in different endocrine organs. In their study, the pituitary gland was abnormal in eight of eleven cases examined, the thyroid in twelve cases, the sex glands in nine, the adrenal glands in three and the pancreas in two cases.

However, endocrine involvement was doubted as early as in 1933 [42] and further ruled out in 1952 [76]. In addition, present-day methods have not revealed any endocrine abnormalities [17, 30, 33, 73, 77]. For example, Piamenta et al [73] have demonstrated that hormonal secretion was normal both basally and during a 24 h period in a patient with Dercum's disease, and no normal hormonal deficiency could be detected after an integrated pituitary stimulus test. The study suggested that there are probably no alterations of the endocrine glands, as regards the pituitary gland, the adrenal glands, the thyroid and the ovaries, in patients with Dercum's disease. In another study, a paradoxical increase in growth hormone was seen after an intravenous injection of thyrotropin [78]. The significance of this finding is unclear. In brief, an endocrine dysfunction as the aetiology of Dercum's disease has little support in the modern literature.

Nervous system dysfunction

Dalziel [79] suggested that the autonomous nervous system mediates pain in Dercum's disease. The theory is supported in that, even though the sympathetic nervous system is efferent, sympathectomy sometimes relieves pain in neuropathic pain, where evidence of damage to neural structures exists [80]. This has been explained by the formation of abnormal connections between autonomic and sensory nerves in the periphery and, as a consequence, abnormal autonomic signalling to the spinal column might activate pain fibres [79]. However, in conditions where neural damage cannot be found, the effect on pain might be caused by the placebo response [81]. Moreover, patients with Dercum's disease could have increased sympathetic activity induced by pain. This theory is supported by a study where a patient with Dercum's disease did not have any vasoconstrictor response to arm and leg lowering. A normalised vasoconstrictor response could be created by lidocaine infusion that is thought to decrease the local or central sympathetic vasoconstrictor tone [82].

Furthermore, visceral pain may be generated by the autonomic nervous system, and factors that induce visceral pain could also have the ability to induce pain in the adipose tissue. Examples of such factors are anoxemia, formation and accumulation of pain-producing substances, traction or compression of vessels, inflammatory states, and necrosis [79]. Nonetheless, any substantial evidence of nervous system dysfunction has never been found in Dercum's disease and is hence merely a theory.

Mechanical pressure on the nerves

Pain has been suggested to arise from the stretching of and pressure on nerves by growing fatty masses [34, 83]. However, this theory has never been confirmed histopathologically (cf. *Adipose Tissue Histology*, pp. 40-42).

Adipose tissue dysfunction

Another aetiology that has been proposed for Dercum's disease is a local defect in lipid metabolism [30]. An investigation [30] of fatty acid biosynthesis in two patients with Dercum's disease suggested that there might be a deficit in the formation of mono-unsaturated fatty acids in subjects affected by the disease. In one of these cases, there was a discrepancy in the formation of long-chain mono-unsaturated fatty acids (16:1 and 18:1) (fatty acids are denoted as number of carbon atoms:number of double bonds) in painful adipose tissue, whereas the formation in the unaffected adipose tissue was normal. In the other case, synthesis of C₁₆ fatty acids was detected; on the other hand, the synthesis of C₁₈ fatty acids seemed to be completely blocked in painful adipose tissue. However, contradictory findings were revealed in another study, comprised of 13 patients with Dercum's disease [84]. This investigation showed that the proportion of monounsaturated fatty acids (16:1 and 18:1) was significantly higher in the patients with Dercum's disease than in the healthy controls. On the other hand, the proportions of saturated (14:0 and 18:0) and some other unsaturated fatty acids (18:3 and 20:1) were increased.

Another finding that supports a local defect in lipid metabolism is corticosteroid-induced juxta-articular Dercum's disease [85]. A causal relationship between corticosteroids and Dercum's disease was suggested as the symptoms of Dercum's disease developed in one case when the patient was temporarily treated with high-dose corticosteroids; the symptoms later resolved when the dosage was reduced. The authors suggested that the effect of corticosteroids on lipid metabolism could have caused the temporary onset of Dercum's disease.

In summary, lipid metabolism in Dercum's disease, and the pathophysiological and clinical significance of the findings described above, are unclear.

Pimenta et al performed an *in vitro* study on normal and painful fat from a patient with Dercum's disease. The study revealed that the

painful adipose tissue had reduced responsiveness to norepinephrine and a lack of response to the anti-lipolytic effect of insulin compared to non-painful adipose tissue [73]. In another *in vitro* study, a sample of painful adipose tissue from a subject affected with Dercum's disease converted glucose to neutral glycerides at a significantly lower rate than non-painful adipose tissue from the same subject [78].

In addition, one of the studies [84] also revealed that patients with Dercum's disease have significantly higher fat-cell heat production, compared to obese healthy controls, expressed in $\mu\text{W/g}$, as well as in pW/cell . The authors speculated on whether this could be explained by higher sympathetic activity due to nociceptive stimuli in the painful adipose tissue. However, one patient in the study had unilateral disease, and adipose cells from the painful side demonstrated lower heat production than cells from the pain-free side. This contradicts the theory of higher sympathetic activity described earlier (cf. *Nervous System Dysfunction*, p. 36). Furthermore, a study [86] performed on 10 patients with Dercum's disease concluded that women with Dercum's disease have lower resting energy expenditure on the basis of total body mass (kg) than healthy controls. The relevance of these findings is unclear.

In conclusion, as regards adipose tissue function in Dercum's disease, the findings are inconclusive.

Inflammation

An inflammatory aetiology has been proposed for Dercum's disease [13, 38, 87]. However, laboratory markers for inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are usually normal in the condition [15-18, 21, 22, 30, 38, 39, 46, 85, 88-90]. However, a few studies have revealed that some patients have elevated levels of CRP and ESR. In a study from 1937, including 112 females, reported that 66% of the patients with Dercum's disease have been observed to have $\text{ESR} > 15$ [12]. In a study by Herbst and Asare-Bediako [21], 33.4% of the patients with Dercum's disease had elevated CRP levels and 37.5% had elevated ESR levels. However, 38.2% of the patients included in the study had

autoimmune disease, such as rheumatoid arthritis and lupus. Furthermore, markers for autoimmune disease, such as rheumatoid factor (RF), antinuclear antibodies (ANA), anticardiolipin antibodies (ACA), perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), cytoplasmic anti-neutrophil cytoplasmic antibodies (cANCA) and antibodies against native DNA, are commonly negative in Dercum's disease [15, 16, 18, 38]. In the study by Herbst and Asare-Bediako [21], 31.2% of the patients had positive titres for ANA. However, it is unclear if these patients were among the 38.2% that had an autoimmune disease.

A study on adipokines in Dercum's disease has indicated that there is no difference in the levels of tumour necrosis factor (TNF)- α , leptin, adiponectin, plasminogen activator inhibitor-1, interleukin (IL)-1 β , IL-8, IL-10, macrophage inflammatory protein (MIP)-1 α , and monocyte chemotactic protein (MCP) compared to controls. Nonetheless, significantly lower MIP-1 β expression [86] and a trend toward higher levels of IL-13 and lower levels of fractalkine were seen. The authors concluded that the lowered fractalkine levels were logical, since with prolonged release of fractalkine as seen in neuropathic pain, the receptors to which fractalkine binds are upregulated. This suggests that there is shift from sfractalkine release to receptor-bound fractalkine. The lower levels of fractalkine found in Dercum's disease could thus suggest that the substance is receptor-bound. When receptors are occupied by fractalkine, pain and resistance to opioid analgesia are promoted. This is in accordance with the symptoms in Dercum's disease [86].

In brief, there are no uniform findings pointing to an inflammatory aetiology in Dercum's disease.

Trauma-induced Dercum's disease

Two cases of trauma-induced [46, 91] Dercum's disease have been described. The first patient developed a painful fatty tumour, which was very sensitive to pressure and gave rise to much spontaneous pain, after falling on a stone pavement. The painful adipose tissue lingered for a year after the disappearance of the bruises [91]. In the

second case, the patient fell down a tree and landed on his right shoulder one year before the onset of Dercum's disease. No fracture could be detected. One year after the accident, a painful adipose tissue tumour started to grow on his right shoulder. Five years after the injury, an x-ray of the painful shoulder was performed and a humeral fracture that appeared pathological was found. However, the origin of the pathological fracture is unclear [46].

All in all, evidence that painful adipose tissue is the result of injury is circumstantial.

Adipose tissue histology in Dercum's disease

In previous reports and studies, an inconsistent picture of the histological appearance of the adipose tissue in Dercum's disease has been found. Fat biopsies from a total of 151 patients, in 33 different case reports, have revealed histologically normal adipose tissue, without inflammation [10, 12, 14, 16, 18, 22, 33, 37, 38, 41, 42, 44, 69, 71-73, 77, 83, 85, 88, 89, 92-103]. Furthermore, one case has been reported where a fine needle aspiration of painful fat revealed normal adipose cells without inflammatory mononuclear cells [19]. However, pathological findings have been described in other studies. Dercum originally considered the most interesting histological finding to be interstitial inflammation of the nerves in the adipose tissue of the painful sites (Figure 7) [4, 104, 105]. However, this finding has only been confirmed in one more case, published in 1900 [106].

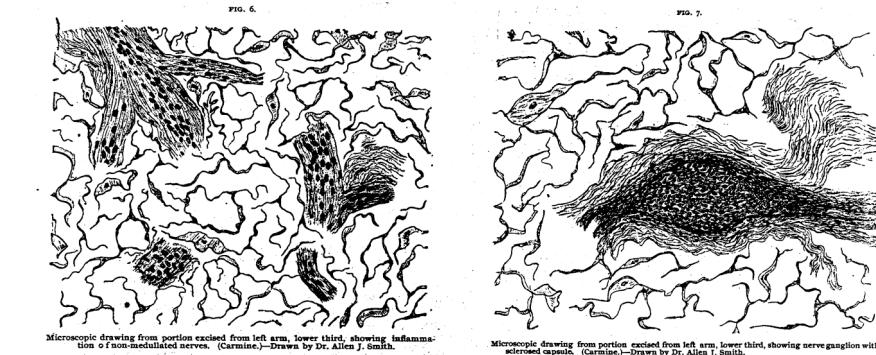


Figure 7. Drawing of the histological findings in the first patient with Dercum's disease. The drawing to the left shows 'inflammation of non-medullated nerves' and the drawing to the right shows a 'nerve ganglion with sclerosed capsule'. *The University Medical Magazine*, 1888, pp. 9-10 [4]. Article in the public domain. [Reprinted with permission from University of Pennsylvania].

Regarding inflammatory signs, leukocytes and plasma cells have been detected in two cases [31, 87]. In addition, Herbst et al [86] found multi-nucleated giant (MNG) cells in three Dercum's patients ($n=5$) and in none of the controls ($n=5$) in one study. MNG cells are produced by macrophages that are activated and pro-inflammatory. However, no differences in the number of macrophages could be found between the patients and the controls.

Blomstrand et al [30] found incomplete dissolution of fat and granuloma formation with giant cells, similar in appearance to a foreign body reaction, in the biopsies from painful sites. A clear histological difference between biopsies from painful and non-painful sites in two patients with Dercum's disease was seen.

Herbst et al [86] noted a significantly higher level of connective tissue in fat biopsies from five women with Dercum's disease compared to five healthy obese controls. Connective tissue in the adipose tissue has also been reported by Myers [107]. He described dense strands of fibrous tissue, and a large number of fibroblasts and small blood vessels in the adipose tissue. Furthermore, a fibrolipoma, with numerous embryonic vessels, has been described in one case [23]. Eyckmans reported adipose tissue with reactive infiltration of fibrotic elements and small angiomes [108].

In terms of vascularisation, Lemont et al [34] found numerous capillary microthrombi in a biopsy of painful fatty tissue in one patient. One case of richer than normal vascularisation has also been reported [87].

Treatment

No convincing large studies on the treatment of Dercum's disease have been conducted. However, a number of different treatment strategies exist, all based on case reports. The described treatments are summarised below.

Liposuction and surgical treatment

A number of patients treated with liposuction have been presented (Table II). In all cases, suction-assisted liposuction was used. The 'dry' technique was applied by all investigators, with the exception of Wollina et al., who used the tumescence technique with 0.1 percent prilocarpine solution. The mechanism behind pain relief following liposuction is thought to be that nerve plexuses in the adipose tissue are destroyed [79].

