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Liposuction for the Treatment of Lipedema: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

AE	Adverse event
CBT	Cognitive behavioral theray
CDT	Complex decongestive therapy
CI	Confidence intervals
MLD	Manual lymph drainage
NRS	Non-randomized study
PRO	Patient-reported outcome
QoL	Quality of life
SD	Standard deviation
VAS	Visual analog scale

Context and Policy Issues

Lipedema is a disorder characterized by large amount of subcutaneous fat in the upper and lower legs due to both hyperplasia and hypertrophy.[1] It occurs almost exclusively in females, although a few cases in men have been reported.[1,2] The condition is relatively rare and often seen in patients with a family history of the disease.[1,2] Lipedema does not yet have a registered diagnosis in the International Classification of Diseases (ICD-10) of the World Health Organization (WHO), making it difficult to establish its prevalence.[2] However, lipedema is believed to affect nearly 11% of adult women,[3] with noted significant differences in prevalence worldwide.[2,4,5] The literature search for this report did not find epidemiological data for lipedema in Canada.

The cause of lipedema is unknown, and it is likely that the condition is frequently misdiagnosed or wrongly diagnosed as lifestyle-induced obesity or lymphedema (i.e., localized fluid retention and tissue swelling).[2,6] However, although lipedema and obesity can co-occur, unlike obesity, lipedema usually targets the legs and thighs, without affecting the feet or hands, and the adipose tissue in lipedema is painful.[1,4,7-9] The lymphatic system remains unimpaired in the initial stages and can keep up with the increased amount of interstitial fluid.[1,7] However, patients with lipedema may develop secondary lymphedema (lipolymphoedema) if the fatty deposits compromise the lymphatic system.[8]

Lipedema targets both legs (and sometimes, also both hands) to the same extent and has a bilateral, nearly symmetrical presentation.[2-5] The excessive fat deposits are typically unresponsive to traditional weight loss interventions such as physical activity or dietary measures.[1,6,9] Symptoms of the condition include pain in the lower extremities, particularly with pressure, loss of strength, easy bruising, and deterioration in daily activity levels that can greatly impact the health and quality of life of the individual with lipedema.[1,2,6]

Untreated lipedema may result in secondary problems including osteoarthritis, reduced mobility, psychological impairment, and lowered self-esteem.[4] Over time, the weight of the excessive fat build-up can cause the knees to knock inward or droop to the side of the leg, and impair the inability to walk.[10] As mentioned, in the later stages, secondary lymphedema can occur due to imbalance in the amount of fluid produced and drained by the lymphatic system.[1-3,6,7,10] Lipedema poses a significant psychosocial burden for most patients, and associated effects often limit capacity for exercise. In severe cases, lipedema may lead to absence from work or occupational disability.[1]

There is no known curative therapy for lipedema. The primarily focus of treatment is to reduce its related lower extremity symptoms, disability, and functional limitations to improve patients' quality of life, as well as preventing disease progression.[1-3,6,11] Treatment is divided into conservative therapy and surgical interventions. The conservative therapy includes promotion of individually adjusted healthy lifestyle, combined decongestive therapy (CDT), and other supportive measures, such as psychosocial therapy and orthopedic counseling.[2] Conservative therapy can alleviate some lipedema symptoms such as heaviness, pain, and secondary swelling.[12] However, these benefits are short-lived, usually requiring repeat treatment within days.[9]

Liposuction is the main surgical interventions for lipedema.[5] Commonly used liposuction methods for lipedema are tumescent anesthesia (TA) liposuction, and water assisted liposuction (WAL).[2] 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.[3,13,14] Water assisted liposuction uses a pressure spray of tumescent fluid to dislodge the fat from the connective tissue, rather than utilizing a cannula.[10] Unlike traditional liposuction, both TA and WAL rely on the local anesthetics in the tumescent fluid and do not require general anesthesia.

The objective of this report is to summarize the evidence regarding the clinical effectiveness of liposuction for the treatment of lipedema and the recommendations of evidence-based clinical guidelines regarding its use for this condition.

Research Questions

1. What is the clinical effectiveness of liposuction for the treatment of lipedema?
2. What are the evidence-based guidelines regarding the use of liposuction for the treatment of lipedema?

Key Findings

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 patients' 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.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including OVID Medline, OVID Embase, PubMed, the Cochrane Library, University of York

Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were liposuction and lipedema. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2009 and May 09, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles, and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Individuals with lipedema (also called lipoedema), or lipolymphedema (individuals with lipedema and secondary lymphedema)
Intervention	Liposuction (any type)
Comparator	Q1: No treatment; wrapping/compression; drainage; combined decongestive therapy (e.g., manual lymphatic drainage and wearing compression garments) Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., reduced swelling, pain, bruising or discomfort; easier ambulation; improved quality of life) and safety Q2: Guidelines
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1; they were duplicate publications or were published before 2009. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included uncontrolled, before-and-after studies were critically appraised using the Downs and Black checklist,[15] and the clinical guidelines[2] were critically evaluated using the Appraisal of Guidelines for Research & Evaluation, version 2 (AGREE II instrument.[16] Summary scores were not calculated for the included studies; instead, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 128 citations were identified in the literature search. Following screening of titles and abstracts, 111 citations were excluded, and 17 potentially relevant reports from the electronic search were retrieved for full-text review. The grey literature search did not identify any additional relevant publications. Of the 17 potentially relevant articles, 11

papers were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised five uncontrolled before-and-after studies,[1,4,9,11,12] and one clinical guideline.[2] Appendix 1 presents the PRISMA[17] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Five uncontrolled before-and-after studies[1,4,9,11,12] and one clinical guideline[2] were included in this report. The before-and-after studies[1,4,9,11,12] were published between 2011 and 2019. They were designed to explored postoperative changes in complaints among lipedema patients who underwent liposuction using questionnaires and evaluating outcomes of interest quantitatively.

The clinical guideline[2] was published in 2017. It was developed by a task force of medical professionals from diverse specialties organized by the Dutch Society of Dermatology and Venereology Inputs were invited from Dutch organizations and patient representatives. Evidence for the guideline was based on a systematic analysis of English and German literature published up to June 2013. The studies were retrieved from PubMed, MEDLINE, COCHRANE, and Cinahl databases. However, the study designs included in the literature search were not reported. The method of guideline development was based on both the Chronic Care Model of Wagner and the International Classification of Functioning, Disability and Health of the World Health Organization Recommendations were based on consensus using the available evidence and experience of the members of the task force. However, ratings of the quality of evidence and strength of recommendations concerning the use of liposuction for lipedema were not reported.

Country of Origin

All five uncontrolled before-and-after studies[1,4,9,11,12] were conducted in Germany and the clinical guideline was for practice in The Netherlands. The study by Wollina and Heinig was conducted at an academic teaching hospital, whereas the studies by Baumgartner et al., Dadras et al., Schmeller et al., and Rapprich et al., 2011[11] were conducted in specialized plastic surgery clinics.

