The Mythology Behind Subcutaneous Adipose Tissue Disorders (a.k.a Lipedema)

Elliott Weiss MD FRCPC

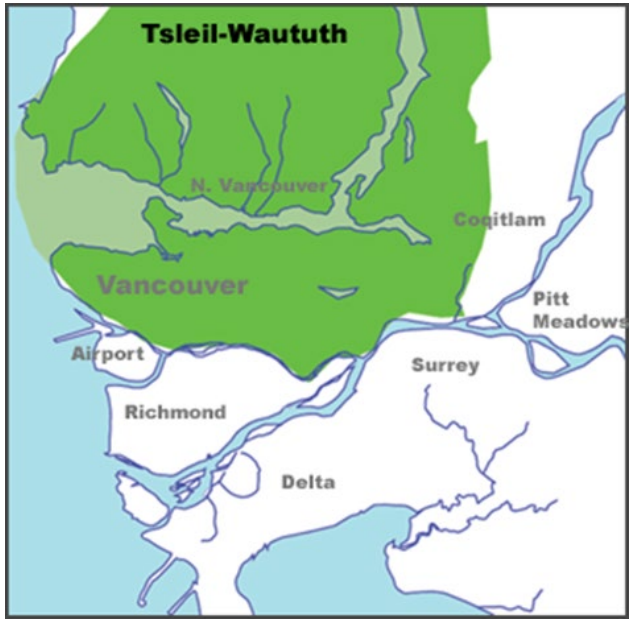
Consultant, Physical Medicine & Rehabilitation

VCH Family Practice Rounds

Tuesday, January 24, 2023

We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



Relevant Disclosures

- none

Objectives

- Define lipedema versus lymphedema versus obesity
- Diagnosis and differential diagnosis
- Pathology
- Management including controversies

While not directly discouraging consultations, the role of this talk is to reduce the need for consultations through improved primary care

Why would a physiatrist present on Lipedema?

- Historically, an orphan diagnosis but not a ‘rare disease’
- In Europe, it does not belong to the Orphanet nomenclature of rare diseases.
- Can be superficially mistaken for lymphedema
- Historically, management was physical modalities (massage, compression)
- With no pharmacological or surgical treatments, lipedema fell off the radar of medical education and clinical practice.

(https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=77243)

Lymphedema on the Run

Elliott Weiss MD FRCPC

Physical Medicine and Rehabilitation

November 26th, 2021


LYMPHEDEMA
LIPEDEMA

Why present on this topic?

1. relevant
2. common
3. poorly understood
4. patients are understandably upset by our collective lack of knowledge and solutions

The ‘champion’ in the US: Dr. Herbst: Endocrinologist

- She is well published
- i.e. Buck, Donald W. II MD; Herbst, Karen L. MD, PhD†, Lipedema: A Relatively Common Disease with Extremely Common Misconceptions. Plastic and Reconstructive Surgery - Global Open 4(9):p e1043, September.
- Dr Karen Herbst is an American endocrinologist. She is noted for her work in endocrinology, Dercum's Disease, diabetes and metabolism at VA San Diego Hospital and research into Lipedema at University of Arizona College of Medicine, Tucson

What's going on with fat tissue and cells (adipocytes) in obesity

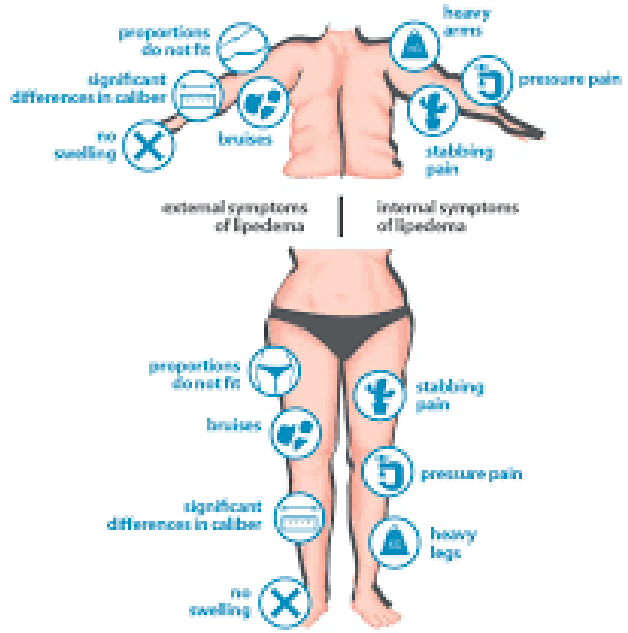
- Largest endocrine organ in the body and is hormonally active
- Host for immune cells (monocytes/macrophages, mast cells, lymphocytes)
- Excessive fat is associated with an inflammatory response
- With fat accumulation, decreased blood and lymphatic flow
- Accumulation of fluid, cellular waste, proteins, and metabolic byproducts within the extracellular matrix (ECM)
- A hypoxic environment with adipocytes most affected being the most distant from their nutrient and oxygen sources.
- Localized hypoxia associated with scarring and fibrosis of underlying tissues within the ECM, which leads to additional hypoxia.