Table II. Liposuction in Dercum's disease (in reverse chronological order)

Study	Journal	Year	Number of patients	Follow-up time	Results
Wollina et al [102]	G Ital Dermatol Venereol	2010	4	Not stated	Pain relief
Berenguer et al [109]	Aesthetic Plast Surg	2000	1	Not stated	Pain relief
De Franzo et al [110]	Plast Reconstr Surg	1990	1	2 years	Pain-free
De Silva et al [111]	Ann Rheum Dis	1989	2	1 year	Pain-free
Scheinberg [14]	Arthritis Rheum	1987	1	Not stated	Pain-free

Lipectomy has been tried in a few cases [12, 22, 34, 36, 83, 89, 93, 112]. The treatment was effective, but the pain returned in all cases but one.

Traditional analgesics

The pain in Dercum's disease is often refractory to analgesics and to non-steroidal anti-inflammatory drugs (NSAIDs) [14, 18, 78, 89, 90, 92, 94, 111, 113-115]. However, this has recently been contradicted by the findings of Herbst et al. [21]. They reported that the pain diminished in 88.8% of patients (n=89) when treated with NSAIDs and in 97.3% of patients when treated with narcotic analgesics (n=37). Nonetheless, the dosage required and the duration of the pain relief were not precisely stated in the article.

Lidocaine

An early report from 1934 showed that intralesional injections of procaine (NovocainTM) relieved pain in six cases [116]. More recently, other types of local treatment of painful sites with lidocaine, such as lidocaine 5% patches (LidodermTM) [39, 117] or lidocaine/prilocaine (25 mg/25 mg) cream (EMLATM) [101] have shown a reduction of pain in a few cases.

In the 1980s, treatment with intravenous infusions of lidocaine (XylocaineTM) in varying doses was reported in nine patients [16, 32, 33, 78, 82, 99, 113, 115]. The resulting pain relief lasted from 10 hours [32] to 12 months [113]. In five of the cases, the lidocaine treatment was combined with mexiletine (MexitilTM), which is a class 1B anti-arrhythmic with similar pharmacological properties as lidocaine [16, 17, 44, 99].

The mechanism by which lidocaine reduces pain in Dercum's disease is unclear. It may block impulse conduction in peripheral nerves [32], and thereby disconnect abnormal nervous impulse circuits [99]. Nonetheless, it might also depress cerebral activity that could lead to increased pain thresholds [32]. Iwane et al. [32] performed an EEG during the administration of intravenous lidocaine.

The EEG showed slow waves appearing 7 minutes after the start of the infusion and disappearing within 20 minutes after the end of the infusion. On the other hand, the pain relief effect was the greatest at about 20 minutes after the end of the infusion. Based on this, the authors concluded that the effect of lidocaine on peripheral nerves most likely explains why the drug has an effect on pain in Dercum's disease. In contrast, Atkinson et al. [113] have suggested that an effect on the central nervous system is more likely, as lidocaine can depress consciousness and decrease cerebral metabolism [113]. In addition, Skagen et al. [82] demonstrated that a patient with Dercum's disease lacked the vasoconstrictor response to arm and leg lowering, which indicated that the sympathicus-mediated local veno-arteriolar reflex was absent. This could suggest increased sympathetic activity. An infusion of lidocaine increased blood flow in subcutaneous tissue and normalised the vasoconstrictor response when the limbs were lowered. The authors suggested that the pain relief was caused by a normalisation of up-regulated sympathetic activity.

Methotrexate and infliximab

One patient's symptoms were improved with methotrexate and infliximab (RemicadeTM) [98]. However, in another patient with Dercum's disease, the effect of methotrexate was discreet [70]. The mechanism of action is unclear. Previously, methotrexate has been shown to reduce neuropathic pain caused by peripheral nerve injury in a study on rats.

The mechanism in Singal et al.'s case was thought to be a decrease in microglial activation subsequent to nerve injury [118]. Furthermore, a study has shown that infliximab reduces neuropathic pain in patients with central nervous system sarcoidosis. The mechanism is thought to be mediated by tumour necrosis factor inhibition [119].

Interferon α -2b

Two patients were successfully treated with interferon α -2b [120]. The authors speculated on whether the mechanism could be due to the antiviral effect of the drug, the production of endogenous substances, such as endorphins, or interference with the production of interleukin-1 and tumour necrosis factor. Interleukin-1 and tumour necrosis factor are involved in cutaneous hyperalgesia.

Corticosteroids

A few patients noted some improvement when treated with systemic corticosteroids (prednisolone) [77, 92, 121], whereas others experienced worsening of the pain [85]. Weinberg et al [19] treated two patients with juxta-articular Dercum's disease with intralesional injections of methylprednisolone (Depo-MedrolTM). The patients experienced a dramatic improvement.

The mechanism for the pain-reducing ability of corticosteroids in some conditions is unknown. One theory is that they inhibit the effects of substances, such as histamine, serotonin, bradykinin, and prostaglandins [122].

Calcium-channel modulators

Several calcium-channel modulators have been tried; for instance, pregabalin (LyricaTM) (anticonvulsant) [15] and oxacarbazepine (TrileptalTM) (anticonvulsant) [17, 88, 123].

Calcium-channel modulators inhibit the activation of neuronal calcium channels and thereby inhibit the release of substances, such as excitatory amino acids, that are necessary for central sensitisation (cf. p. 51). These drugs are used to treat neuropathic pain [124]. Several of these substances have a broad range of pharmacological actions and other mechanisms beyond calcium-channel modulation which might contribute to their effectiveness in treating neuropathic pain [124].

D-thyroxine

D-thyroxine (LevaxineTM) has not given any symptomatic relief in Dercum's disease [84]. This further supports that the thyroid gland is not involved in the pathogenesis of the disease.

Rapid cycling hypobaric pressure

A pilot study [125], including 10 patients, has suggested that rapid cycling hypobaric pressure might decrease pain in treating patients with Dercum's disease. Different mechanisms have been proposed for the effect: pneumatic displacement of fluid, that is, a decrease in tissue oedema, improved blood flow through intermittent compression and an increase in arterial oxygen saturation and an decrease in hypoxia in the painful tissue [125].

Pain

The pain pathway

The classic pain pathway consists of a three-neuron chain that transmits noxious signals from the periphery to the cerebral cortex. The first-order neuron is a primary afferent neuron; its peripheral end is composed of a receptor that responds to a stimulus, transduces it and transmits the information to the central nervous system. The majority of first order neurons end in the dorsal horn of the spinal cord, where they synapse with the second-order neurons. The second-order axons cross the spinal cord through the white commissure and ascend in the spinothalamic tract to the thalamus, where they synapse with the third-order neurons, which are located in one of the nuclei of the thalamus. In these nuclei, information is transformed and then projected through the internal capsule and corona radiata to the post-central gyrus of the cerebral cortex, where it is further processed. The information received by the cerebral cortex results in the perception of pain, that is, the conscious awareness of it [126].

Pain receptors

In the periphery, pain is detected by two main types of receptors: high-threshold mechanoreceptors with fast-conduction myelinated A-delta fibres, and polymodal nociceptors with slow-conducting unmyelinated C fibres. High-threshold mechanoreceptors are recruited first and transmit ‘first pain’, which is a well-localised discriminative sensation that lasts as long as the acute nociceptive stimulus. When the nociceptive stimulus is strong enough, the polymodal nociceptors are recruited. These receptors transmit ‘second pain’, which is a more diffuse and persistent sensation that lasts beyond the termination of the acute nociceptive stimulus. ‘Second

pain' is associated with the affective-motivational component of pain. Nociceptive stimuli of cutaneous origin often elicit both 'first' and 'second pain', whereas stimuli of visceral origin predominantly activate 'second pain'.

The receptors can be activated directly, by for example mechanical stimulation, as well as indirectly, by intermediaries, such as histamine, serotonin, bradykinin, prostaglandins, adenosine triphosphate and potassium and hydrogen ions.

Neurotransmitters

Pain receptors use neurotransmitters to signal pain. The pain receptors use neurotransmitters to signal pain. Neurotransmitters can be subdivided into small-molecule neurotransmitters, such as amino acids, purins, catecholamines, serotonin and histamine and peptide neurotransmitters, that is neuropeptides, such as substance P and calcitonin gene-related peptide. Both mechanoreceptors and polymodal nociceptors contain small-molecule neurotransmitters as transmitters. Polymodal receptors also contain a number of neuropeptides, such as substance P and calcitonin gene-related peptide. The substances are released when the receptors are stimulated by direct stimuli or during painful inflammatory conditions or tissue damage [122]. A summary of the neuropeptides that are studied in this thesis (paper III) can be found in Table III.

Table III. Neuropeptides studied in paper III and their role in pain and inflammation. Classification and facts are from Fleur L. Strand's book *Neuropeptides. Regulators of physiological processes* [127].

Neuropeptide	Role in pain and inflammation
Hypophysiotropic neuropeptides	
Somatostatin (SOM)	Analgesic effect via interaction with opiate receptors
Anterior pituitary neuropeptides (POMC-derived)	
γ 2-melanocyte-stimulating hormone	Produces pain by antagonizing the

(MSH)	effects of opiates, including β-endorphin, possibly via opiate receptors. Inhibits inflammation via pathways involving both central and peripheral sites of action.
<i>Endogenous opiate neuropeptides</i>	
Met-enkephalin (mENK)	Analgesic effect via the opiate receptor. Important in pain regulation at spinal and supraspinal level. Responsible for the anti-nociception that accompanies stress.
β-endorphine (B-END)	Analgesic effect via the opiate receptor. Touch and proprioception are not affected. Contributes to the individual pain threshold and tolerance level. Endorphin levels rise following nerve injury.
Dynorphin (DYN)	Analgesic effect via the opiate receptor.
<i>Tachykinins</i>	
Substance P (SP)	Produces pain via the NK1 receptor. Is released by noxious stimuli. Is increased in chronic pain and chronic inflammation. Participates in inflammatory reactions.
<i>Gut and brain neuropeptides</i>	
Vasoactive intestinal peptide (VIP)	Acts as an anti-inflammatory agent in the respiratory tract. Has a vasodilatory effect and may be involved in the pathogenesis of cluster-type headache.
Neuropeptide Y (NPY)	No known effect on pain and inflammation. Has a role in obesity as it has a strong stimulatory effect on food intake. Is elevated in obesity.
Calcitonin-gene-related peptide (CGRP)	Modulates the effect of SP. Elevated CGRP decreases food intake.

Substance P (SP) has a role in several neural pathways [128, 129] and is a potent mediator of neurogenic inflammation [130]. Indeed, previous studies on patients with diseases involving chronic idiopathic pain, for example fibromyalgia, have demonstrated a clear elevation in cerebrospinal fluid (CSF) levels of SP [131, 132].

Calcitonin gene-related peptide (CGRP) is a spinal pain neurotransmitter and has been proposed to be involved in the pathogenesis of, for example, migraine [133, 134]. CGRP regulates blood flow and mediates vasodilatation in cerebral vessels [135], as well as hyperalgesia, and central sensitisation [136]. Furthermore, functional CGRP receptors have been discovered on cultured trigeminal ganglia neurons and glial cells [137, 138], cell types that play a role in the pathogenesis of pain [139, 140]. Moreover, CGRP mediates the release of different cytokines, chemokines and nitric oxide [141] that maintain pain [142].

Pain modulation

In the pain pathway, the pain is subjected to both segmental and descending modulation. At the spinal cord level, the modulation is generally inhibitory, and hence constitutes a powerful negative feedback system that is activated by nociceptive stimuli. The dorsal horn harbours an interneuronal system which modulates signals that are about to ascend to the spinal cord. Moreover, the dorsal horn contains a number of neurotransmitters that affect pain transmission.

Supraspinally, descending pathways can modulate pain transmission in the brain stem and thalamus. Stimulation of the sensory and motor cortex can induce inhibitory, excitatory, and mixed effects on dorsal horn neurons, via descending fibres or intermediary brain stem structures. Important transmitters at the supraspinal level include epinephrine, norepinephrine, and serotonin [122].

Sensitisation

Sensitisation is responsible for hyperalgesia, which is defined as the exaggerated response to noxious stimuli, and for allodynia, which is defined as non-noxious stimuli that normally would not cause pain being perceived as painful, such as light touch, mild warmth or cold [126].

Peripherally, receptors might be sensitised when noxious substances are released, which means that the threshold for activation can be decreased, the intensity of the response to a stimulus be increased, or spontaneous activation may occur [122].

Centrally, sensitisation results in the activation of nociceptive neurons by previously sub-threshold inputs. The nociceptive neurons gain a lower threshold, an enhanced responsiveness and a greater receptive field. Central sensitisation comprises changes in synaptic modulators and excitatory amino acids, ion channel properties, and activation of kinases pre- and post-synaptically [122].