Patient Population

The five uncontrolled before-and-after studies[1,4,9,11,12] included female patients diagnosed with lipedema. Four of the studies provided details about the three stages of severity of the patients' condition. Stages of lipedema are defined as follows:

- Stage I: Thickening and softening of the subcutis with small nodules; skin is smooth.
- Stage II: Thickening and softening of the subcutis with larger nodules; skin texture is uneven.
- Stage III: Thickening and hardening of the subcutis with large nodules, disfiguring lobules of fat on the inner thighs and inner aspects of the knees.

The following paragraphs describe some characteristics of patients specific to each included study. Further details are provided in Appendix 2.

In the study by Wollina and Heinig,[18] data from 111 patients, treated consecutively between 2007 and 2018 were analyzed. The median age of the patients was 44 years (range: 20 to 81 years) Seven patients had lipedema Stage I, 50 patients had Stage II, and 48 patients had Stage III. Patients had previously been treated with combined decongestive therapy (CDT) for least six months before the liposuction. The median follow up was 2.0 years (i.e., 24 months), with follow-up of between five and seven years available in 18 patients.

The study by Dadras et al.[1] analyzed data from 33 patients treated with liposuction from July 2010 to July 2013 in a plastic surgery clinic. The median age of the patients was 45 years (range: 23 to 64 years). One patient had stage I lipedema, 11 patients had stage II lipedema, and 13 patients had stage III lipedema. Patients had already received at least six months of CDT without improvement of symptoms. The mean follow-up after the last liposuction procedure was 37 months.

The study by Baumgartner et al.[12] included 85 patients who had undergone liposuction in a plastic surgery clinic. The average age of the study population at the time of the first liposuction was 40.1 years (range: 22 to 68). Twenty-four patients (28%) had stage I lipedema and 61 patients (72%) had stage II lipedema. The specific period of the liposuction procedures was not reported. However, at the time of assessment, the patients had been followed-up for an average of 90 months (range: 56 months to 130 months) after the last liposuction.

In the study by Schmeller et al.,[9] data from 112 (68%) of 165 female lipedema patients who had been treated with liposuction from January 2003 to December 2009 in a plastic surgery clinic were analyzed. The mean age was 38.8 years (range: 20 to 68 years). Thirty-five patients presented with lipedema stage I, 75 patients with stage II, and two patients with stage III. Before the liposuction, the patients had undergone conservative therapy over years (actual duration not specified) without adequate response. The mean follow-up duration at the time of data collection was 35 months (range: 8 months to 82 months) following the last surgery.

Rapprich et al.[11] examined data from 25 (23.8%) of 105 lipedema patients, treated between 2006 and 2008. The median age of the patients was 34 years (range: 22 to 25 years). Previous CDT use among the patients was not adequately reported. Although the authors stated that about two-thirds of patients were treated with manual lymph drainage and compression before liposuction,[11] the length of time for which they used such treatment was not specified. Also, it was not reported whether or not the remaining third of the participants had received any previous therapy before liposuction. The severity of the patients' conditions, as indicated by lipedema stages, was not reported. Assessment for this publication used data collected six months follow-up after the last liposuction procedure.

The target population and intended users of the included clinical guideline[1] were lipedema patients and healthcare professionals respectively.

Interventions and Comparators

All five included uncontrolled before-and-after studies[1,4,9,11,12] used liposuction to treat patients with lipedema. One study[4] stated that mechanical liposuction or laser-assisted liposuction were used. Three studies[4,9,11] used liposuction under tumescent local anesthesia which requires no general anesthesia. In these studies, tumescence was

achieved with solution of epinephrine and a local anesthetic, such prilocaine or lidocaine in a physiological solution such as normal saline or Ringer's solution. In one study,[1] tumescent liposuction was performed using saline with epinephrine liposuction solution under general anesthesia and without local anesthetics. Patients in all four studies[1,4,9,11] were treated in multiple sessions depending on the severity of their condition. Three studies[1,4,11] reported that patients were instructed to wear compression garments after the liposuction, and then as needed. In the study by Wollina and Heinig,[18] patients were instructed to wear flat-knitted compression garments for at least six months. Patients in the study by Rapprich et al.[11] performed compression around the clock during the first seven days after liposuction, after which compression therapy continued during the daytime only for four to six weeks. In the study by Dadras et al.,[1] new garments were measured three weeks after liposuction and after swelling had decreased, and manual lymphatic drainage was allowed after postoperative day two. One study[12] did not provide any details about the liposuction method that was used.

The guideline[2] provided recommendations for multidisciplinary treatment for lipedema, and follow-up tailored treatment and support. The interventions considered in the guidelines were conservative therapy and liposuction. Liposuction is the treatment of interest for this report.

Outcomes

All five included uncontrolled before-and-after studies[1,4,9,11,12] evaluated changes in patients' complaints after liposuction. Assessment was done using standardized questionnaires, with complaint severity measured on visual analog scales (VAS). None of the the questionnaires had previously been validated for the assessment of lipedema-related complaints. Common efficacy outcomes reported by all five studies were spontaneous pain and bruising. Four studies[1,4,9,11] reported on sensitivity to pressure and impairment of quality of life (QoL), whereas three studies each reported on reduction in edema (swelling)[1,9,12] and restrictions to movement.[4,9,12] One study evaluated post-procedure reduction in feeling of tension.[1] Using the individual complaint scores, some studies[1,9,11,12] calculated reduction in overall impairment as general or total score. Other outcomes assessed were reductions in CDT use[1,9,11,12] and extremity sizes.[4,11,12] Adverse events were reported in four studies.[1,4,9,11] A minimal clinically important difference (MCID) was not reported for any of the outcome measures.

The outcomes of interest of the guidelines were to define criteria to make a medical diagnosis of lipedema to ensure early detection, provide an outlined follow-up plan on which individualized conservative treatment should be based and recommendations on surgical treatment options. The clinical guidelines[2] provided directions on clinical issues and made recommendations based on available evidence and the experience of the members of the guidelines development task force.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3.

All the included studies had uncontrolled before-and-after design.[1,4,9,11,12] Therefore, they were inherently likely to have systemic biases because the lack of the risk-diminishing property associated with randomization. The objectives of each study and the interventions of interest, as well as the main outcomes to be measured, and the main findings of the

studies, were reported clearly. The general characteristics of the patients in each study were described. In one study,[4] 80% of patients had at least one comorbidity, including obesity, lymphedema, and diabetes. The extent to which these concurrent diseases affected patients' initial complaints and the reported outcomes after liposuction is unclear. One study[4] enrolled patients who were treated consecutively, and there did not appear to be preferential selection. However, the remaining studies[1,9,11,12] did not provide details about how patients were enrolled. Thus, the risk of selection bias cannot be ruled out in these studies.[1,9,11,12] In all the studies,[1,4,9,11,12] the results were from self-assessment data provided by patients in response to standardized questionnaires that had not been validated for the evaluation of lipedema-related outcomes. Given the subjectivity of patient-reported outcomes), the risk of detection bias was high.