Disorders of Fat Metabolism: Obesity

- Obesity is a chronic disease characterized by the abnormal or excessive accumulation of body fat, affecting more than 1 billion people worldwide.
- Obesity is commonly associated with other metabolic disorders, such as type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular diseases, chronic kidney disease, and cancers.
- Factors such as a sedentary lifestyle, overnutrition, socioeconomic status, and other environmental and genetic conditions can cause obesity.
- Many molecules and signaling pathways are involved in the pathogenesis of obesity, such as nuclear factor (NF)-κB, Toll-like receptors (TLRs), adhesion molecules, G protein-coupled receptors (GPCRs), programmed cell death 1 (PD-1)/programmed death-ligand 1 (PD-L1), and sirtuin 1 (SIRT1).

Ming Yang, et al. The Related Metabolic Disease and Treatment of Obesity. Healthcare 2022, *10*(9), 1616;

Lipedema



Locations of excess fat accumulation

- upper arms especially triceps folds
- hips
- buttocks
- thighs
- lower legs

- spares feet and upper trunk
- can feel nodular, tender to touch, prominent superficial veins
- can develop in the lateral abdomen
- in severe disease, can develop pannus with secondary lymphedema

Incidence

“Lipedema is one of the most underdiagnosed fat disorders worldwide. It is estimated that anywhere from 10 to 18 million women in the USA alone have Lipedema. That means nearly 11 percent of the female population suffers from this connective tissue disorder”.

https://totallipedemacare.com

What are Subcutaneous Adipose Tissue Diseases/Adipofascial Disorders (SAT)?

- Involves adipose tissue including adipocytes and fascial tissues.
- Falls within the spectrum of “obesity”
- Definition of obesity:
    - Overweight and obesity are defined as abnormal or excessive fat accumulation
    - Presents a risk to health.
    - A body mass index (BMI) over 25 is considered overweight, and over 30 is obese. (WHO)
- SAT: generalized (obesity) versus localized (lipedema)
- Rare Conditions (out of scope today)
    - familial multiple lipomatosis,
    - angiolipomatosis,
    - Dercums Disease
    - multiple symmetrical lipomatosis (Madelung Disease)
- Lipedema primarily affects women

Adipofascial Tissue Disorders (Persistent Fat)

- Difficult to lose weight through standard non-surgical (dietary choices/exercise) or surgical weight loss approaches
- Tissue fibrosis
- Rule out hypothyroidism and other metabolic conditions (typically endocrinological)
- Considered to be a condition where fat grows abnormally (amount or structurally)
- Changes occur within blood/lymphatic vessels, immune and mesenchymal cells, fascia, interstitial matrix (loose connective tissue)

Other fat disorders: Lipodystrophies, cellulite, obesity, visceral fat, perivascular fat are out of scope in this discussion

Cellulite (wiki)

The herniation of subcutaneous fat within fibrous connective tissue that manifests as skin dimpling and nodularity, often over the pelvic region (specifically the buttocks), lower limbs, and abdomen.

Cellulite occurs in most post-pubescent females.

A review gives a prevalence of 85–98% of women indicating that it is physiological rather than pathological.