Following a noxious stimulus, the nervous system is sensitised for a few minutes; this phenomenon is called wind-up, and defends the body against further injury [143]. However, in conditions such as fibromyalgia, sensitisation becomes chronic and dysfunctional [144]. If the receptor develops a background discharge, spontaneous pain is produced [126].

Types of pain

Pain can be classified as nociceptive, inflammatory, neuropathic, and dysfunctional pain. They are briefly summarised below. The different types of pain can co-occur in some conditions [145].

Nociceptive pain

Nociceptive pain occurs in response to noxious stimuli and lasts as long as the stimulus lasts. It guards against tissue injury. Nociceptive pain is mediated by A-delta fibres and C-fibres, and follows the classic pain pathway. Certain conditions generate recurrent or ongoing noxious stimuli resulting in chronic nociceptive pain. An example of such a condition is osteoarthritis [145].

Inflammatory pain

Inflammatory pain is produced in response to tissue inflammation. To aid in healing, the responsiveness of the pain system changes. In brief, innocuous stimuli start to produce pain and the response to noxious stimuli is enhanced and prolonged. These changes are the result of plasticity in the receptors and in the central sensory pathways. Normally, inflammatory pain disappears when the tissue injury has healed and the inflammation has subsided [145].

The neuronal pathway responsible for inflammatory pain is different than the neuronal pathway producing nociceptive pain [145]. Inflammatory pain comprises the release of inflammatory mediators, that is, neurotransmitters such as SP and CGRP from C-fibres, which in turn results in the release of potassium and hydrogen ions, acetylcholine, histamine and bradykinin that promote the production of prostaglandins and leukotrienes, which maintain pain.

Inflammatory pain can spread to surrounding tissue by travelling along the sensory axons, a phenomenon referred to as spatial diffuseness [122].

Neuropathic pain

Neuropathic pain arises when the nervous system is damaged peripherally, by mechanical trauma, metabolic disease, neurotoxic chemicals, infections, or tumour invasion, or centrally, by spinal cord injury, stroke, or multiple sclerosis [145].

This type of pain is a reaction to damage, and the development of it involves multiple pathophysiological changes, including the appearance of novel receptors and channel proteins at the membrane of the neurons, changes in signal processing in the peripheral and central nervous system and anatomical rewiring of afferent connections [124]. Furthermore, when the nervous system is damaged, peripheral immune cells and microglia in the spinal cord begin to produce the same inflammatory mediators that are produced in inflammatory pain. These substances contribute to the pain by activating nociceptive neurons [145].

This type of pain is an example of maladaptive plasticity in the nervous system and results in chronic pain and hypersensitivity [145].

Dysfunctional pain

Dysfunctional pain is caused by a malfunction of the somatosensory system. The pain is maladaptive, as it does not protect the individual, nor does it support healing. This type of pain occurs in situations where there are no noxious stimuli or any detectable inflammation or damage to the nervous system; for instance, in conditions such as fibromyalgia, irritable bowel syndrome, and interstitial cystitis. It is unclear what causes this type of pain, but it seems to be a consequence of altered sensory processing in the central nervous system and autonomous amplification of the nociceptive signals. Some of the mechanisms responsible for this type of pain are the same as in inflammatory and neuropathic pain [145].

Inflammation

Inflammation is a complex biological response of tissues to harmful stimuli, such as pathogens or cell injury. The process comprises four different components:

- Increased blood flow in the local vessel bed.
- Increased vascular permeability and dilation, with accompanying efflux of fluid and proteins to the tissue.
- Recruitment of leukocytes from the bloodstream to the tissue.
- Changes in the metabolism and other bodily functions. For instance, fever leads to increased blood flow and thereby a quicker inflammatory process. Fatigue and loss of appetite make the individual save his or her energy to fight the harmful stimuli. The release of the hormone cortisol increases blood glucose levels, which facilitates the function of the inflammatory cells, as they are dependent on glucose as a fuel [146].

The purpose of the inflammatory reaction is to protect the body from and remove the harmful stimuli and initiate the healing process [146].

The cardinal symptoms of inflammation are *rubor* (redness), *calor* (heat), *tumor* (swelling), *dolor* (pain), and *functio laesa* (loss of function). Redness and heat are caused by increased blood flow. Swelling is produced by the exudation of fluid from vessels to the tissue. Pain depends on swelling and on a number of substances that are produced and stimulate the pain receptors in the tissue [146] (cf. *Inflammatory pain*, p. 52).

According to which leukocyte subsets are recruited to the tissue, inflammation can be classified as acute or chronic. Acute inflammation is characterised by an accumulation of neutrophil granulocytes and oedema in the tissue. Typical examples of acute

inflammation are bacterial infections and tissue injury caused by, for instance, infarcts or surgery. In chronic inflammation, lymphocytes, macrophages and plasma cells can be found in the tissue. Furthermore, there is often an increased amount of connective tissue fibrosis. The principal cells in chronic inflammation are tissue macrophages and CD4+ helper T cells that activate each other in a reciprocal interplay and produce the mediators that control the inflammatory process. The reaction continues as long as the antigen that has initiated the process is present. In some conditions, it is unclear what initiates and drives the inflammatory process. T cells and monocytes are recruited from the bloodstream to the tissue by chemokines that are produced by activated macrophages. Examples of conditions involving chronic inflammation include tuberculosis and autoimmune diseases, such as rheumatoid arthritis [146].

Many of the mediators produced and released in the inflammatory process can give rise to pain. Some examples of these mediators are different arachidonic acid metabolites, such as prostaglandins, and neuropeptides, such as SP, CGRP, and vasoactive intestinal peptide (VIP) [146].

Sensory innervation of the adipose tissue

Pre-clinical studies have examined the sensory nerve supply to adipose tissue. Studies on rats have demonstrated that the neuroanatomical tracer True Blue can be found in the spinal cord seven days after injection into adipose tissue. This is neuroanatomical evidence of sensory innervation in adipose tissue [147]. Moreover, neurons containing neuropeptides similar to SP, VIP, and neuropeptide Y (NPY) have been found in the adipose tissue of dogs [148]. These neuropeptides are released by sensory neurons and can therefore be considered markers of sensory innervation. These findings support the idea that there is sensory innervation of adipose tissue, even though it is well-known clinically that adipose tissue is less sensitive than, for example, the skin.

Liposuction

The first attempt to remove subcutaneous fat was performed in France 1921 by Charles Dujarrier. He used a uterine curette to remove fat from a dancer's calves and knees. Unfortunately, a major vessel was injured and the attempt ended in amputation. The next attempts included extraction of fat with a curette through a small skin incision and bloc removal of both fat and skin, and were performed throughout the 1960s [149]. These techniques were quickly abandoned because of the abundant complications that followed [150].

The original form of modern liposuction, the 'dry' technique, was invented by the Italians Arpad and Giorgio Fischer in 1974 [151]. They created a hollow cannula equipped with suction and employed criss-cross tunnel formation from multiple incisions. However, the procedure was often complicated by haematomas and seromas. Nonetheless, the number of complications was fewer than with the sharp suction curettage technique that was introduced by Kesselring and Meyer in 1978 [152].

Around 1978 Pierre Fournier and Yves G Illouz in France, further developed Fischer's technique. Fournier is thought to be the first person who used the 'wet' technique. To diminish blood loss by 'dissection hydrotomy', which facilitates the removal of fat, he distended the skin by infiltrating fluid into the adipose tissue prior to liposuction [153]. Nonetheless, despite this 'wet' technique, excessive bleeding was still a problem. However, in 1987, liposuction surgery was revolutionised by the American dermatologist Jeffrey A Klein [154]. Klein found a way to reduce bleeding by adding local anaesthesia and epinephrine to the injected solution. With this new solution, the 'wet' technique was developed into the tumescence technique, that is, very large volumes of saline solution could be injected. The solution contains low concentrations of lidocaine (0.05%), epinephrine (1:1,000,000) and sodium bicarbonate (12.5 meq/L). The local anaesthesia reduces the risk of general anaesthetics and the epinephrine makes the vessels contract and thereby minimises

bleeding. Furthermore, Klein developed smaller, blunt cannulas that were able to bypass vital anatomical structures, such as nerves and vessels. The technique further diminished bleeding and reduced the incidence of seromas and infections. A year later, a study demonstrated that up to 55 mg/kg of lidocaine could be used during tumescent liposuction [155], making large volume liposuction possible.

In 1992, Zocchi introduced ultrasound-assisted liposuction. The ultrasound was thought to help with the dissolution of adipose tissue, and thereby facilitate skin retraction and reduce the physical workload on the surgeon. However, the method soon became defunct because complications, such as skin burns, seromas and paradoxically increased blood loss, were frequent [152].

Today, the blunt tumescent technique with postoperative compression garments is considered the gold standard by most plastic surgeons [152], and several studies have demonstrated that modern tumescent liposuction is a safe procedure [156]. Nonetheless, complications can occur. These include bleeding and haematomas, chronic oedema, fat embolisms in the kidneys and lungs, fibrosis, infection, necrosis, neurological problems, perforations of vessels or viscera, pulmonary oedema, scars, seromas, thromboembolism, and adverse reactions to the tumescence fluid [157, 158].

Numerous non-cosmetic applications of liposuction are now in use. For example, it is used to remove lipomas [159] and angioliomas [160], to improve hyperhidrosis [161], and to treat gynecomastia [162], Madelung's disease [163], Cushing's disease [164], insulin-induced lipohypertrophy [165], post-traumatic asymmetry [109] and lymphoedema [166-169]. Despite a long-term reduction in body fat, the removal of a large amount of abdominal subcutaneous adipose tissue using liposuction does not improve coronary heart disease metabolic risk factors associated with abdominal obesity [170, 171], but glucose uptake may be facilitated and insulin sensitivity increased from a short-term perspective [172]. Liposuction of an arm is depicted in Figure 8 and the instruments used during the procedure in Figure 9.



Figure 8. Liposuction of arm.



Figure 9. Instruments used for liposuction.

Aims

Aims of the study

With this background in mind, in view of the limitations of previous treatment techniques and the promising preliminary results of liposuction, the aims of the present studies became:

- to investigate the effect of liposuction on thermal and sensory sensation (I);
- to examine the effect of liposuction on pain experienced among patients (II);
- to analyse the significance of neuropeptide levels in Dercum's disease by measuring neuropeptides in cerebrospinal fluid and plasma (III);
- to investigate adipose tissue histology in Dercum's disease (IV)

Material

Patients

A total of 111 patients fulfilling the clinical criteria of Dercum's disease, that is obesity and chronic pain (>3 months) in the adipose tissue [12], were diagnosed by and referred consecutively to our clinic by the same consultant in internal medicine. Diagnosis was based on the medical history evaluated from a standardised questionnaire and a systematic physical examination on three separate visits. Dercum's disease was defined as chronic pain (>3 months) in the adipose tissue and adiposity. The disease was classified as Type I (juxta-articular), Type II (diffuse-generalised) or Type III (nodular) [13]. All the patients in the study had Type II (diffused-generalised) Dercum's disease. The first 53 referred patients were consecutively operated on with liposuction. This group was referred to as 'Dercum operated'. The patients were operated on in 1989-1992. The following 58 women with Dercum's disease were recruited as controls. This group was called 'Dercum controls'. The patients in the two groups were of similar age and BMI. The last patient in the group was referred to our clinic in 1994. The patient profiles are shown in Table VI, p. 77. The patients were given no restriction in terms of traditional pain medication and no particular advice regarding lifestyle. No other treatment, such as lidocaine infusions or steroids, was commenced during the course of the study.

Healthy controls

In addition, 41 women, with no acute or chronic pain, that were to be operated on with abdominoplasty, were recruited as healthy controls. This group was named ‘Healthy controls’ or ‘Abdominoplasty patients’. The control patient profiles are shown in Table VI, p. 77. The patients and controls were of similar age and BMI. In one of the studies an additional control group composed of normal weighted healthy women was included.

Evaluation

The operations were performed in 1989-1992. The controls were recruited in 1992-1994. The evaluations were performed in 1989-1999. The results were analysed in 2005-2011.

Ethics

The studies were approved by the Ethics of Human Investigation Committee at Lund University (LU 236-89 and LU and LU 422-91). Permission to create a computer database of the subjects was obtained separately in accordance with the Swedish Privacy Protection Law. All participants gave their informed written consent to participate. The procedures followed were in accordance with the Declaration of Helsinki of 1964, as revised, and the Good Clinical Practice guidelines.