In general, the statistical tests used to assess the main outcomes were appropriate in all the studies.[1,4,9,11,12] However, sample size calculations were not performed in any of the studies. The authors of one study[9] stated that the results were exploratory because the statistical analysis was performed without alpha adjustments.Two studies[9,12] reported the magnitude of changes in measured outcomes with effect sizes, which relate better to clinical relevance. However, in the absence of defined MCID for lipedema outcomes, the clinical relevance of the reported results from all the studies[1,4,9,11,12] is uncertain. One study[4] used a mixed intervention approach with subsequent surgical techniques such as thigh lifts, laser lipolysis, or debulking surgery after liposuction in 4.5% of patients to obtain best possible results. The study did not analyze results for this subgroup separately; thus the specific contribution of liposuction to the results achieved in the complete study population is unclear.

Overall, the quality of the evidence[1,4,9,11,12] for the effectiveness of liposuction for lipedema is limited.

Although the authors of the clinical guidelines systematically searched multiple databases for relevant evidence, no information was provided about the types of included studies. Further, the methodological quality of the studies that provided evidence for the guidelines was not assessed. Therefore, the strength of evidence supporting the specific recommendations is unknown. Also, a link between the evidence base and the recommendations concerning liposuction for lipedema was not provided.

All the uncontrolled before-and-after studies[1,4,9,11,12] were conducted in Germany, and the guidelines[2] are intended for clinical practice in the Netherlands. Therefore, the generalizability of the findings of the studies and the recommendations of the guidelines in the Canadian contex is unclear, given the potential for different practice patterns in those countries that might impact the interpretation of findings and the resources needed to achieve them.

Summary of Findings

Clinical effectiveness of liposuction for the treatment of lipedema

Appendix 4 presents tables of the main clinical-effectiveness findings and authors' conclusions on the use of liposuction for the treatment of lipedema from the studies[1,4,9,11,12] included in this report. The following paragraphs summarize the clinical effectiveness and safety outcomes following liposuction for the treatment of lipedema.

Reduction in size of extremities

Three studies found that patients' extremities reduced in size from before to after liposuction. After a median follow-up of 24 months, Wollina and Heinig[4] reported a median decrease in thigh circumference of 6 ± 1.6 cm, whereas Schmeller et al.[9] found a mean reduction of 8 cm (range: 1 to 23) after a mean follow-up of,35 months. in the thighs and 4 cm in the middle of the lower legs after the procedure. In the study by Rapprich et al.,[11] a mean (standard deviation [SD]) reduction in leg volume of 18.0 (3.8) L to 16.8 (3.5) L was observed using 3D imaging, corresponding to an average decrease of 6.9%. The average followed-up duration at the time of assessment was six months after the last procedure.

Reduction in restriction to movement

Three studies found that lipedema patients who complained about restricted mobility before liposuction reported improvement in ability to move after the procedure. After a median follow-up of 24 months, Wollina and Heinig[4] found that all patients (100%) achieved improvement in movement, with 86% of patients reporting marked improvement or complete loss of impairment, while 14% of patients reported minor to medium improvement. Baumgartner et al.[12] and Schmeller et al.[9] reported a significant reduction in the mean restriction in movement score compared to baseline. The effect sizes in the two studies were 1.51 and 1.58, respectively (P<0.001 in all comparisons). The average followed-up durations at the time of assessments were 90 months and 35 months, respectively

Spontaneous pain or discomfort

Five studies found that complaint scores for spontaneous pain among lipedema patients were significantly reduced after liposuction compared to preoperative values. In the study by Wollina and Heinig,[4] the median pain level on a 10-point the VAS reduced from 7.8 before liposuction to 2.2 after the procedure.The median follow-up was 24 months after the last procedure. Dadras et al.[1] reported a significant reduction in the mean spontaneous pain score, with a mean difference of 3.5 (95% CI: 2.83 to 4.17; P<0.001) after a mean follow-up of 37 months after the last liposuction procedure. Similarly, the mean spontaneous pain score decreased significantly from a preoperative value in the studies by Baumgartner et al.,[12] Schmeller et al.,[9] and Rapprich et al.,[11] (P < 0.001 in all cases). The average followed-up durations at the time of assessments 90 months, 35 months, and six months, respectively.

Sensitivity to pressure

Four studies found that complaint scores for sensitivity to pressure among lipedema patients were significantly reduced after liposuction compared to preoperative values. In the study by Dadras et al.,[1] the mean (SD) sensitivity to pressure score decreased from a preoperative value of 7.38 (1.79) to 3.98 (1.83) (P<0.001), after mean follow-up of 37 months after the last liposuction procedure. Baumgartner et al.[12] and Schmeller et al.[9] also reported significant reductions in sensitivity to pressure scores, with effect sizes of 2.04 and 2.01, respectively (P<0.001 in each case). The average followed-up durations at the time of assessments were 90 months and 35 months, respectively. In the study by Rapprich et al.,[11] the mean sensitivity to pressure score decreased from a preoperative value of 6.4 to 1.9 six months after liposuction (P < 0.001).

Edema/Swelling

Two studies found that complaint scores for edema among lipedema patients were significantly reduced after liposuction compared to baseline. In the studies by Baumgartner

et al.[12] and Schmeller et al.,[9] the mean (SD) edema score decreased significantly from a preoperative value with effect sizes of 1.85 and 1.88, respectively (*P*<0.001 in each case). The average followed-up durations at the time of assessments were 90 months and 35 months, respectively.

Bruising

All five included studies reported reductions in complaint scores for bruising after liposuction among lipedema patients compared to before the procedure. In the studies by Wollina and Heinig,[4] bruising after minor trauma improved somewhat in 20.9% and completely or almost completely in 29.1% of patients (*P* < 0.5) after a median follow-up of 24 months. Dadras et al.[1] found that the mean (SD) bruising score decreased from a preoperative value of 6.96 (1.58) to 4.64 (1.83) (*P*<0.001), after a mean postoperative follow-up of 37 months after the last procedure. Baumgartner et al.[12] and Schmeller et al.[9] also reported significant reductions in bruising scores after liposuction, with effect sizes of 1.72 and 1.63, respectively (*P*<0.001 in each comparison). The average followed-up durations at the time of assessments were 90 months and 35 months, respectively. In the study by Rapprich et al.,[11] the bruising score decreased significantly from 7.9 before liposuction to 4.2 six months after the operation, indicating improvement (*P* < 0.001).

Feeling of tension

One study (Dadras et al.)[1] reported that the mean (SD) feeling of tension score decreased significantly from a preoperative value of 7.52 (1.36) to 3.26 (2.28) (*P*<0.001),after a mean follow-up of 37 months after the last liposuction procedure.