- hormones to heredity
- metabolism and physiology
- diet and exercise habits
- obesity
- sex-specific dimorphic skin architecture
- alteration of connective tissue structure
- the microcirculatory system
- the extracellular matrix
- subtle inflammatory alterations

Lipedema: Stage 1:

Fat accumulation: pelvis, buttocks, hips distal to ankles; smooth skin with enlarged s/c fat
Skin surface is normal
Palpable pea-sized nodules within the adipose tissue
(enlarging areas of fibrosis within the ECM surrounding a fat lobule)

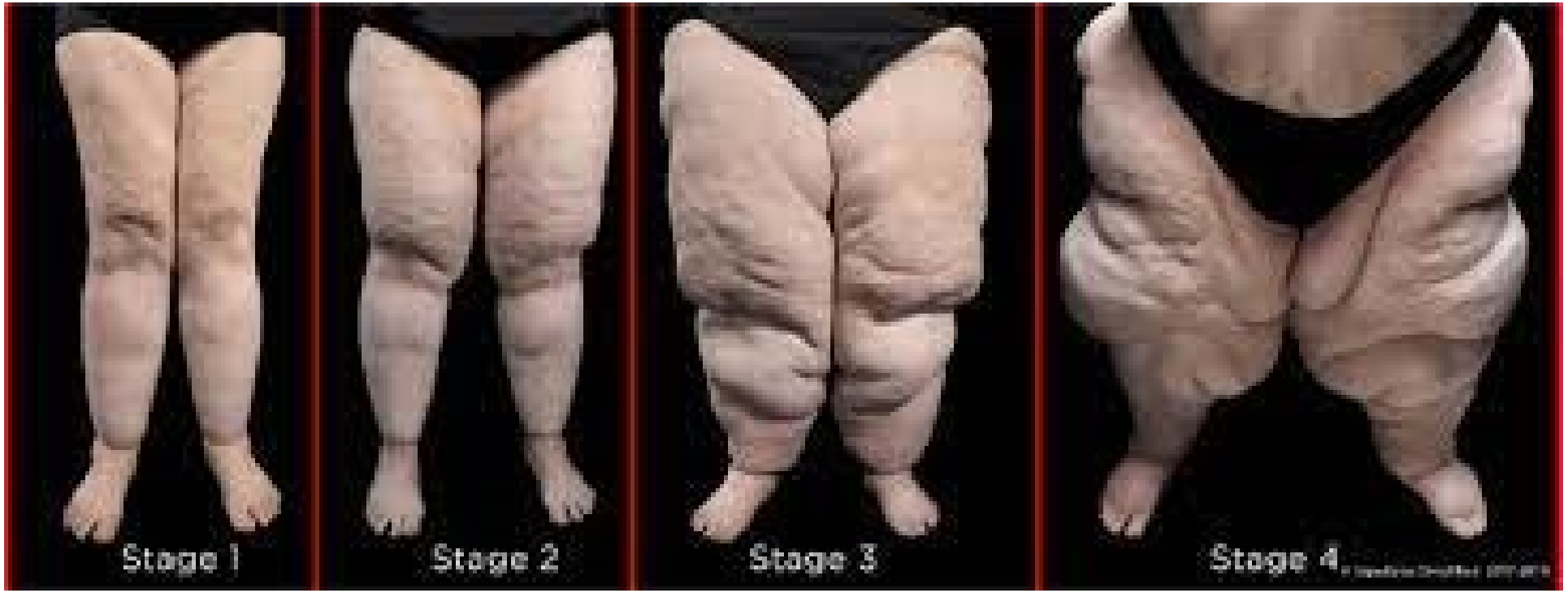
Lipedema: Stage 2:

Uneven skin with indentations in the tissue and lipomatous masses
Skin is uneven, with indentations similar to cellulite
Thickening and contractures of underlying connective tissue/fascia with a variety of hypodermal collections

Lipedema: Stage 3

Large extrusions of fat tissue with deformity around knees and thighs.
Lobular extrusions of skin, fat and fascial tissue
Loss of tissue elasticity with fascia thickening.
Blood and lymphatic fluid flow diminished
Increased inflammation producing fibrosis which superficially becomes palpable.
Skin becomes looser and less adherent to subdermal tissues