Methods

Surgical technique

Liposuction was performed under general anaesthesia, epidural or spinal block. Neither local anaesthetic nor epinephrine was injected locally, hence the ‘dry technique’ [173] was used. Painful areas, such as the abdomen, flanks/hips and gluteal regions, proximal thighs/legs and arms and the medial areas of the knees were operated on. Four mm incisions were made and a bullet-shaped cannula, with two or three openings distally and an outer diameter of 5-6 mm, was used (Figure 10). A vacuum pump connected to the cannula gave rise to a negative atmospheric pressure of 0.9.

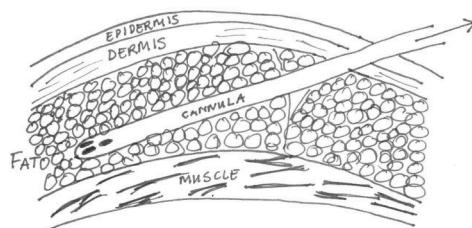


Figure 10. Drawing of liposuction technique. Copyright 2011: Arthur W. Perry, MD [Reprinted with permission].

All operations were performed by the principal supervisor of this thesis (HB). All patients received anticoagulants, the great majority in the form of dextran, during surgery. Following liposuction, the treated areas were firmly compressed, by means of compression garments on the legs, elastic bandages on the arms, and an elastic corset on the torso, to achieve haemostasis and to prevent postoperative oedema in

the operated areas. Compression was maintained for at least 6 weeks. No symptomatic postoperative deep venous thrombosis was seen.

Calculation of the aspirated fat weight

The aspirate (Figure 11) was collected in 2000 ml plastic containers graded to an accuracy of 20 ml. The aspirate was homogenised by vigorous shaking and 2-3 samples of 50 ml each were centrifuged for 20 minutes at 3000 rpm. Following centrifugation, the percentage of adipose tissue in the aspirate was measured.



Figure 11. The aspirate after liposuction.

The fat weight was calculated using the known density of fat ($0.9167 \text{ g/ml} \approx 0.92 \text{ g/cm}^3$) [174]. Five of the patients were also subjected to abdominoplasty. The weight of the excised fat was added to the weight of the fat in the aspirate, thus giving the total weight of removed fat.

Weight and body mass index (BMI)

The patients' body weight was measured on the same scale by the same nurse. The weight was registered on the scale with an accuracy of 0.1 kg.

BMI values were calculated as the ratio of body mass in kilograms and the square of height in metres.

Quantitative sensory testing (I)

Sensory laboratory tests were performed at the Department of Clinical Neurophysiology. All patients described their abdomen and the knees as painful, and so these areas were chosen for liposuction and subsequent examination with sensory thresholds. The subjects were not able to see the results on the computer screen during the testing. Quantitative sensory testing was performed preoperatively and 3 and 12 months postoperatively.

Measurements of vibratory thresholds

To measure the vibratory threshold, electronically-generated mechanical stimulation produced by a Goldberg-Lindblom vibrometer (Somedic AB, Hörby, Sweden) was applied to the subjects' skin. The vibration threshold was determined by the method of limits, that is the intensity of the vibrations was steadily increased until the subject first perceived vibration (vibration perception threshold); upon which the intensity was increased a further 50 percent, followed by a gradual reduction until the subject no longer felt vibrations (vibration disappearance threshold). The patient was asked to report when the vibratory sensation started and stopped. The vibration thresholds were defined as the points (micrometres (μm) from peak to peak) where the perception appeared and disappeared [175].

Measurements of thermal thresholds

To measure warm and cold detection thresholds, a contact thermode thermostimulator (Thermotest, Somedic AB, Hörby, Sweden) was applied to the skin. The perception threshold of cold and warmth induced by contact application was assessed by the method of limits. The baseline temperature of the thermode was set at 32.5°C. The rate of the temperature change was linear at 1°C/second. The subject was instructed to press a switch whenever she felt the onset of a change in temperature (cold or warmth). She was asked to push a button when she felt sensations of warmth and cold, respectively, at which moment the temperature of the probe returned to baseline. The thermal thresholds were defined as the degrees Celsius where the perception appeared and disappeared [176, 177].

Measurements of pain (II)

Pain was measured preoperatively and then repeated after 3 months and after 1, 2, 3, and 5 years.

Subjective pain sensation

To evaluate the patients' subjective pain sensation, a modified version of the Pain-O-Meter was used [178]. The method consists of a questionnaire comprising a Visual Analogue Scale (VAS) and Number of Words Chosen (NWC). In combination, the two tools evaluate both the quality and the intensity of the pain sensation, as validated by Gaston-Johansson [178]. In addition, the operated patients were asked to indicate, ticking 'yes' or 'no' on a questionnaire, whether they thought that the liposuction had

diminished their pain or not. All patients received careful instructions on how the VAS and NWC questionnaires should be filled out.

VAS is widely used as an easy, reliable and sensitive means with which to evaluate patients' subjective opinion of the outcome of various treatments in clinical studies, particularly on pain [179, 180]. The scale used was a straight line (10 cm) on which the patient made a mark corresponding to her appraisal of pain (Figure 12) [181].

How much pain do you experience right now?

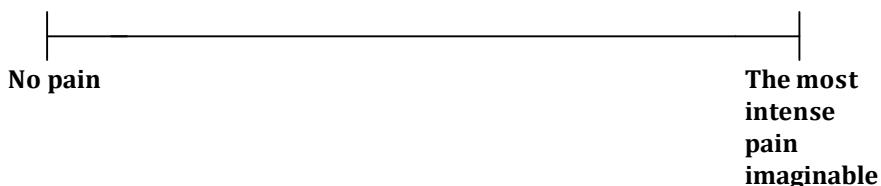


Figure 12. The Visual Analogue Scale used. The VAS distributed to the patients and controls was exactly 10 cm long.

The NWC questionnaire comprises a list of twelve sensory and eleven affective pain descriptors (Table IV). NWC aims to evaluate the sensory and affective dimension of the pain experienced. The patients were shown a list of the words and asked to select and mark the words that described their pain. The patients could choose as many words as needed to describe their pain. Each descriptor was then assigned a weighted value (range 1-5) giving a total pain score, one for the sensory component of pain, and one for the affective component [182].

Table IV. The sensory and affective words in English/Swedish, and their assigned intensity values in parentheses

Sensory words	Affective words
cutting/skärande (5)	irritating/irriterande (2)
grinding/molande (2)	troublesome/besvärlig (3)
pricking/stickade (1)	frightening/skrämmande (4)
squeezing/klämmande (2)	suffocating/kvävande (4)
cramping/krampaktig (4)	killing/mördande (5)
tearing/sönderslitande (5)	unbearable/odräglig (4)
aching/värkande (3)	terrible/fruktansvärd (5)
smarting/svidande (2)	tiring/tröttande (3)
burning;bränndande (4)	worrying/oroande (1)
sore/ömmande (1)	excruciating/outhärdlig (5)
gnawing/gnagande (3)	torturing/torterande (5)
pressing/tryckande (4)	

The words used were based on Gaston-Johansson's validity and reliability research [178] on a translated, shortened and modified version of the McGill Pain Questionnaire (MPQ) [182]. The Swedish short form McGill Pain Questionnaire (SF-MPQ) has been validated among different patient groups [183, 184].

Objective pain sensation

To evaluate the patients' objective pain sensation, an algometer was used. The analogue algometer was constructed during the initial course of the study by the Department of Biomedical Engineering in our hospital, and aimed at measuring the mechanical Pressure Pain Threshold (PPT) in N/cm². The diameter of the probe used was 14 mm.

The PPT was measured on the right and left side of the abdomen and on the knees bilaterally (Figure 13). In order to locate the measure points at follow-up, photos were taken of the subjects with the measuring points marked, indicating distances (cm) to well-known fixed anatomical landmarks. Measurements were performed on folds containing skin and adipose tissue, thus underlying muscle tissue was not involved.

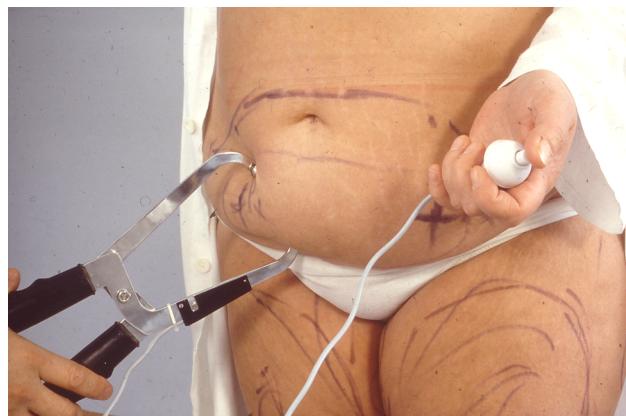


Figure 13. Measurement of the PPT of the abdomen with the algometer

The patients were instructed to press a button giving a light indication to the investigator, when the pain became unbearable. The readout on the algometer was then noted (Figure 14).

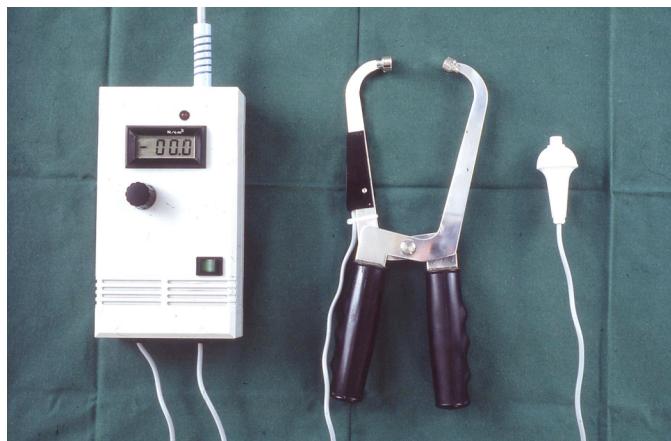


Figure 14. The algometer.

Care was taken to always use the same rate of pressure application. The same investigator performed all measurements. Three measurements were obtained on each measuring point and the mean was calculated and used as the observation value.

Validation of the algometer

The algometer was repeatedly tested with known weights during the trial and showed no drift. To evaluate the test-retest reliability, three measuring procedures were performed by one investigator on three consecutive days in 27 Dercum patients. Mean differences of the pressure with 95% limits of agreements (prediction limits for differences between individual measurements) and the 95% confidence interval to the limits of agreement were calculated between days (1, 2, and 3) for four different locations (left abdomen, right abdomen, left knee and right knee). Bland-Altman plots were made to estimate whether difference and variance was constant across the range of measurements [185].

Measurements of neuropeptides (III)

To evaluate the levels of neuropeptides in Dercum's disease, the substances were quantified with radioimmunoassays in cerebrospinal fluid (CSF) and in plasma (P). The measurements were performed preoperatively. The examined neuropeptides in CSF were: substance P-like immunoreactivity (SP-LI), neuropeptide Y-like immunoreactivity (NPY-LI), β -endorphin-like immunoreactivity (β -END-LI), calcitonin gene-related peptide-like immunoreactivity (CGRP-LI), met-enkephalin-like immunoreactivity (m-ENK-LI), vasoactive intestinal polypeptide-like immunoreactivity (VIP-LI), somatostatin (SOM-LI), γ_2 -melanocyte-stimulating hormone-like immunoreactivity (γ_2 -MSH-LI), and dynorphin-like immunoreactivity (DYN-LI). The same substances were analysed in plasma with the exception of DYN and γ_2 -MSH. The erythrocyte sedimentation rate (ESR) was also measured. All substances were measured in the Dercum group. The control group was used for analysis of three peptides in CSF, namely SP-LI, NPY-LI and β -END-LI.

Samples were collected after overnight fasting: CSF samples (12 ml) were taken preoperatively and blood samples were taken upon

admittance to hospital before the surgery. No complications developed following the collection of the specimens. The CSF samples were collected in unprepared plastic tubes and the blood samples, except those for the analysis of SOM-LI, in EDTA tubes. SOM-LI samples were collected in tubes containing sodium citrate. All samples were immediately cooled in ice water and centrifuged at 4°C. The plasma, as well as the supernatants of the CSF samples, were divided into three portions and stored in plastic tubes at -20 °C (SOM at -70°C) until assayed.

Quantitative analysis of SP-LI, CGRP-LI, SOM-LI, β -END-LI and NPY-LI was performed using different radioimmunoassay systems. For the radioimmunoassays of the various peptides, the samples were analysed in serial dilutions, optimised to the linear part of the standard curve and corrected for non-specific binding. Since cross-reactivity with other peptides or proteins, sharing immuno-determinants with the analysed peptide, cannot be excluded, it is appropriate to refer to like immunoreactivity, for example SP-LI, rather than to the respective peptide.