Reduction in quality of life Impairment

Four studies found that complaint scores for impairment in QoL among lipedema patients were significantly reduced after liposuction compared to preoperative values. After a mean follow-up of 37 months in the study by Dadras et al.,[1] the mean (SD) impairment in QoL score decreased significantly from a preoperative value of 8.38 (1.06) to 5.16 (1.60) (P < 0.001). Baumgartner et al.[12] and Schmeller et al.[9] reported significant reductions in impairment in QoL scores with effect sizes of 2.89 and 2.95, respectively (*P*<0.001 in both cases). The average followed-up durations at the time of assessments were 90 months and 35 months, respectively. In the study by Rapprich et al.,[11] the results showed a reduction in mean (SD) score from 8.7 (1.7) before liposuction to 3.6 (2.5) six months after the procedure, representing significant improvement (*P* < 0.001).

Overall impairment

General (total) impairment scores were reported by three studies. Both Baumgartner et al.[12] and Schmeller et al.[9] found significant reductions in overall impairment scores with effect sizes of 2.58 and 2.93, respectively, at the the last follow-up assessment (*P*<0.001 in both cases). The average followed-up durations at the time of assessments were 90 months and 35 months, respectively. In the study by Rapprich et al.,[11] the mean (SD) total impairment score significantly decreased from 92.0 (21.3) before liposuction to 39.0 (23.2) six months after the procedure, corresponding to 58% improvement over the baseline (*P* < 0.001).

Reduction in conservative therapy score

Four studies found that lipedema patients who underwent liposuction had a reduced CDT use compared to preoperative usage. Twenty-one patients (84%) in the study by Dadras et al.[1] who had pre- and post-operative data to calculate CDT score reported a decreased in

mean (SD) CDT score from 20.48 (4.13) at the preoperative assessment to 13.9 (7.32) after a mean follow-up of 37 months after the last liposuction procedure. .While 66.7% of patients reported decreased need for conservative therapy (including 14.3% of patients who no longer required further CDT), 14.3% showed no change, and 19.0% reported an increase in their CDT scores after liposuction. Similarly, in the studies by Baumgartner et al.,[12] Schmeller et al.,[9] and Rapprich et al.,[11] patients reported various reductions in CDT use after liposuction. The average followed-up durations at the time of assessments were 90 months, 35 months, and six months, respectively.

Safety

Overall, liposuction was well-tolerated. Adverse events or complications were reported by four of the included studies. In the study by Wollina and Heinig,[4] temporary methemoglobinemia occurred in all patients (100%), and bruising and temporary burning sensations were reported in 98% and 82% of patients, respectively. Other complications which occurred less frequently were mild arm-vein phlebitis (1.8%), postsurgical anemia requiring a blood transfusion (0.9%), and microscopic pulmonary fat embolism (0.9%). In the study by Dadras et al.,[1] one patient (4.0%) developed erysipelas after a liposuction procedure, which required antibiotic treatment. Five patients (4.5%) in the study by Schmeller et al.[9] had postoperative wound infections. Four patients (3.6%) with erysipelas were treated at home with oral antibiotics, whereas one patient (0.9%) with an abscess of the lower leg was treated in hospital. Also, postoperative bleeding occurred in one patient (0.9%) with one liposuction, although the incident did not repeat in three subsequent operations. In the study by Rapprich et al.,[11] one patient (4.0%) with a previous history of deep vein thrombosis of the lower leg, experienced deep vein thrombosis of the lower leg one week after the liposuction. The complication was treated promptly, and there were no further complications or worsening of the condition.

Guidelines for the use of liposuction for the treatment of lipedema

Appendix 5 presents a table of the main guideline recommendations on liposuction for the treatment of lipedema from the evidence-based guideline[2] included in this report.

One clinical guideline[2] with recommendations for the use of liposuction for lipedema was included in this report. The key recommendation of the clinical guideline[2] is that tumescent liposuction, performed by a skilled healthcare professional at a specialized facility, is the treatment of choice for patients with a suitable health profile and/or inadequate response to conservative and supportive measures. Suitable health profile was not defined. However, it was recommended that deteriorating conditions associated with lipedema, such as edema, obesity, unhealthy lifestyle, lack of physical activity, lack of knowledge about the disease, and psychosocial distress, should be addressed before using tumescent liposuction. Also, after liposuction, patients generally require conservative therapy, and weight normalization should remain a goal. Although the authors of the guidelines[2] reported that the recommendations were based on available evidence and the experience of the members of the guidelines development task force, details about the evidence base and the strength of evidence supporting the specific recommendations were not provided.

Two other guidelines[5,8] that were excluded from the main report due to unclear methodology have been listed in Appendix 5.

Limitations

The key limitation of all the included studies[1,4,9,11,12] regarding the clinical effectiveness of liposuction for the treatment of lipedema is that they were uncontrolled before-and-after studies with results based on subjective, self-assessment by the patients. The data underlying the findings were collected using standardized questionnaires which have not been validated for the assessment lipedema-related complaints, and the VAS tools that were used to quantify results were also not validated for such use in lipedema. Thus, in addition to a high potential for systematic biases associated with non-randomized studies, there is uncertainty about the reliability of the reported outcomes. Also, none of the studies performed sample size calculations. The authors of one study[9] stated that the results were exploratory because the statistical analysis was performed without alpha adjustments. Although lipedema is more common in females, no evidence for males was identified in this report; results are not generalizable to males. All the studies were conducted in Germany. It is unclear whether practice patterns in Germany that might impact the interpretation of the findings or the resources used to achieve them and present generalizability concerns in the Canadian context. Another limitation is that there were no studies identified regarding the effectiveness of liposuction for the treatment of patients with lipedema and secondary lymphedema, or regarding the effectiveness of other liposuction modalities such as water jet-assisted liposuction.

The main limitation of the clinical guideline[2] was that it did not provide a link between the evidence base and the recommendations concerning liposuction for lipedema, and the strength of evidence supporting the specific recommendations was not assessed.