Lipedema Stage 4

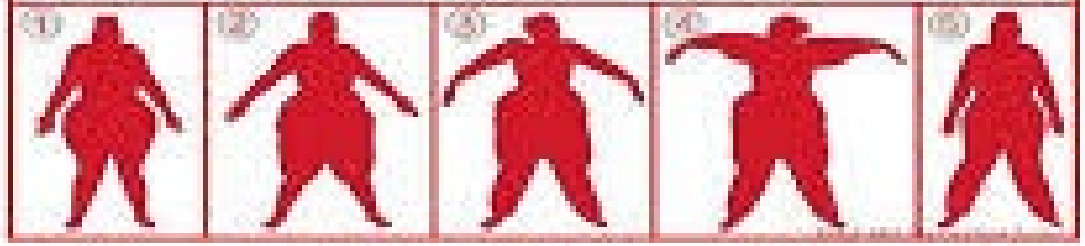


Not included in some classification systems
Referred to as lipo-lymphedema

4 Stages of Lipedema

Stage 1	Stage 2	Stage 3	Stage 4
Smooth and soft skin, enlargement of the underlying hypodermis	Skin indented over palpable pearl sized nodules ("peau d'orange")	Folds and divots over defining, larger fat masses	Concomitant lymphedema (lipo-lymphedema)

5 Types of Lipedema



Type 1	Type 2	Type 3	Type 4	Type 5
Pelvis, buttocks & hips	Buttocks to thighs	Buttocks to ankles	Arms	Lower legs

Lipedema: Clinical Diagnosis/Characteristics

- Women thru puberty, childbirth, menopause
- Typically, buttocks, thighs and legs but 80% have it in arms
- Don’t need to be obese
- Waist relatively normal with no obesity
- Painful fat not necessary/often complains of aching
- Hands/feet unaffected
- Positive Cuff Sign (not pathognomonic)
- Thickening of subdermal deeper tissue with fibrosis
- Family history (women)
- Loss of tissue elasticity
- Easy bruisability

Types of Lipedema:
most common is a combination of II and IV or III and IV

AN OVERVIEW FOR CLINICIANS

LIPEDEMA

the DISEASE THEY CALL FAT

Erez Dayan, MD | Harvard Medical School
Julie N. Kim, MD | University of Texas Health Science Center
Mark L. Smith, MD, FACS | Zucker School of Medicine at Hofstra/Northwell
Catherine A. Seo, PhD | The Lipedema Project
Robert J. Damstra, MD, PhD | Nij Smellinghe Hospital
Prof. Wilfried Schmeller, MD | Hanse-Klinik
Yvonne Frambach, MD | Hanse-Klinik
Matthew A. Carmody, MD | Harvard Medical School
Prof. Etelka Földi, MD | Földiklinik for Lymphology

Foreword by Stanley G. Rockson, MD
Stanford University School of Medicine

Pathophysiology

- In women: ?hormonally related as soft tissue flexibility can apparently be influenced by estrogen levels (noted between ovulations and post-ovulation)
- In men (rare): ?association with lowered testosterone levels/liver disease (testosterone/estrogen ratio)
- Current theories are only speculative

a. Hypoxemia Theory: Herbst and others

- Increased compliance from connective tissue structures affect ability of ECM to maintain fluid, protein, homeostasis, etc.
- Is there a relationship between hypermobility (EDS) and lipedema?
- ?malfunctioning lymphatic vessels affect compliance in fascia, cellular composition or function, with decreased lymphatic efficiency
- Producing local areas of hypoxia within the ECM – secretion of “hypoxia inducible factor” by local adipocytes which stimulates vascular endothelial growth factor, which turns on stem cells within the adipose tissue.
- In Lymphedema, lymphatic fluid induces adipogenesis.
- Does dysfunctional lymphatic vessels cause leakage, increased inflammatory response in lipedema?

b. **Abnormal Lymphatic Theory**

- Primary defect in lymphatic function (not structural)
- Mismatch between number of lymphatic vessels versus blood micro-vessels
- Normal lymphangioscintography, especially in early stages discounts this but issue may not be structural and/or resolution of current technologies is insufficient.

Obesity and Cardio-Metabolic Health

- Femoral adipose tissue is considered cardioprotective
- In later stages of Lipedema, this capacity is diminished as reflected in LDL and cholesterol levels, HbA1c, and BP.
- TTE may demonstrate changes within left ventricular function (apical rotation)

Biomarkers for Lipedema (Is Lipedema a form of Lymphedema?)

- Ma, Rockson, and Oliver postulated that Platelet Factor 4 levels might be useful to identify obese individuals in which at least some of the underlying pathogenesis of excessive fat accumulation could be subtle and associated with asymptomatic lymphatic leakage.
- They hypothesize that in lipedema, lymphatic dysfunction plays a role in the pathogenesis of the disease.
- The discovery of this biomarker creates potential for a blood test to diagnose lymphatic diseases in outpatient settings including lipedema.