SP-LI was quantified using a rabbit antiserum (SP-2, provided by Dr E Brodin, Stockholm, Sweden) [186] at a final solution of 1:50 000 with (Tyr^8)-SP as the tracer. The SP-2 antiserum does not detect any known tachykinin besides SP [186]. The detection limit was 0.5 pmol/l and the interassay variation was <8%.

NPY-LI was analysed as previously described [187]. A rabbit antiserum raised against porcine NPY (provided by Dr PC Emson, Cambridge, UK) was used. The antiserum cross-reacts with peptide YY (PYY) to 33%, but not with C-terminal fragments of NPY and PYY. The detection limit was 11 pmol/l and the interassay coefficient of variation was <7%.

β -END-LI was quantified using a rabbit antiserum (K-7762, and antiserum 5422, provided by Dr D Marshak, Houston, Texas, USA) [188] raised against unconjugated synthetic human β -END. The antiserum was used at a final dilution of 1:25,000 and has negligible cross-reactivity against β -lipotropin (<1.5%). The detection limit in a direct assay was 10 pmol/l and the interassay coefficient of variation <10%.

CGRP-LI was quantified using a rabbit antiserum (R-8429) [189] raised against synthetic rat CGRP. CGRP was conjugated to bovine serum albumin and used at a final dilution of 1:37,500. This allowed measurements of CGRP-like material with a minimum volume of 10 pmol/l. The interassay variation was 12%.

ENK-LI was determined using a rabbit antiserum (5422, provided by Dr K H Voigt, Ulm, Germany) [188] in a final dilution of 1:20 000 with a detection limit of 10 pmol/l. The antibody recognises the C-terminus of ENK and does not cross-react with leu-enkephalin, β -END, or dynorphin (DYN). The interassay variation was <10% [188].

VIP-LI was determined using a rabbit antiserum (code 7852, Milab, Malmö, Sweden). The antiserum was used at a dilution of 1:60,000 and does not cross-react with the peptides histidine, isoleucine, secretin, or glucagon. The detection limit was 6 pmol/l and the interassay variation was 8.5% [186].

SOM-LI was determined using a rabbit antiserum (K18, Milab, Malmö, Sweden) at a final solution of 1:25,000. The antiserum has not shown cross-reaction with any other known neuropeptide except cyclic SOM (100%), linear SOM (50%) and (Tyr^1)-SOM (100%). The detection limit was 6 pmol/l, expressed as SOM-LI 15-28 equivalents. The interassay variation was <12% [190].

γ_2 -MSH-LI was determined using a rabbit antiserum at a final dilution of 1:75,000 (K-8032) [191, 192]. The antiserum does not show cross-reaction with related peptides such as γ_1 -MSH, γ_3 -MSH or other peptides containing the MSH sequence (α -MSH, β -MSH, ACTH 4-10). The detection limit for the assay was 5 pmol/l and the interassay variation was <11%.

DYN-LI was determined using a rabbit antiserum (K-8027) [193] at a final dilution of 1:12,500. The antiserum was directed against the C-terminal portion of dynorphin 1-13 and cross-reacted with dynorphin 1-9, 1-10, and 1-11 < 3.3%. The detection limit was 20 pmol/L and the interassay coefficient of variation was <12% [193].

The erythrocyte sedimentation rate (ESR) was measured using the Westergren method, i.e. four parts blood were diluted with one part isotonic citric solution. The level of sedimentation was measured after one hour [194].

Adipose tissue histology (IV)

To evaluate inflammatory signs in adipose tissue, biopsies were obtained by open surgical biopsy. They were taken in the same way, measuring about 15x15 mm. There were no complications following the procedure. The biopsies were fixed and transported in a 4% formaldehyde medium and embedded in paraffin. Two consecutive sections were cut from each biopsy and stained with hematoxylin-eosin. The whole sections were examined by the same pathologist (US) in a blinded manner. The inflammatory reaction consisted of lymphocytes, macrophages and possibly some fibroblasts. All the mentioned cells were differentiated from their appearance in the haematoxylin-eosin staining. A few solitary lymphocytes were also seen. The extent of the inflammatory reaction was evaluated subjectively as described in Figures 19 to 21, p. 85, taking into consideration number of and size of the inflammatory infiltrates. There is thus a continuum of changes. Inflammatory reactions were given a score between 0 and III, where 0 equalled no inflammation, I slight, II moderate and III pronounced inflammatory reaction.

Calculations and statistical methods

The statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) 15.0 for Windows (SPSS Corporation) and 17.0 for Macintosh (SPSS Corporation). Values are given as medians and range or means and standard deviations (SD) when appropriate. Histograms were drawn to test if the material had a normal distribution. When the measured factors were not normally distributed, standard non-parametric tests were used, such as the Wilcoxon rank-sum test (paper I-II) and the chi-squared (χ^2) test (IV) to analyse differences between groups and the Wilcoxon signed-rank test (I, III) and McNemar's test (IV) to analyse differences within groups. In paper II, differences between groups were analysed using

mixed model analyses. The residuals were normally distributed. The mixed models were performed on the repeated measures of the difference of pain scores from baseline as dependent variables; group, follow-up time, and their interaction as fixed factors, and subject as random factor. The mixed model analyses included age, BMI and each dependent variable's preoperative value as covariates. AR(1) was chosen as the covariance structure. In paper III, the patients' values and reference values were all converted to logarithms, to create values with a normal distribution, and tested against each other with the one-sample *t*-test. A p-value of 0.05 or less was considered to indicate a statistically significant difference.

Review of the Present Investigations

Our 53 operated Dercum patients participated in papers I-IV in varying degrees; we think it is important to show their participation in different studies. Participation in papers I-IV is summarised in Table V.

Table V. Participation in papers I-IV

Pat no	Paper I Vibration and thermal thresholds		Paper II Pain measurements			Decreased pain-question	Paper III Neuropeptides	Paper IV Fat biopsy
	Abdomen	Knee	VAS	NWC	PPT			
1			•	•	•		•	•
2	•		•	•	•		•	•
3	•		•	•	•		•	•
4			•	•	•		•	•
5		•	•	•	•		•	•
6	•		•	•	•		•	•
7			•	•	•		•	•
8			•	•	•		•	•
9			•	•	•		•	•
10	•		•	•	•		•	•
11	•		•	•	•		•	•
12	•		•	•	•		•	•
13			•	•	•		•	•
14	•		•	•	•		•	•
15	•		•	•	•		•	•
16	•		•	•	•		•	•
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46	•		•	•	•	•	•	•
47			•	•	•	•	•	•
48			•	•	•	•	•	•
49			•	•	•	•	•	•
50			•	•	•	•	•	•
51			•	•	•	•	•	•
52			•	•	•	•	•	•
53			•	•	•	•	•	•
Total	38	28	53	53	29	27	53	53

All the patients and controls were of similar age and had a BMI in the same span (Table VI).

Table VI. Patient profiles. Mean and SD.

		Dercum operated (n=53)	Dercum controls (n=58)	Healthy controls (n=41)
Age (years)	At inclusion	51.7±10.0	50.8±10.9	49.4±10.7
Height (cm)		164±9	164±7	165±5
Weight (kg)	Preop.	90.8±16.0	94.1±18.9	89.5±15.1
	3months	87.9±12.1	94.9±19.9	85.7±18.9
	1 year	87.5±18.6	93.5±19.7	88.8±14.6
	2 years	90.4±15.2	93.4±17.3	87.4±14.4
	3 years	90.0±14.7	94.3±17.0	88.8±15.6
	5 years	91.7±16.5	95.0±18.1	90.6±16.3
BMI (kg/m²)	Preop.	34.3± 5.7	35.0±6.8	33.2±5.5
	3months	32.9±4.2	35.3±7.0	31.6±6.6
	1 year	32.9±6.7	34.9±7.0	32.8±5.0
	2 years	34.1±5.2	34.7±6.0	32.4±4.6
	3 years	33.9±4.9	35.2±5.8	32.7±5.0
	5 years	34.4±5.6	35.5±6.3	33.4±5.3

The average amount of fat removed (liposuction and abdominoplasty) was (mean±SD) 3749±2325 g (median 3456, range 580–10430 g).

I. Thermal and vibratory thresholds do not differ after liposuction in patients with Dercum's disease

The thermal and vibratory thresholds were examined preoperatively, and three and 12 months after liposuction in 39 patients with Dercum's disease. There were no dropouts during the course of the study. The vibratory thresholds are given in Table VII and the thermal thresholds in Table VIII.

Table VII. The vibratory thresholds. Median and range. VPT = Vibratory perception threshold. VDT = Vibratory disappearance threshold.

Time	Abdomen (n=39)		Knee (n=28)	
	VPT (μm)	VDT (μm)	VPT (μm)	VDT (μm)
Pre-op	9.9 (0.4-55.0)	8.5 (0.4-47.0)	7.8 (0.35-73.0)	7.6 (0.3-61.7)
After 3 months	10.1 (1.0-70.0)	8.7 (0.5-102.5)	7.5 (1.1-72.0)	5.5 (0.2-66.0)
After 12 months	10.5 (1.5-55)	10.2 (1.3-62.5)	5.1 (2.1-53.0)	5.3 (1.4-47.0)

Table VIII. The thermal thresholds. Median and range. WDT= Warm detection threshold. CDT=Cold detection threshold.

Time	Abdomen (n=39)		Knee (n=28)	
	WDT ($^{\circ}\text{C}$)	CDT ($^{\circ}\text{C}$)	WDT ($^{\circ}\text{C}$)	WDT ($^{\circ}\text{C}$)
Pre-op	5.5 (2.8-13.5)	2.3 (1.3-8.0)	5.1 (1.3-9.3)	2.0 (1.0-4.8)
After 3 months	6.5 (3.3-15.8)	2.8 (1.0-9.8)	5.4 (1.3-11.0)	2.3 (1.3-5.8)
After 12 months	5.8 (2.5-14.8)	2.5 (1.0-9.5)	5.0 (2.0-10.0)	2.5 (1.0-9.0)

There were only small differences in thermal and vibratory thresholds three and 12 months after liposuction compared with preoperative values; none of these differences were statistically significant.

II. Liposuction may reduce pain in Dercum's disease

Pain was evaluated in 53 patients with Dercum's disease that had been operated on with liposuction. As controls, 58 non-operated subjects with Dercum's disease and 41 obese abdominoplasty patients were followed for five years. Pain was examined preoperatively and at 3 months, and 1, 2, 3, and 5 years after liposuction. Subjective pain sensation was evaluated with a Visual Analogue Scale (VAS) and Number of Words Chosen (NWC), and objective pain sensation was evaluated with the mechanical Pressure Pain Threshold (PPT). The PPT was determined in a smaller number of patients as this method was first introduced when the 26th patient was operated on. The validation of the algometer revealed that there were no inter-day differences in our measurements, when performed by the same investigator. Subjective pain sensation was only evaluated in the subjects with Dercum's disease. Missing values were due to patients missing scheduled appointments.

Both subjective (Figures 15-16) and objective (Figure 17-18) pain measurements revealed a statistically significant decrease in the pain experienced by Dercum patients after surgery as compared to preoperative levels ($p<0.001$). However, the improvement faded over time. Nonetheless, it was still statistically significant five years postoperatively ($p<0.001$).

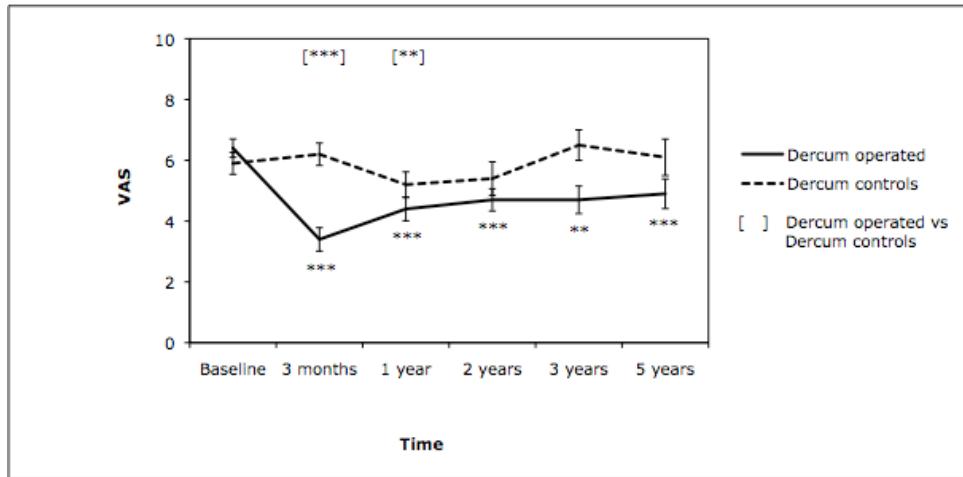


Figure 15. Pain intensity. The VAS values are given as the mean. The maximum VAS value was 10. Mean significant differences within the groups depicts differences in changes over time from baseline and are shown adjacent to the respective error bars. Significant differences between the groups depict differences in changes over time from baseline and are shown in the upper part of the figure. * p=0.05, ** p=0.01 *** p=0.001. Only significant differences are shown.