Conclusions and Implications for Decision or Policy Making

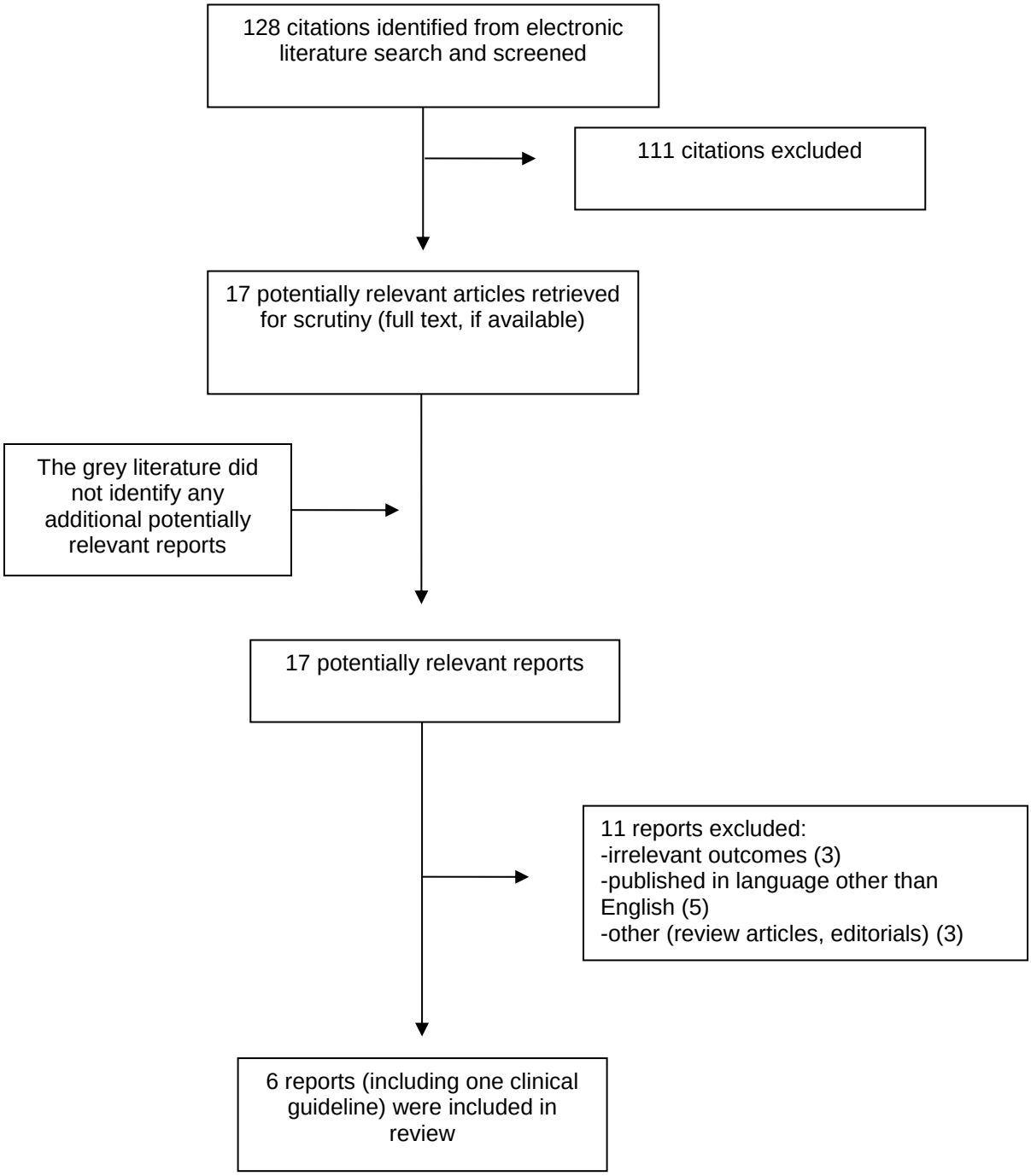
Information about the clinical effectiveness of liposuction for the treatment of lipedema was sourced from five uncontrolled before-and-after studies.[1,4,9,11,12] Data from the studies indicated that in patients with lipedema, treatment with liposuction resulted in a significant improvement of pain, sensitivity to pressure, edema, bruising, feeling of tension, and quality of life. The patients also experienced significant reductions in size extremities and restriction of movement, and the need for conservative therapy for lipedema. The benefits of liposuction remained even at long-term (up to 88 months) follow-up assessments. Liposuction was generally well tolerated; most adverse events occurred in <5% of patients. The clinical guideline[2] recommends that tumescent liposuction, performed by a skilled healthcare professional at a specialized facility, be considered the treatment of choice for patients with a suitable health profile and/or inadequate response to conservative and supportive measures. The quality of the supporting evidence and the strength of the recommendations were not provided.

The quality of the evidence[1,4,9,11,12] was limited, with sources of uncertainty such as systematic biases due to lack of randomization, and the use of instruments that have not been validated for the collection of data and assessment in lipedema-related complaints.Studies to validate tools to assess lipedema-related outcomes and define a minimally clinically important difference for the condition may also be necessary to put the benefit of liposuction for the treatment of lipedema in a clinical perspective.

References

1. Dadras M, Mallinger PJ, Corterier CC, Theodosiadi S, Ghods M. Liposuction in the treatment of lipedema: a longitudinal study. *Arch Plast Surg.* 2017;44(4):324-331.
2. Halk AB, Damstra RJ. First Dutch guidelines on lipedema using the international classification of functioning, disability and health. *Phlebology.* 2017;32(3):152-159.
3. Buck DW, 2nd, Herbst KL. Lipedema: a relatively common disease with extremely common misconceptions. *Plast Reconstr Surg Glob Open.* 2016;4(9):e1043.
4. Wollina U, Heinig B. Treatment of lipedema by low-volume micro-cannular liposuction in tumescent anesthesia: Results in 111 patients. *Dermatol Ther.* 2019;32(2):e12820.
5. Reich-Schupke S, Schmeller W, Brauer WJ, et al. S1 guidelines: lipedema. *J Dtsch Dermatol Ges.* 2017;15(7):758-767.
6. Warren Peled A, Kappos EA. Lipedema: diagnostic and management challenges. *Int J Women Health.* 2016;8:389-395.
7. Felson S. Lipedema. *WebMD* 2017; https://www.webmd.com/women/guide/lipedema-symptoms-treatment-causes#1.
8. Wounds UK. Best practice guidelines: the management of lipoedema. London (UK): Wounds UK; 2017: https://www.lipoedema.co.uk/wp-content/uploads/2017/05/WUK_Lipoedema-BPS_Web.pdf. Accessed 2019 May 28.
9. Schmeller W, Hueppe M, Meier-Vollrath I. Tumescent liposuction in lipoedema yields good long-term results. *Br J Dermatol.* 2012;166(1):161-168.
10. Basic overview of liposuction for lipedema. *Lipedma* https://www.lipedema.net/overview-liposuction-lipedema.html.
11. Rapprich S, Dingler A, Podda M. Liposuction is an effective treatment for lipedema-results of a study with 25 patients. *J Dtsch Dermatol Ges.* 2011;9(1):33-40.
12. Baumgartner A, Hueppe M, Schmeller W. Long-term benefit of liposuction in patients with lipoedema: a follow-up study after an average of 4 and 8 years. *Br J Dermatol.* 2016;174(5):1061-1067.
13. Fetzer A. Specialist approaches to managing lipoedema. *Br J Community Nurs.* 2016;Suppl:S30-35.
14. Rapprich S, Baum S, Kaak I, Kottmann T, Podda M. Treatment of lipoedema using liposuction: results of our own surveys. *Phlebologie.* 2015;44(3):121-132.
15. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2019 Jun 07.
16. Agree Next Steps Consortium. The AGREE II Instrument. Hamilton (ON): AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Jun 07.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
18. Wollina U. Lipedema-an update. *Dermatol Ther.* 2019;32(2):e12805.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up

Wollina and Heinig, 2019[4]
 	
Germany
	Single-arm, single-centre before-and-after NRS	111 female lipedema patients, treated consecutively between 2007 and 2018. The median age of the patients was 44 years (range: 20 to 81 years). Patients' conditions had not responded to at least six months of previous CDT.	Micro-cannula liposuction in tumescent anesthesia, using mechanical liposuction or laser-assisted liposuction. The procedure was performed as low-volume liposuction with <4 L lipoaspirate per session during several sessions six to eight weeks apart.	• Reduction of
				  ○ Limb circumferences
				  ○ Pain (on a VAS)
				  ○ Bruising
				• Improvement of mobility
				• Adverse events
				
				The median (SD) follow-up was 2.0 (2.1) years. Eighteen patients had follow-up of between five and seven years.