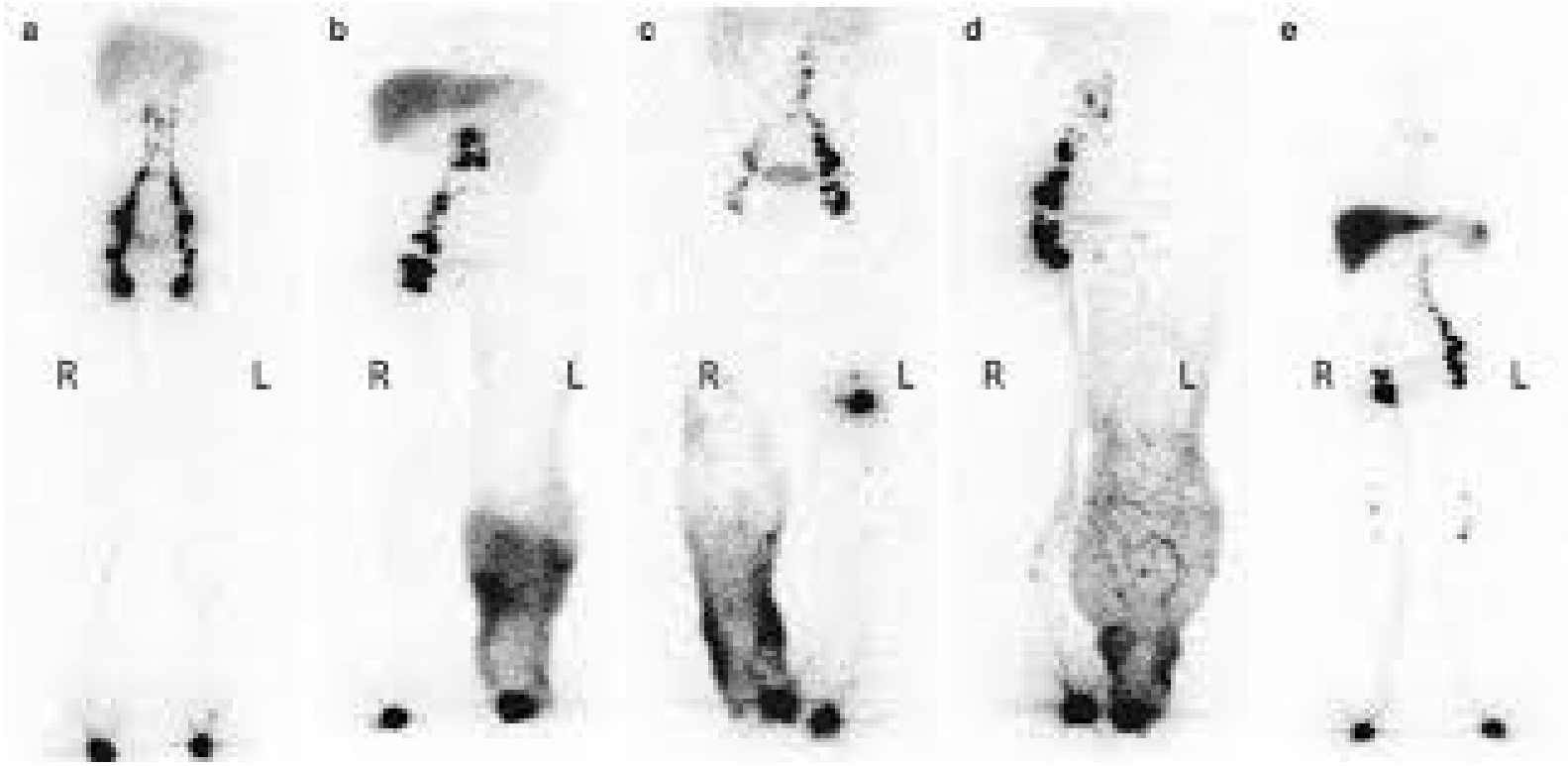
Ma, W et al. Platelet Factor 4 is a Biomarker for Lymphatic-Promoted Disorders. JCI Insight. 2020;5(13):e135109