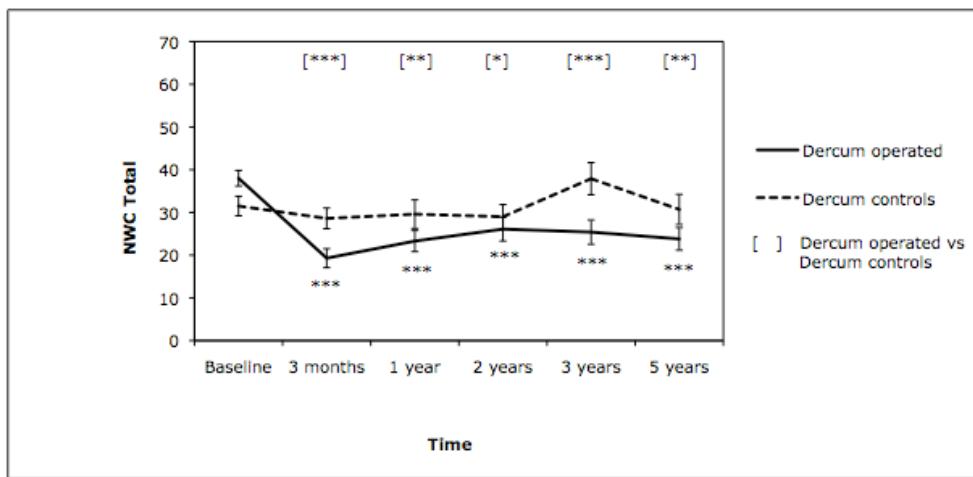


Figure 16. Number of words chosen. The NWC values are given as means. Mean significant differences within the groups depict differences in changes over time from baseline and are shown adjacent to the respective error bars. Significant differences between the groups depict differences in changes over time from baseline and are shown in the upper part of the figure. * p=0.05, ** p=0.01 *** p=0.001. Only significant differences are shown.

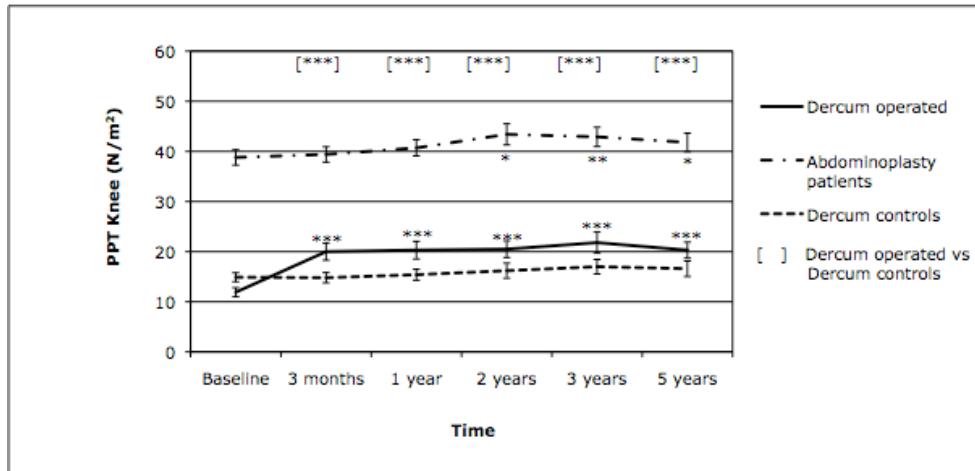


Figure 17. PPT for the knee. The PPTs are given as means. Mean significant differences within the groups depict differences in changes over time from baseline and are shown adjacent to the respective error bars. Significant differences between the groups depict differences in changes over time from baseline and are shown in the upper part of the figure. * p=0.05, ** p=0.01 *** p=0.001. Only significant differences are shown.

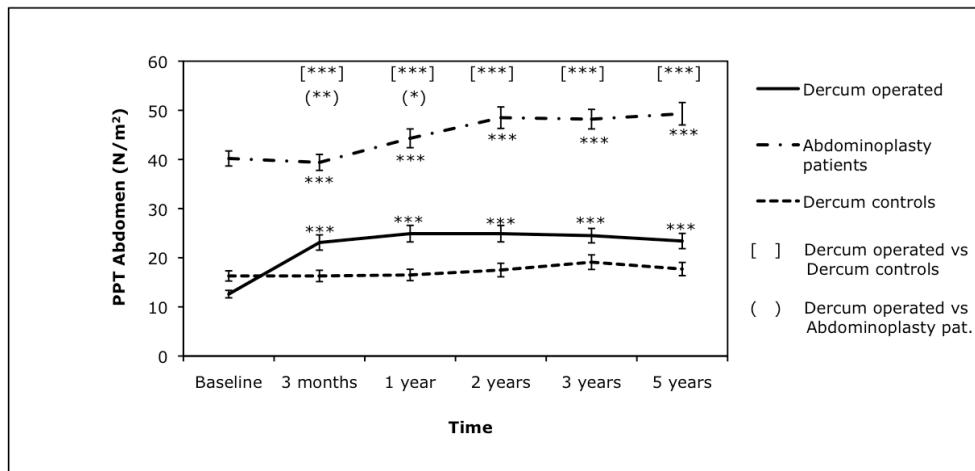


Figure 18. PPT for the abdomen. The PPTs are given as means. Mean significant differences within the groups depict differences in changes over time from baseline and are shown adjacent to the respective error bars. Significant differences between the groups depict differences in changes over time from baseline and are shown in the upper part of the figure. * p=0.05, ** p=0.01 *** p=0.001. Only significant differences are shown.

Postoperatively, a significant postoperative difference could be seen between the Dercum operated group and the Dercum controls. The difference decreased over time but still lingered five years post-operatively (Figures 15-18).

The results suggest that liposuction might alleviate pain in patients with Dercum's disease. However, it is difficult to determine whether the effect is due to the actual surgery or to other factors.

III. Neuropeptide alteration in Dercum's disease

Substance P-like immunoreactivity (SP-LI), neuropeptide Y-like immunoreactivity (NPY-LI), β -endorphin-like immunoreactivity (β -END-LI), calcitonin gene-related peptide-like immunoreactivity (CGRP-LI), met-enkephalin-like immunoreactivity (m-ENK-LI), vasoactive intestinal polypeptide-like immunoreactivity (VIP-LI), somatostatin (SOM-LI), γ_2 -melanocyte-stimulating hormone-like immunoreactivity (γ_2 -MSH-LI), and dynorphin-like immunoreactivity (DYN-LI) were measured in cerebrospinal fluid (CSF) and in plasma (P) from 53 patients with Dercum's disease. Three of the substances were also measured in the healthy control group. The CSF concentration of SP was significantly lower in the Dercum group than in the control group, whereas NPY and β -END were borderline significantly lower and higher, respectively, in the Dercum group (Table IX).

Table IX. Measured substances and results (cases and controls). CSF = cerebrospinal fluid. LI = like immunoreactivity.

Substance (pmol/l)	Group	n	Median (range)	Difference between groups (p-value)
CSF-SP-LI	Dercum	51	12 (6-45)	<0.001
	Control	40	17(8-60)	
CSF-NPY-LI	Dercum	52	119 (44-266)	0.053
	Control	40	130 (25-205)	
CSF- β -END-LI	Dercum	51	110 (81-178)	0.080
	Control	40	107 (17-177)	

Compared to references values, CSF-MSH levels were slightly elevated and CSF-NPY levels were slightly lower in the Dercum group. The other substances, in both CFS and plasma, were within the reference values with a high degree of statistical significance ($p<0.005$) (Table X).

Table X. Measured substances and results in patients compared to the laboratory reference values. CSF = cerebrospinal fluid. P = plasma. LI = like immunoreactivity. A significant difference indicates that the measured values are within the reference limits.

Substance (pmol/l)	n	Median (range)	Reference	Test value (before log)	p-value
CSF-SP-LI	51	12 (6-45)	<10	10	<0.001
CSF-NPY-LI	51	119 (44-266)	120-170	120	0.35
				170	0.157
CSF-β-END-LI	51	110 (81-178)	80-110	80	<0.001
				110	<0.001
CSF-CGRP-LI	44	4 (4-7)	<10	10	<0.001
CSF-m-ENK-LI	45	99 (60-271)	30-150	30	<0.001
				150	<0.001
CSF-VIP-LI	44	16.5 (3-59)	<20	20	<0.001
CSF-SOM-LI	45	27 (14-78)	20-50	20	<0.001
				50	<0.001
CSF-γ2-MSH-LI	18	27 (10-82)	<20	20	0.048
CSF-DYN-LI	45	24 (12-69)	20-50	20	<0.001
				50	<0.001
P-SP-LI	47	2 (1-7)	<4	4	0.005
P-NPY-LI	47	119 (60-278)	<130	130	<0.001
P-β-END-LI	47	38 (26-70)	30-45	30	<0.001
				45	<0.001
P-CGRP-LI	47	15 (10-80)	<40	40	<0.001
P-m-ENK-LI	47	20 (20-48)	<60	60	<0.001
P-VIP-LI	47	5 (3-15)	<20	20	<0.001
P-SOM-LI	47	6 (4-14)	<12	12	<0.001
ESR (mm)	48	11 (4-38)	<21	21	<0.001

In conclusion, altered levels of neuropeptides that have previously been seen in different pain conditions cannot clearly be demonstrated in Dercum's disease.

IV. Adipose tissue histology in Dercum's disease

Fat biopsies, obtained by surgical biopsy, were sampled from 53 women with Dercum's disease. Biopsies were taken from painful subcutaneous fat from the abdomen and the knee region. In 28 cases, a control adipose tissue biopsy was taken from a location where the patient did not experience any pain, 21 from non-painful abdomen and 7 from non-painful knee. Fat biopsies were also sampled from the abdomen and knee regions of 41 obese control patients and from the knee region of 11 normal weight control patients.

In Dercum's disease patients, 75% of the biopsies from painful areas and 71% of the control biopsies from non-painful areas demonstrated an inflammatory reaction with lymphocytes and macrophages (Figures 19 to 21). An inflammatory reaction judged as grade I can be seen in Figures 19 and 20; grade II is shown in Figure 21.

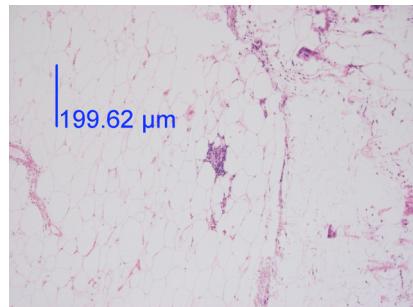


Figure 19. Low-power image of fat tissue from the knee with an infiltrate of inflammatory cells. Haematoxylin-eosin staining. The infiltrate is displayed at a higher magnification in Figure 2. The photo was taken with a 10x objective.

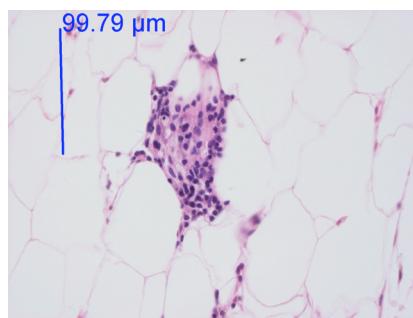


Figure 20. High-power image of Figure 1. Adipose tissue from the knee. Haematoxylin-eosin staining. One infiltrate of this size and only a few additional inflammatory cells gave a score of 1. Two infiltrates of this size gave a score of 2. The photo was taken with a 40 x objective.

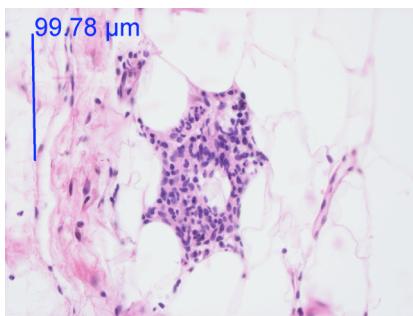


Figure 21. High-power image of fat tissue from the knee. Haematoxylin-eosin staining. One infiltrate of this size and a few additional inflammatory cells gave a score of 2. Three or more infiltrates of this size gave a score of 3. The photo was taken with a 40x objective.