Dadras et al., 2017[1]
 	
Germany
	Single-arm, single-centre before-and-after NRS	Thirty-three female lipedema patients treated with liposuction procedures from July 2010 to July 2013 in a plastic surgery clinic. The median age of the patients was 45 years (range: 23 to 64 years) and their mean BMI at baseline was 35.3 kg/m^2 (range: 24.5 to 50.6 kg/m^2). They had already received at least six months of CDT without improvement of symptoms.	Tumescent liposuction using saline with epinephrine (1:1,000,000). The procedure was performed under general anesthesia.
			
			Patients received an average of three procedures (range; 1 to 7 procedures). The mean volume of removed fat per liposuction was 3,106 mL (range: 1,450 to 6,600 mL)
				• Changes in weight (BMI)
				• The severity of
				  ○ spontaneous pain
				  ○ pain upon pressure
				  ○ feeling of tension
				  ○ bruising
				  ○ cosmetic impairment
				  ○ general impairment of quality of life before and after liposuction treatment
				• CDT score*
				Assessments were performed in postoperative follow-up periods. The first was after a mean of 16 months follow-up (range: 4 and 34 months), and the second after a mean 37 months follow-up (range: 25 to 56 months).

Baumgartner et al., 2016[12]	Single-arm, single-centre before-and-	85 female patients with lipedema. The average age of the	Liposuction (details of the procedure were not	• Spontaneous pain • Sensitivity to pressure • Edema/Swelling

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Germany	after NRS	study population at the time of the first liposuction was 40.1 years (range: 22 to 68). Twenty-four patients (28%) with stage I lipedema and 61 patients (72%) with stage II lipedema.	provided)..	• Bruising • Restriction of movement • Cosmetic impairment • Quality of life • Reduction in amount of conservative treatment Assessments were performed in postoperative follow-up periods by means of a questionnaire. The follow-up observation took place an average of 8 years and 3 months (range 5 years and 1 month to 11 years and 4 months) after the first liposuction and 7 years and 6 months (range 4 years and 8 months to 10 years and 10 months) after the last liposuction.

Schmeller et al., 2012[9]
 	
Germany
	A long-term follow-up assessment of a single-arm, single-centre before-and-after NRS. Standardized questionnaire was used and the results were reported quantitatively.	A total of 112 female lipedema patients (68% of the original 165 patients) who had been treated with liposuction from January 2003 to December 2009, and assessed after a mean of 2 years and 11 months (range: 8 months to 6 years and 10 months) following the last surgery. The mean age was 38.8 years (range: 20 to 68 years) and average weight was 79.3 kg (range: 50 to 123 kg). Thirty-five patients presented with lipedema stage I, 75 patients with stage II and two patients with stage III. Before the liposuction, the patients had undergone conservative therapy	Liposuction under tumescent local anesthesia with vibrating microcannulas. Patients were treated in a median of two sessions (range: 1 to 7 sessions). The average amount of fat removed per session was 3,077 mL (range 450 to 7,000 mL).	• Change of body shape
				  ○ circumference of extremities
				  ○ average weight
				• Improvement of complaints
				  ○ spontaneous pain
				  ○ sensitivity to pressure
				  ○ edema
				  ○ bruising
				  ○ restriction of movement
				  ○ cosmetic impairment,
				  ○ changes in quality of life
				  ○ general impairment (total score)
				The mean follow-up duration after the last liposuction procedure was 2 years and 11 months (range: 8 months to 6 years and 10 months).

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		over a period of years without adequate response.		
Rapprich et al., 2011[11] **Germany**	A single-arm, single-centre before-and-after NRS.	Twenty-five patients with lipedema treated with liposuction between April 2006 and July 2008. The median age was 34.0 years (range: 22 to 65 years).	Liposuction was performed with under tumescent local anesthesia with vibrating micro-cannula. Patients were treated in a median of two sessions (range: 1 to 5 sessions). The average (SD) aspiration volume per session was 2, 482 (968) mL with an average (SD) pure fat component of 1,909 (874) ml, equivalent to 77%	• Reduction of leg volume • Pain • Sensitivity to pressure • Bruising • Reduction in quality of life impairment • Total score The follow-up duration after the last liposuction procedure was 6 months

CDT = combined decongestive therapy; NRS = non-randomized study; SD = standard deviation, VAS = visual analog scale.

* The CDT score was derived from the sum of the frequency of manual lymphatic drainage per month and the number of hours per day the patient wore compression garments.[1]

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
First Dutch Guidelines on Lipedema – Halk, 2017[2]						
The intended users are healthcare professionals. The target population is lipedema patients	Lipedema diagnostics, multidisciplinary treatment (including liposuction), and follow-up with tailored	• Making the diagnosis of lipedema; • Defining clinimetric	A systematic review of English and German literature published up to June 2013 retrieved from	Not reported	Answers to the clinical issues were formed, and recommendations were stated based on the available evidence and the experience of the members of the task force.	It was unclear if a formal validation was conducted. However, the guideline development task force was

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
	treatment and support.	measurements to ensure early detection and functional, holistic follow-up; and • Patient treatment and support.	PubMed, MEDLINE, COCHRANE and CINAHL databases.		The Chronic Care Model (CCM) of Wagner and the International Classification of Functioning, Disability and Health (ICF) of the WHO were used.	made up of multi-disciplinary professionals from dermatology, surgery, radiology, psychology, physical therapy, dietetics, and skin therapy organized by the Dutch Society of Dermatology and Venereology. In addition, inputs were invited from representatives of several relevant Dutch organizations and patients. Also, an initial draft of the guidelines was presented for review in December 2013, before the guidelines were finalized and published in April 2014.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Clinical Studies using Down and Black Checklist[15]