Stem Cell Research

- Ishaq et al found significant differences in gene expression and lipid and metabolite profiles in tissue, ADSCs, and adipocytes from lipedema patients compared to non-affected controls.
- Functional assays demonstrated that dysregulated Bub1 signaling drives increased proliferation of lipedema ADSCs, suggesting a potential mechanism for enhanced adipogenesis in lipedema.
- Importantly, the characterization of signaling networks driving lipedema identifies potential molecular targets, including Bub1, for novel lipedema therapeutics

Ishaq, Musarat, et al. Key signaling networks are dysregulated in patients with the adipose tissue disorder, lipedema. International Journal of Obesity. https://doi.org/10.1038/s41366-021-01002-1

Nuclear Medicine Lymphangiography



Imaging of Lipedema

- Lymphangioscintography: can differentiate between primary lymphedema (abnormal) and lipedema (normal).
- DEXA: used to assess whole body composition including lean body mass (research)
- Ultrasound: thinner skin and thicker/hypoechogenic subcutaneous fat (research)
- MRI: non-specific changes without a standardized technique or approach (not MRI-lymphangiography)


LIPEDEMA
be GONE
with VASER
sculptor that eliminates
fat and smoothes
the skin's surface

Treatment: Diet

- Few quality studies regarding dietary approaches
- Patients self-report that they lose weight in non-affected areas, disproportionately affecting body image
- Lipedema fat is generally resistant to weight loss
- Excessive intake associated with disproportionate fat accumulation.
- Reduce processed carbohydrates to reduce adipogenesis
- There is no evidence for long-term weight loss management

Is there a truly a role for pumps?

Treatment: Physical Modalities

- Complete Decongestive Therapy
- Manual Lymphatic Drainage
- Pneumatic Devices
- Compression garments
- Deep Tissue massage

Treatment: Compression Garments (CG)

- No quality evidence CG are helpful in lipedema
- Primarily for ’fluid/edema’ reduction but not clearly measurable except with secondary lymphedema
- Challenging to fit
- Challenging to don and doff
- Expensive: Usually need to customize
- Cosmetic benefits
- Yoga wear/tights better tolerated and improved compliance

Off the Shelf Compression

- https://knix.ca/collections/activewear/products/hitouch-high-rise-legging

- HiTouch High Rise Legging XXXXL $98.00

Treatment: Exercise

- Improves blood and lymphatic flow
- Graded exercise
- Fibrosis from fatty tissue may affect muscle function, structure and/or metabolism accounting for a relative loss of quadriceps strength (age and weigh-matched)
- Water-based exercises endorsed due to compressive effects of water to soften fibrotic tissues

Treatment: Venous Disease

- Co-morbidity present in 25% of cases
- No evidence surgical management is of benefit
- Some literature indicates lymphedema can develop following surgical treatment of venous insufficiency

Treatment: Bariatric Surgery

- Women without upper body obesity may respond poorly to bariatric surgery
- Lack of reduction in lower abdomen, thigh and leg dimensions post-operatively may retrospectively establish or confirm the diagnosis of lipedema
- Role of bariatric surgery could improve glucometabolic outcomes rather than body mass.
- Potentially could worsen body image anxieties.

Treatments: medications to avoid

- Thiazolidinediones (rosiglitazone): increased fluid retention
- Calcium Channel Blockers: fluid retention
- Oral Corticosteroids: weaken tissue/fluid retention/rebound inflammation
- NSAID: fluid retention
- Sex Hormones: fluid retention/possible link of estrogens to development)
- Beta-Blockers: fluid retention
- Clonidine: fluid retention
- Gabapentin: fluid retention
- Furosemide: concentrates protein in interstitial organ halting fluid flux

Liposuction

After being approved for full body surgeries, 3 Winnipeg women said Manitoba Health denied further treatment CBC News January 15, 2023

“Province pulls medical coverage for 3 Winnipeg women suffering from chronic disease” CBC News January 15, 2023

- To remove painful fat nodules and diseased tissue caused by lipedema, surgeons use specialized liposuction throughout multiple surgeries. There are currently no surgeons in Canada who are qualified to perform the procedure, so lipedema patients need to go through Manitoba Health's out-of-province medical referrals and look to the U.S. or Germany.
- All three women maintain the surgeries to treat lipedema are life-sustaining and life-changing, as it allows them to move more freely and reduces their pain and swelling.
- Manitoba Health wrote that it consulted with the Section of Plastic Surgery of Manitoba — a unit within the Max Rady College of Medicine at the University of Manitoba — and found there wasn't enough objective data that surgery on late-stage lipedema patients is the standard of care.