There was no difference between adipose tissue from painful and non-painful abdomen ($p=0.4$) or knee ($p=0.5$). Furthermore, no differences in extent of inflammation were detected between Dercum patients and obese control patients regarding the biopsies from the knee region ($p=0.33$, $\chi^2= 22.2$, $df=20$). A significant difference in extent of inflammation was observed between Dercum patients and obese controls patients for the biopsies from the abdomen ($p=0.022$, $\chi^2= 29.3$, $df=16$). There were no differences in extent of inflammation between Dercum patients and normal weight controls ($p=0.81$, $\chi^2= 6.1$, $df=10$) (knee). However, a difference was detected between obese controls and normal weight controls ($p<0.001$, $\chi^2= 31.4$, $df=8$) (knee).

In conclusion, our findings reveal that there is an inflammatory response in the adipose tissue in patients with Dercum's disease. However, this response might not be more pronounced than that in healthy obese controls. This contradicts inflammation as the aetiology of Dercum's disease.

General Discussion

Considerations regarding ethics

These studies were approved by the Ethics of Human Investigation Committee at Lund University (LU 236-89 and LU and LU 422-91). To determine if liposuction could diminish pain in Dercum's disease, a pilot study was performed before this study was commenced [195]. In 2004, a new bill encompassing research involving living people (SFS 2003:460) was passed. This law is aimed at further increasing the security of participants. The only evaluation in this study that could potentially put the participants at risk of developing side effects was the performance of lumbar puncture (III) and adipose tissue biopsies (IV). The ethics of these procedures were thoroughly vetted in the second ethical permission (LU 422-91).

Considerations regarding follow-up

The patients included in this study were followed and evaluated for a period of five years. Five years is quite long for a clinical evaluation of surgical treatment and was hence considered an adequate time to evaluate and assess the outcomes of treatment.

The drawback with long-term follow-ups from a scientific point of view is the fading of information and drop-out over the years. It is unclear whether the reason for patient refusal was dissatisfaction with the outcome of the treatment or due to other factors. Nonetheless, the phenomenon of drop-out cannot be avoided in a clinical study, and we had the opportunity to evaluate the effect of the treatment in the great majority of the patients.

Considerations regarding the sample and the statistical methods used

Misdiagnosis

Following the complex issue of defining Dercum's disease (cf. *Symptoms and diagnostic criteria*, pp. 23-26), we used a 'minimal definition', including only adiposity and pain. We consider that this may limit the problem of misclassification with regard to other inflammatory or psychiatric conditions. However, it is unclear how many of the patients that fulfilled the criteria of Dercum's disease used in this study also fulfilled the criteria for for example fibromyalgia and other pain syndromes. In fact, there is a clear overlap in diagnostic criteria symptoms for Dercum's disease and other conditions [196]. These syndromes are sometimes referred to as functional somatic syndromes and their aetiology is unclear. The functional somatic syndromes have a number of features in common, that is, no objectively observable abnormalities can be found in the patients. These syndromes often affect predominately females, are negatively affected by stress, and demonstrate co-existing emotional disorders. Moreover, the syndromes have a similar prognosis and respond to different treatments in a similar way [196]. In fact, Wessely et al. have proposed that the similarities between the functional somatic syndromes outweigh the differences, and that the existing classification in different syndromes is therefore of limited value. Wessely et al suggest that more general strategies should be developed for the management of functional somatic syndromes [196].

The Classification and Response Criteria Sub-committee, supported by the American College of Rheumatology, have developed recommendations for the development and validation of criteria sets [197]. According to these recommendations, criteria should be developed using appropriate consensus methodology, and all of the criteria should be reliable, that is, they should be stable

when there is no clinical change, precise in their measurement, easy to measure and clinically sensible. The criteria should be validated for content and criterion validity [197], that is, the criteria should appear valid to the patients, should be relevant for the diagnosis, and should be able to identify or measure the variables or the constructs that it proposes to identify or measure. Moreover, the criteria should be tested for sensitivity and specificity, and for responsiveness [197]. Sensitivity measures the percentage of sick people who are correctly identified as having the condition, whereas specificity measures the percentage of healthy people who are correctly identified as not having the condition. The responsiveness is the criteria's sensitivity to differences in clinical changes over time.

Selection bias

As the prevalence of Dercum's disease is unknown, it is difficult to know how many patients could be eligible for inclusion in the study. However, the strength of the present study is that the same consultant diagnosed all the patients. Nonetheless, a weakness is that only the patients examined by the same consultant had the possibility of being included in the study. It cannot be assessed if patients seeking medical treatment differ from patients that abstain from contact with physicians. It is likely that patients with pronounced pain seek medical care more readily than patients with little pain. Moreover, only patients interested in surgical treatment of their condition were referred to us. For these reasons, it cannot be judged if our sample was representative for Dercum's disease in a wider perspective. It is likely that the patients in the study actually experienced more pain than other Dercum patients. The prospect of finding differences and treatment effects for Dercum's disease would seem apparent in our study group if such differences exist.

The composition of the groups and time intervals

In this study, the first consecutive patients with Dercum's disease referred to the clinic were operated on, and the last were used as controls. Hence, consecutive sampling was used. This is not the most ideal form of randomisation. Nonetheless, as all referred patients were included, there is a good chance that the subjects are representative of the entire population of Dercum patients that would be interested in surgical treatment. The number of patients in the two groups, as well as the end-points of the series, became arbitrary.

Moreover, even though there was no difference in age or BMI between the groups, differences at baseline were apparent for several measures, for example experienced pain. However, a statistical method that corrects for this difference was used, and therefore it should not have affected the results.

Attrition bias

Regarding clinical studies of this kind, the participation rates in this study must be considered high, especially taking into consideration that our patients did not receive any active treatment during the follow-up and therefore did not directly benefit from it. However, in this study, the dropout rate was low and should not have affected the characteristics of the different groups, or the outcomes.

Chance

The results presented in this thesis could have been influenced by the statistical analyses performed. A type I error (alpha-error) means that the null hypothesis is falsely rejected, giving a 'false positive' result. The risk of occurrence of a type I error increases with the number of comparisons conducted. However, in some studies, we saw

considerably more statistically significant results than would be expected by chance alone.

Type II error (beta-error) means that the null hypothesis fails to be rejected and, as a consequence, an actual difference between populations is missed. A limitation of this study is that Dercum's disease is a rare condition, and, as a consequence, the statistical power might be low.

Considerations regarding potential confounding factors

It is possible that factors other than the surgical procedures affected the perception of pain in Dercum's disease. Such factors are discussed below.

The natural history of Dercum's disease

There has been little research conducted on the natural history of Dercum's disease, but case reports have suggested that the pain might be aggravated over time [70]. However, this is not clearly supported by the measurements in our control group (Figures 15-18, pp. 80-81). In fact, it is difficult to determine whether the pain relief experienced was due to the specific efficacy of the treatment, the natural history of the disease or the phenomenon of regression to the mean [198]. Regression to the mean is a measurement error and can be described as the tendency to score closer to the mean the second time a measurement is performed [199]. Nonetheless, the fact that a difference could be detected over time in the Dercum operated group, but not in the Dercum control group, supports an actual effect of the treatment.

The placebo response

It has been shown that surgery can evoke a placebo response, including both subjective changes and objective effects [200]. However, the magnitude and the duration of the placebo effect varies considerably between different studies [201]. A review on the placebo theory made by Koshi and Short [201] found a study demonstrating a duration of the placebo response up to one year [202] and another up to five years [203]. In terms of the degree of the effect, several studies have demonstrated that the placebo analgesic effect across all individuals is of magnitude 2 out of 10 on a visual analogue scale [201]. In summary, it cannot be excluded that pain relief, at least to some degree, was due to the placebo response and not the surgical treatment.

Other Uncontrollable factors

A limitation of the present study is that we had no possibility to control the use of over-the-counter analgesics. It is possible that such drugs could have affected the levels of neuropeptides and inflammation in adipose tissue.

Considerations regarding the methods of evaluation used

Evaluation of sensitivity (I)

In paper I, validated tests included in the guidelines of quantitative sensory testing proposed by the American Academy of Neurology [204] were used. Previous studies have shown that the reliability of sensitivity tests can be poor if they are not given in a standardised

fashion[205]. However, great care was taken to give them in the same way and by the same trained personnel in all cases.

Other factors that could have influenced the measurements are different uncontrollable variables, such as systolic blood pressure [206], age [207], psychological factors [208], and painful stimuli [209]. However, the patients served as their own controls, so such factors should have less influence.

Evaluation of pain (II)

Measuring pain is a difficult task due to the subjective character of this entity. In paper II, we chose a number of different validated pain assessments to evaluate the effect of liposuction on Dercum's disease.

In terms of the VAS test, Bigatti et al [210] have shown that it has a high correlation with other pain measurements and a high correlation with symptoms in syndromes that encompass pain, such as fibromyalgia.

In terms of the NWC test, Perry et al have concluded it might be less valid for idiopathic chronic pain syndromes because this instrument is sensitive to psychological aspects and could give rise to a distorted perception of pain [211]. On the other hand, Melzack has shown that changes in different psychological variables do not create variability in the word choices [182].

In terms of the PPT measurements, our validation demonstrated that there was no inter-day difference in our measurements. This is in accordance with a study conducted by Nussbaum et al [212]. They concluded that PPT measurements are reliable from day to day, particularly when performed by the same investigator, as in our case. Hence, it is a strength that all measurements were performed by the same investigator. However, some factors might have influenced the results. For example, even though care was taken to always use the same rate of pressure application, our investigator was not timed and therefore differences in the applied rate cannot be excluded. Moreover, investigator expectancy and knowledge of measurement site characteristics could have caused a measurement bias [213].

Instrumental factors are also important. The PPT results are affected by the size of the probe, since the probe diameter determines in which tissue layer the PPT is measured. In fact, Takahashi et al [214] have demonstrated that PPT measured with small probes (1.0 mm diameter) is affected by surface anaesthetics, whereas large probes (1.6 and 15 mm diameters) are not. In other words, the skin nociceptors are suggested to play an insignificant role in the total pain measured when larger probes are used, as they probably measure the pain experienced in deeper tissues. Our probe had a diameter of 14 mm so deeper tissues, such as adipose tissue, were measured. Moreover, pressure transmission is influenced by tissue properties such as thickness [214]. Therefore, we believe that in the investigated patients, with pronounced obesity, mainly adipose nociception was measured and not that of the skin.

Neuropeptides (III)

To measure neuropeptides, laboratory tests with low coefficients of variation were used. This is an obvious strength of the study. However, a weakness is that there are some missing values, as only three substances were measured in the control group. Unfortunately, during the period in which the samples from the controls were analysed, the laboratory could only analyse Sp-SP, Sp-NPY, and Sp- β -End due to administrative reasons. Nonetheless, we had the opportunity to measure all the substances in the operated Dercum patients.

Evaluation of adipose tissue histology (IV)

In this study, all the adipose tissue biopsies were judged by the same pathologist. Studies in anatomical pathology as gold standard has been challenged because of the difficulties in reproducibility of histological diagnosis due to inter-observer variation. This can be explained by the fact that interpretive judgement and personal experience have to be used

by the pathologist to be able to make a histopathological diagnosis [215]. However, in the present study, as the same pathologist judged all the fat biopsies in a blinded fashion, and hence, such factors should be of less influence in this study.

Considerations regarding the results

Pain and the effect of liposuction

Liposuction causes local sensitivity loss. Different mechanisms have been suggested for this loss; however, the main theory concerns direct nerve trauma caused by the cannula. Furthermore, formation of neuromas and other pathophysiological processes of the nerves, during various stages of the healing process, may contribute to sensory loss [216]. However, it has been reported that both subjective and objective normal sensation is restored within ten weeks [216] to eight months [217] postoperatively; even though patchy areas with decreased sensation can remain for longer periods of time if the treated area is large [217]. Our patients were all operated on with suction-assisted liposuction, and should have suffered direct mechanical nerve trauma, and as a consequence have elevated thresholds for sensory perception. However, the first postoperative measurement in this study was conducted three months postoperatively, when sensitivity could have returned to almost normal levels. In other words, the trauma generated by the suction cannulas during liposuction does not seem to have caused permanent nerve damage [218]. Furthermore, in the previously mentioned study [217], sensation was measured with a Vitapul, a device that generates an electric current on the skin. In our study, a vibratory stimulus was used. The vibratory stimulus could spread also to deep or adjacent, normally innervated, tissue and hence these measurements perhaps did not detect local nerve lesions [175]. Nociception is conducted by two types of nerve fibres: the myelinated A-delta fibres, which also conduct the sensation of cold; and more slowly conducting C fibres,

which also conduct the sensation of warmth. Experienced pain therefore has two phases. The first phase is mediated by the fast-conduction A-delta fibres and is associated with an initial sharp pain. The second phase is mediated by the more slowly conducting C-fibres and gives rise to a prolonged, less intense feeling of pain [143]. Based on this, an elevation of thermal thresholds could be expected after liposuction. However, thermal and vibratory thresholds did not differ after liposuction in patients with Dercum's disease.