Strengths	Limitations
Wollina and Heinig, 2019[4]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly • Patients were treated consecutively and there did not appear to be preferential selection • The statistical tests used to assess the main outcomes were appropriate • The authors declared no potential sources of conflict of interest.	• The non-randomized design of the study lacks the risk-diminishing property of randomization, making it inherently likely to have more systemic biases. • Mixed intervention combining liposuction with other surgical techniques such as thigh lifts, laser lipolysis, or debulking surgery was used in 4.5% of patients to obtain best possible results. Thus the specific contribution of liposuction to the results achieved in these patients was unclear. • Eighty percent (80%) of patients in the study had at least one comorbidity, including obesity, lymphedema, and diabetes. The extent to which these concurrent diseases affected patients' initial complaints the reported outcomes after liposuction is unclear. • With no indication of monitoring between the last procedure and the long-term assessment, it is uncertain whether the reported outcomes had been influenced by factors other than the procedure, such as life-style changes and other interventions (e.g., CBT) • Patient-reported outcomes (PROs) with data collected based on a standardized questionnaire, using a VAS score to assess severity. PROs are known to be subjective; therefore; findings could vary from patient to patient. • The study was conducted in Germany. Thus, it is unclear whether there exists any difference in the practice pattern in that country that might impact the interpretation of the findings or the resources used to achieve them and pose generalizability concerns in the Canadian context
Dadras et al., 2017[1]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly • The statistical tests used to assess the main outcomes were appropriate • The authors declared no potential sources of conflict of interest.	• The non-randomized design of the study lacks the risk-diminishing property of randomization, making it inherently likely to have more systemic biases • The study was based on data collected by means of a standardized questionnaire which has not been validated for the assessment of lipedema-related complaints. • Details were not provided about how patients were enrolled. Thus, the risk of selection bias cannot be ruled out.

Strengths	Limitations
	• The preoperative data used in analysis were collected retrospectively, and present a high potential for bias. • Results were derived from PROs. Therefore, there is a high potential for subjectivity, and thus variability of the findings from patient to patient. • Data for this long-term evaluation study were obtained from 25 (75.6%) of the 33 patients who underwent liposuction for lipedema. However, the difference in characteristics between patients who responded to the questionnaires and those who did not respond was not provided. Thus, it is unclear whether the participating patients were representative of the entire population from which they were recruited. • The measure of the need for summary CDT score after liposuction was derived in-house by the investigators and had not been independently validated. Thus its accuracy and reliability are unclear. • Quality of life assessment was done on a using VAS scale without using any instrument validated for lipedema patients. • It is unknown whether the sample size of the study was adequate to determine statistically significant differences in outcomes from before to after the intervention • The study was conducted in Germany. Thus, it is unclear whether there exists any difference in the practice pattern in that country that might impact the interpretation of the findings or the resources used to achieve them and pose generalizability concerns in the Canadian context.
Baumgartner et al., 2016[12]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly • Statistical analysis expressed the magnitude of the changes between the measurement time points by effect size which relate better to clinical relevance that statistical significance. However, it could not be ascertained whether an established MCID is available for liposuction in lipedema • The authors declared no potential sources of conflict of interest.	• The non-randomized design of the study lacks the risk-diminishing property of randomization, making it inherently likely to have more systemic biases. • Details were not provided about how patients were enrolled. Thus, the risk of selection bias cannot be ruled out. • The study was based on data collected by means of a mail questionnaire which has not been validated for the assessment of lipedema-related complaints. • Results were derived from PROs. Therefore, there is a high potential for subjectivity, and thus variability of the findings from patient to patient. • The number of patients enrolled for the initial study was not reported. For the current analysis, data were obtained from 85 (75.9%) of the 112 patients who had been evaluated earlier (i.e., four years after the last liposuction). However, the difference in characteristics

Strengths	Limitations
	of patients at baseline, at the four-year assessment, and at the current (eight-year) evaluation was not provided. Thus, it is unclear whether the participating patients in the current analysis were representative of the entire population from which they were recruited. • Quality of life assessment was done on a VAS scale without using any instrument validated for lipedema patients. • No sample size calculation was performed. • The study was conducted in Germany. Thus, it is unclear whether there exists any difference in the practice pattern in that country that might impact the interpretation of the findings or the resources used to achieve them and pose generalizability concerns in the Canadian context
Schmeller et al., 2012[9]	
• The objective of the study, the characteristics of the patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly • The statistical tests used to assess the main outcomes were appropriate • The authors declared no potential sources of conflict of interest.	• The non-randomized design of the study lacks the risk-diminishing property of randomization, making it inherently likely to have more systemic biases. • Details were not provided about how patients were enrolled. Thus, the risk of selection bias cannot be ruled out. • The study was based on data collected by means of a standardized questionnaire which has not been validated for the assessment of lipedema-related complaints. • The findings were derived from PROs. Therefore, there is a high potential for subjectivity, and thus variability of the results from patient to patient. • Of 164 lipedema patients treated with liposuction who received the survey, 112 (68.3%) returned them with data that could be evaluated for the study. However, the difference in the characteristics between the responding patients and those without evaluable data was not provided. Thus, it is unclear whether the participating patients in the current analysis were representative of the entire population from which they were recruited. • The results were considered exploratory because the statistical analysis was performed without alpha adjustments. • The study was conducted in Germany. Thus, it is unclear whether there exists any difference in the practice pattern in that country that might impact the interpretation of the findings or the resources used to achieve them and pose generalizability concerns in the Canadian context
Rapprich et al., 2011[11]	
• The objective of the study, the characteristics of the	• The non-randomized design of the study lacks the risk-

Strengths	Limitations
patients included, the interventions of interest, main outcomes to be measured, and the main findings of the study were described clearly • The statistical tests used to assess the main outcomes were appropriate • The authors declared no potential sources of conflict of interest.	diminishing property of randomization, making it inherently likely to have more systemic biases. • Details were not provided about how patients were enrolled. Thus, the risk of selection bias cannot be ruled out. • The study was based on data collected by means of a standardized questionnaire which has not been validated for the assessment of lipedema-related complaints. • Severity of lipedema and previous therapy before liposuction were not adequately reported. • The findings were derived from PROs. Therefore, there is a high potential for subjectivity, and thus variability of the results from patient to patient. • The follow-up duration was relatively short (six months) and long-term outcomes were not available. • Of the 105 lipedema patients who underwent treatment, evaluable data for this study were available from 25 (23.8%) who could be followed-up at six months after the last liposuction procedure. Reasons given were therapy had not been concluded at the time of evaluation, or the follow-up visit at six months after the procedure had not yet taken place, or liposuction therapy was not performed due to insurance coverage issues. Thus, it is unclear whether the participating patients in the study were representative of the entire population from which they were recruited. • The study was conducted in Germany. Thus, it is unclear whether there exists any difference in the practice pattern in that country that might impact the interpretation of the findings or the resources used to achieve them and pose generalizability concerns in the Canadian context.