LIPÖDEM UND LYMPHÖDEM
IN DEN WECHSELJAHREN
Wie ich zum
Lipödem und
zum Rock kam

Treatment: Liposuction CADTH 2019

- Evidence of limited quality from five uncontrolled before-and-after studies suggests that liposuction may be effective in reducing the size of the extremities and complaints associated with lipedema such as spontaneous pain, easy bruising, sensitivity to pressure, impairment in quality of life, restrictions to mobility, edema, feeling of tension and general impairment.
- The findings have to be interpretated with caution, given that they are from single arm, non-randomized studies based on patient's self-assessment data collected using tools that have not been validated for the assessment lipedema-related complaints.
- One clinical practice guideline recommends tumescent liposuction, performed by a skilled healthcare professional at a specialized facility, as the treatment of choice for patients with a suitable health profile and/or inadequate response to conservative and supportive measures. The strength of the recommendations in the clinical guidelines and links to supporting evidence were not provided.

https://www.cadth.ca/liposuction-treatment-lipedema-review-clinical-effectiveness-and-guidelines (2019)

Treatment: Liposuction CADTH 2022

Liposuction for Lipedema: 2022 Update

- A 2022 UK guideline recommends that the liposuction procedure for treatment of lipedema should only be used in the context of research because of inadequate efficacy and safety data.
- A 2021 US guideline recognizes that liposuction is currently the only available technique for removing abnormal lipedema tissue. The guideline has a series of consensus statements on patient selection, indications for liposuction, prevention of procedure-related adverse events, and pre- and post-surgical management.
- There were no recent studies on the clinical effectiveness of liposuction compared with no treatment or to alternative treatments for the treatment of lipedema.

Rama B. Rao, M.D et al. Deaths Related to Liposuction.
NEJM May 13, 1999; 340:1471-1475

Abstract

BACKGROUND

- The technique of tumescent liposuction involves the subcutaneous infusion of a solution containing lidocaine, followed by the aspiration of fat through microcannulas. Although the recommended doses of lidocaine are as high as 55 mg per kilogram of body weight, few safety data are available. Since reporting of adverse events associated with tumescent liposuction is not mandatory, the incidence of complications and deaths is unknown.

METHODS

- We identified **5 deaths after tumescent liposuction among 48,527 deaths** referred to the Office of Chief Medical Examiner of the City of New York between 1993 and 1998. The patients' records and post-mortem examination results were reviewed to identify common contributory factors.

RESULTS

- The five patients had received lidocaine in doses ranging from 10 to 40 mg per kilogram. Other drugs, such as midazolam, were also administered. Three patients died as a result of precipitous intraoperative hypotension and bradycardia with no definitively identified cause. Post-mortem blood lidocaine concentrations in two of the patients were 5.2 and 2 mg per liter. One patient died of fluid overload, and one died of deep venous thrombosis of calf veins with pulmonary thromboembolism after tumescent liposuction of the legs.

CONCLUSIONS

- Tumescent liposuction can be fatal, perhaps in part because of lidocaine toxicity or lidocaine-related drug interactions.

National Institute for Health and Care Excellence (UK)

1.1 Evidence on the safety of liposuction for chronic lipoedema is inadequate but raises concerns of major adverse events such as fluid imbalance, fat embolism, deep vein thrombosis, and toxicity from local anaesthetic agents. Evidence on the efficacy is also inadequate, based mainly on retrospective studies with methodological limitations. Therefore, this procedure should only be used in the context of research.

1.2 Further research should report:

- patient selection, including age, effects of hormonal changes (which should include effects seen during puberty and menopause) and the severity and site of disease
- details of the number and duration of procedures, the liposuction technique used (including the type of anaesthesia and fluid balance during the procedure), and any procedure-related complications
- long-term outcomes, including weight and body mass index changes
- patient-reported outcomes, including quality of life.

1.3 Patient selection should be done by a multidisciplinary team, including clinicians with expertise in managing lipoedema.

1.4 The procedure should only be done in specialist centres by surgeons experienced in this procedure.

https://www.nice.org.uk/guidance/ipg721/chapter/1-Recommendations

Standard of Care for Lipedema in the United States (2021)

Extensive review of current approaches and standard of care.

Consensus-based only with eighty-five consensus statements.