The white adipose tissue is innervated by the sympathetic nervous system [219]. Dalziel [79] has proposed that the sympathetic nervous system may cause the pain experienced in disorders of painful adipose tissue disease. The pain is thought to be generated by means of signals to the spinal cord from abnormal connections that have arisen between peripheral autonomic and sensory nerves [79]. Tentatively, liposuction avulses not only the sensory nerves but also these abnormal nerve connections. However, the fraction of nerves that is undamaged during liposuction reasonably also comprises a portion of the abnormal connections, and this might explain why the patients' pain is relieved, but not completely eliminated, after liposuction. Moreover, new abnormal connections might arise, which could explain why the patients in our study regained some of the pain a few years post-operatively. Furthermore, the mechanism could be supported by the fact that intravenous administration of lidocaine temporarily relieves pain in patients with Dercum's disease [16, 32, 90, 99, 113-115, 117], as inhibition of abnormal nervous impulse circuits has previously been put forward as a plausible explanation for the effect of lidocaine [99]. In brief, it is unlikely that direct nerve destruction alone explains the pain reduction seen in our patients following liposuction. Furthermore, the reduction in pain in Dercum's disease persisted longer than sensitivity loss normally persists after liposuction in healthy patients.

Nonetheless, the marked effect of liposuction in our patients and the fact that the effect was stable over a long period of time could indicate that liposuction results in a true treatment effect. However, the mechanism by which liposuction diminishes pain in Dercum's disease remains unclear.

It is therefore difficult to determine whether the experienced pain relief was due to the specific efficacy of the treatment, but there are also other factors that have to be considered, such as the natural history of the disease and the phenomenon of regression to the mean (cf. *Considerations regarding potential confounding factors*, pp. 91-92).

Pain and its relation to neuropeptides and inflammation

In the inflammatory pain that sometimes accompanies the inflammatory processes, nociceptive activation in sensory nerve endings results in pain and the release of proinflammatory neuropeptides. The pain elicits neurogenic inflammation, which induces additional pain and thus generates a vicious circle. The most important neuropeptides in this process are calcitonin gene-related peptide (CGRP) and substance P (SP). They trigger local neurogenic inflammation, vasodilation and plasma extravasation. Previously, it has been suggested that Dercum's disease is an inflammatory disease [13, 38, 87].

In study IV, a difference in the inflammatory reaction in the adipose tissue could be seen between patients with DD and healthy obese controls comparing biopsies from the abdomen but not from the knee. In recent years, research has suggested that the adipose tissue in obesity elicits a chronic low-grade inflammatory response that contributes to co-morbidities such as diabetes, increased cardiovascular risk, and liver disease [220-222]. The expanded pool of adipocytes is responsible for the increased production and release of inflammatory mediators such as cytokines. An increased density of macrophages has been observed in the adipose tissue of obese subjects [222, 223]. This may explain why the Dercum patients and the weight-matched healthy obese controls both had elevated inflammation in the adipose tissue.

In brief, the findings in study IV reveal that there is an inflammatory response in the adipose tissue in Dercum's disease. However, this response is not more pronounced than in healthy obese

controls. This contradicts the idea that inflammation is the aetiology of Dercum's disease.

Further contradicting an inflammatory aetiology are the findings in study III, as altered levels of neuropeptides that have previously been seen in different pain conditions could not be clearly demonstrated in Dercum's disease.

SP-LI is a neuromodulator present in several neural pathways associated with pain. Several previous studies on patients with diseases involving chronic idiopathic pain and with conditions associated with pain such as depression [224] and fibromyalgia [132], have pointed out a clear elevation in SP-LI in CSF. However, there are also studies on chronic pain and SP-LI levels that have suggested significantly lower levels in patients with chronic pain syndromes than in healthy controls, especially among patients with chronic neurogenic or idiopathic pain [225]. This divergence may be explained by findings in animal models where it has been proposed that SP may be an important factor in the early response to pain, but insignificant in the maintenance of central sensitisation [226]. This could also explain the normal SP-LI values among our Dercum patients with chronic pain (>3 months).

It has been suggested that the concentration of NPY-LI is an indicator of sympathetic-neuronal output, as it is a neurotransmitter released principally by sympathetic neurons [227]. Previous research has demonstrated that patients with fibromyalgia have elevated plasma levels of NPY-LI [227, 228]. In fact, Martinez-Lavin et al [227] have suggested that an autonomic nervous system dysfunction might be the crucial factor in the pathogenesis of fibromyalgia. In contrast to this, the subjects in this study had slightly decreased levels of NPY-LI in CSF compared to reference values (Table IX, p. 82) and statistically significantly lower levels than the controls ($p=0.048$).

β -END-LI is an endogenous opioid peptide derived from one of three endogenous opioid systems. It plays an important role in the mechanism of pain and an experimentally elevated level of β -END alters the peripheral pain threshold [229]. Furthermore, a small clinical study has suggested that β -END-LI could be decreased in certain chronic painful conditions and normal in others [230, 231].

This is in accordance with the normal levels of β -END found in the Dercum patients. DYN-LI and m-ENK-LI are peptides from the other major endogenous opioid system. The normal levels of β -END, DYN and m-ENK suggest that there is no endorphin deficiency in Dercum's disease.

MSH-LI is one of the peptides derived from melanocortin and is released at varying sites in both the central nervous system and peripheral tissue. It has a variety of functions including immunomodulation, anti-inflammatory effects and facilitation of nerve regeneration following peripheral nerve injury. Furthermore, MSH-LI and related peptides seem to have a role in pain processing and the induction of analgesia [232]. The median γ_2 -MSH-LI was slightly elevated among our subjects compared to reference values. The clinical relevance of this finding remains unclear.

SOM-LI can be found in both the peripheral and the central nervous system and has several functions. Studies using experimental pain models, mainly regarding acute pain, have demonstrated that SOM-LI release can alter the experience of pain, and the release of other neuropeptides [233]. There are few if any previous studies on SOM-LI in chronic pain, and our findings suggest that pain in Dercum's disease cannot be related to changes in SOM-LI.

Conclusions

The present studies highlight pain and inflammation in Dercum's disease and evaluate the treatment of the condition with liposuction. Valuable insights were gained on the effect of liposuction on experienced pain and on postoperative sensitivity. Further insights were gained on inflammatory cells in the adipose tissue and on neuropeptides in this disease.

More specifically:

- There are no significant differences in vibratory and thermal sensation after liposuction in Dercum's disease.
- Liposuction might alleviate pain in patients with Dercum's disease. However, it is difficult to determine whether the effect is due to the actual surgery or to other factors, and how clinically significant the improvement is. Because of these uncertainties, and since not all patients experienced clear pain relief postoperatively, liposuction cannot currently be recommended as the treatment of choice in Dercum's disease.
- Altered, mostly elevated, levels of neuropeptides that have previously been seen in different pain conditions cannot clearly be demonstrated in Dercum's disease.
- There is an inflammatory response in the adipose tissue in Dercum's disease. However, this response is not more pronounced than in healthy obese controls.

Future Outlook

The aetiology of Dercum's disease is still unknown and hence no optimal treatment can be offered. Not all patients experience pain relief following liposuction, and liposuction is a treatment that involves risks for the patient. These factors could indicate that liposuction should not be the treatment of choice for patients with Dercum's disease.

Furthermore, it is possible that Dercum's disease is one of the so-called functional somatic syndromes [196]. Modern research has also revealed that there is a complex relationship between chronic pain and depression. Previous research has indicated that antidepressants have an effect on both pain and quality of life in patients with chronic idiopathic pain [234-237]. Presently, patients in these domains of disease are probably best treated by more general strategies and a multimodal approach from a holistic perspective [196].

Summary

Dercum's disease is a rare condition characterised by obesity, chronic pain (>3 months) in the adipose tissue and a number of diffuse associated symptoms, such as fatigue and malaise. The aetiology of the disease is unknown. The experienced pains are often disabling and resistant to most tried treatments, such as analgesics. However, a number of case reports have been published on the promising effect of liposuction.

The aims of this study were to investigate the effect of liposuction on thermal and sensory sensation, to examine the effect of liposuction on the pain experienced by patients, to examine neuropeptide levels in cerebrospinal fluid and plasma, and to investigate the inflammatory signs in adipose tissue of patients with Dercum's disease.

A total of 111 patients with Dercum's disease were recruited to the study. The first 53 patients were operated on with liposuction and the following 58 patients were un-operated controls. In addition, 41 healthy obese women and 11 normal weight healthy women were recruited as different control groups. The patients and controls were followed for five years. Not all groups were included in every study.

In study I, vibratory and thermal thresholds were determined preoperatively and after liposuction in women with Dercum's disease. The results showed that there were only small differences in sensation postoperatively, as compared with preoperatively, and none of these were statistically significant. In study II, pain was measured in patients and in controls. The study indicated that liposuction might alleviate pain in patients with Dercum's disease. However, it is difficult to determine whether the effect was due to the actual surgery or to other factors. In paper III, neuropeptides were measured in cerebrospinal fluid and in plasma from patients and controls. The results showed that altered levels of neuropeptides that have

previously been seen in different pain conditions cannot clearly be demonstrated in Dercum's disease. In paper IV, adipose tissue biopsies were obtained by surgical biopsy from all patients and controls. The results revealed that there was an inflammatory response in the adipose tissue of patients with Dercum's disease. However, the response was not more pronounced than in healthy obese controls.

Collectively, we demonstrated that liposuction cannot yet be recommended as the standard treatment for Dercum's disease. Furthermore, we showed that neuropeptide levels seem to be normal and that the aetiology of the disease might not be inflammatory.

Populärvetenskaplig sammanfattning på svenska - Summary in Swedish

Dercums sjukdom är ovanlig sjukdom som kännetecknas av uttalad kronisk smärta (>3 månader) i fettväven, kombinerad med övervikt och ett antal mer diffusa associerade symptom, såsom trötthet och allmän sjukdomskänsla. Orsaken till sjukdomen är okänd. Smärtorna är ofta handikappande och de flesta prövade behandlingar, såsom traditionella smärtstillande, ger otillräcklig effekt på smärtorna. Att ta reda på vad som orsakar Dercums sjukdom samt utveckla nya och förbättrade behandlingar för patienterna är angeläget. Syftet med detta projekt var att undersöka om fettsugning kan ge patienterna smärtlindring samt undersöka orsaken till sjukdomen.

Totalt har 166 kvinnor deltagit i studierna. Av dessa hade 114 Dercums sjukdom och 41 var friska överviktiga kontrollpatienter och 11 friska normalviktiga kontroller. Femtio två av Dercumpatienterna behandlades med fettsugning på de mest smärtsamma områdena. Övriga Dercumpatienter var sjuka kontroller.

I det första delprojektet visades att patienternas vibrations- och temperaturkänslor inte förändras efter fettsugning. I det andra delprojektet visades att Dercumpatienternas smärtor minskades av fettsugningen, men att det är oklart om smärtlindringen beror på själva fettsugningen eller på andra faktorer. I det tredje delprojektet visades att koncentrationen av neuropeptider, ämnen som bildas i nervsystemet och som fungerar som signalmolekyler inte är förändrad i hjärn-ryggmärgsvätskan eller i blodet, vid Dercums sjukdom. Förändrade neuropeptidkoncentrationer har tidigare setts vid vissa andra smärtsjukdomar. I det fjärde delprojektet visades att Dercumpatienterna inte har ökad inflammation i sin fettväv.

Tillsammans har dessa studier visat att fettsugning skulle kunna vara ett behandlingsalternativ vid Dercums sjukdom, men att fler studier behövs innan metoden kan användas som standardbehandling. Dessutom har vi visat att patienterna inte har förändrad neuropeptidkoncentration eller förhöjd inflammation i sin fettväv. Detta talar emot att en förändrad neuropeptidkoncentration eller en inflammatorisk reaktion kan förklara patienternas smärter.

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