Liposuction: Lipedema reduction surgery is currently the only available technique for removing abnormal lipedema tissue such as adipocytes, nodules, fibrotic extracellular matrix, and other non-adipocyte components. It is also the only treatment that slows progression of lipedema and ideally would be performed before complications and disabilities from lipedema develop. (Level C evidence)

Herbst, Karen, et al. Standard of Care for Lipedema in the United States. Phlebology 2021 Dec: 36(10) 779-796

Dr. Granzow's Lymphedema/Lipedema Podcast
with Sean Mulroney & Brandon Glore

Treatment: Liposuction

- Liposuction is the main surgical interventions for lipedema.
- Commonly used liposuction methods for lipedema are tumescent anesthesia (TA) liposuction (lidocaine/epinephrine), and water-assisted (WA) liposuction
- In TA liposuction, tumescent is infused in the subcutaneous tissues to cause the fat cells to swell and vessels to constrict; then blunt micro-cannulas are used to suction the fat.
- WA liposuction uses a pressure spray of tumescent fluid to dislodge the fat from the connective tissue, rather than utilizing a cannula.
- Unlike traditional liposuction, both TA and WA liposuction rely on the local anesthetics in the tumescent fluid and do not require general anesthesia.

CADTH https://www.cadth.ca/liposuction-treatment-lipedema-review-clinical-effectiveness-and-guidelines

LIPEDEMA

is very common, it is often under and misdiagnosed as obesity by the medical community.

Jaime S. Schwartz, MD, FACS

Treatment: Liposuction

- German technique but liposuction is available in Canada and USA.
- Typically considered to be cosmetic surgery and private pay.
- German technique (lymphatic sparing): tumescent (wet) technique (with or without laser)
- Done in stages (up to 5).
- Most of the outcome studies suggest favourable outcomes but not randomized or controlled.
- Reported outcomes: less pain, swelling, skin issues, improved mobility, and appearance.
- Reduced need for decongestive therapy on a sustained basis

Treatment: Liposuction

Herbst: “Liposuction should be considered for women with lipedema who fail conservative measures and following weight loss with medications and/or bariatric surgery”

Treatment Options in Lower Mainland

- Complete Decongestive Therapy: Very Expensive
- Manual lymphatic drainage: Expensive and ongoing costs
- Compression garment: doesn’t need to be custom or medical grade
- Healthy dietary choices
- Maximize activity levels


Is Lipedema
Liposuction
Covered by
Insurance?

- The liposuction procedure was developed as a purely cosmetic surgical procedure to improve the aesthetic appearance of targeted body areas and that is still the goal of most liposuction procedures performed today. **Medical insurance providers consider all liposuction procedures to be cosmetic procedures with a few rare exceptions**. Nearly all insurance plans have a policy exclusion language for liposuction procedures.
- Medical insurance providers in the United States are critical of published research on lymph sparing liposuction for Lipedema. Although there are several surgeons in the US performing the procedure for Lipedema and showing significant improvement in Lipedema symptoms and improved quality of life, most of the larger studies published in peer-reviewed medical journals showing the safety and effectiveness of lymph sparing liposuction have been done in Europe.
- **Most health insurers chose not to pay for lymph sparing liposuction for Lipedema because their medical reviewers are not convinced by the European medical literature on the safety and effectiveness of liposuction or lymph sparing liposuction.** In this case, the insurance company may call the treatment "**experimental".**

Take Home Message 1

Take Home Message 2

- Lipedema is a very different disease than generalized obesity or cellulite.
- It typically does not respond well to obesity treatments, both non-surgical and surgical
- The pathology is complex, has a genetic component, and is probably hormonally related.
- It is a chronic inflammatory condition.
- Treatment: education, education, education
- Lifestyle modification, compression, good dietary practices are all important.
- From a cosmesis perspective, the role for liposuction can be helpful but quality evidence is lacking.
- From a medical management perspective, there is less quality evidence to support liposuction.

Resources:

- BC Lymphedema Association
- Lipedema Foundation: www.lipedema.org
- The Lipedema Project: https://lipedemaproject.org
- Lipedema Simplified: https://lipedema-simplified.org
- Lipoedema UK http://www.lipoedemaladies.com – support group
- Lipoedema Australia Support Society (lass) lipedemaaustralia.com.au


Thank You!
No wonder we got nothing out of it.