CBT = cognitive behavioural therapy; CDT = complex decongestive therapy; PRO =patient-reported outcome; VAS =visual analog scale

Table 5: Strengths and Limitations of Guidelines using AGREE II[16]

Item	First Dutch Guidelines on Lipedema– Halk, 2017[2]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
4. The guideline development group includes individuals from all relevant professional groups.	Yes

Item	First Dutch Guidelines on Lipedema– Halk, 2017[2]
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes
6. The target users of the guideline are clearly defined.	Yes
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	No
9. The strengths and limitations of the body of evidence are clearly described.	Unclear
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	No
13. The guideline has been externally reviewed by experts prior to its publication.	Unclear Inputs were invited from representatives of several relevant Dutch organizations and patients, and an initial draft was presented for review before the guidelines were finalized and published.
14. A procedure for updating the guideline is provided.	No
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes
17. Key recommendations are easily identifiable.	Yes
18. The guideline describes facilitators and barriers to its application.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Unclear
20. The potential resource implications of applying the recommendations have been considered.	Unclear The authors stated that given the reduced in need for conservative treatment after liposuction, health care costs could potentially decrease. However, cost-effectiveness studies were not been performed to ascertain this position.
21. The guideline presents monitoring and/or auditing criteria.	No
22. The views of the funding body have not influenced the content of the guideline.	Yes The author(s) received no financial support for the research, authorship, and/or publication of this article.
23. Competing interests of guideline development group	Unclear

Item	First Dutch Guidelines on Lipedema– Halk, 2017[2]
members have been recorded and addressed.	The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Wollina and Heinig, 2019[4]	
At the time of data collection, the median post procedure follow-up was 24 months. **Reduction of Circumferences** • The median reduction of limb circumference on thighs was 6 ± 1.6 cm. **Pain reduction** • The median pain level before treatment was 7.8 ± 2.1. The median reduction of pain sensations of the VAS 10-point scale was 2.2 ± 1.3 at the end of the treatment (***P*** < 0.3). **Bruising reduction** • Bruising after minor trauma improved somewhat in 20.9% and completely or almost completely in 29.1% (p < 0.5). In 16.4% of patients further CDT was no longer necessary. **Improvement of mobility** • Improvement in mobility was achieved in all patients (100%), with 86% of patients reporting marked improvement or complete loss of impairment, while 14% of patients reported minor to medium improvement. **Relapse of Lipedema** • After a median (SD) follow-up of 2.0 (2.1) years (with follow-up duration of between five and seven years for 18 patients), none of the patients had a relapse of lipedema suggesting a long-term benefit. **Adverse events** The procedure was usually well tolerated, with no fatalities, or wound infections, and no surgical interventions required due to AEs. The most common AEs were: • Temporary methemoglobinemia in all patients (100%), including one patient (0.9%) who had a single epileptic attack during methemoglobinemia. The AE was treated by intravenous injection of toluidine blue. • Bruising and temporary burning sensations reported in 98% and 82% of patients, respectively, but which	• "Micro-cannular liposuction in TA offers an effective treatment modality for patients with lipedema not responding to CDT with a favorable safety profile. There is a significant burden of comorbidities among these patients which need consideration for surgical interventions." ,[4] p.4 • "Nevertheless, the procedure needs a professional surgical experience and setting. Patients should be monitored carefully for 24 hr. Centers offering liposuction for lipedema patients must be able to deal with possible complications."[4] p.4

Main Study Findings	Authors' Conclusion
disappeared without any specific intervention. • Mild arm-vein phlebitis observed in two patients (1.8%). One case was treated by a combination of oral herbal enzymes and the other by prophylactic antibiosis, prednisolone, and compressions treatment. • An episode of postsurgical anemia requiring a blood transfusion was reported in one patient (0.9%). • Microscopic pulmonary fat embolism was reported in one patient (0.9%) two days after release from the hospital after first liposuction. She was treated by active direct factor Xa inhibitor rivaroxaban. • A suspected acute pulmonary edema requiring intensive care admission was reported in one patients (0.9%) about 24 hours after liposuction. However, the condition was final diagnosed as a retarded community acquired atypical pneumonia with aggravation of pre-existent comorbidities.	
Dadras et al., 2017[1]	
Complaint outcomes were assessed using a 0 to 10 VAS. Data were collected after a mean follow-up time of 37 months (range: 25 to 56 months) after the last procedure. **Spontaneous pain** • The mean VAS (SD) spontaneous pain score decreased significantly (P<0.001) from a preoperative value of 7.2 (1.46) to 4.28 (2.10) at the last postoperative follow-up assessment. **Sensitivity to pressure** • The mean VAS (SD) sensitivity to pressure score decreased from a preoperative value of 7.38 (1.79) to 4.42 (2.08) at the last postoperative follow-up assessment (P<0.001). **Feeling of tension** • The mean VAS (SD) feeling of tension score decreased from a preoperative value of 7.52 (1.36) to 4.06 (2.18) at the last postoperative follow-up assessment (P<0.001). **Bruising** • The mean VAS (SD) bruising score decreased from a preoperative value of 6.96 1.58 to 4.64 (1.83) at the last postoperative follow-up assessment (P<0.001). **Impairment to quality of life**	"Liposuction is effective in the treatment of lipedema and leads to an improvement in quality of life and a decrease in the need for conservative therapy."[1] p.324

Main Study Findings	Authors' Conclusion
• The mean VAS (SD) impairment in QoL score decreased significantly (P<0.001) from a preoperative value of 8.38 (1.06) to 5.16 (1.60) at the last postoperative follow-up assessment (P<0.001). **Cosmetic impairment** • The mean VAS (SD) cosmetic impairment score decreased from a preoperative value of 8.98 (0.81) to 7.36 (1.66) at the last postoperative follow-up assessment (P<0.001). **Combined decongestive therapy score** • As at the last postoperative follow-up assessment, the CDT scores of 14 (66.7%) had decreased after liposuction treatment, with 3 patients (14.3%) no longer requiring further conservative therapy. Three patients (14.3%) showed no change in their CDT scores, while 4 patients (19.0%) showed an increase in their CDT scores. **Weight** • After treatment, the mean BMI reduced to 33.9 kg/m^2 (range: 22.7 to 47.2 kg/m^2) from a mean of 35.3 kg/m^2 (range: 24.5 to 50.6 kg/m^2) at pre-operative presentation. It was not reported whether or not the difference was statistically significant. **Adverse events** • One (4.0%) patient developed erysipelas after a liposuction procedure, which required antibiotic treatment. There were no other complications during the study period.	
Baumgartner et al., 2016[12]	
Complaint outcomes were assessed on a 5-point scale as follows: 0, none; 1, minor; 2, medium; 3, strong; 4, very strong. An effect size of 0.5 is evaluated as average and an effect size of ≥ 0.8 as high. The average followed-up duration at the time of assessment was 90 months (range: 56 months to 130 months). **Spontaneous pain** The mean (SD) spontaneous pain score decreased significantly from a preoperative value of 1.86 (1.33) to 0.37 (0.57) during last postoperative follow-up assessment. Effect sizes for comparison were 1.38 and 1.50 at the two post-surgery assessment points respectively (P<0.001 for each comparison).	"In conclusion, an average of 8 years (range 5 years and 1 month to 11 years and 4 months) after liposuction, a noticeable improvement in findings and complaints was seen, with unchanged highly significant differences from the initial findings. No clinically relevant worsening of complaints occurred in the past 4 years. In addition, an unchanged significant reduction in the extent of the conservative treatment (CDT) still required or used was also observed. However, it is not possible to say whether the results still in place after 8 years can be considered 'permanent'. Based on the present data, liposuction appears to be the most effective and long-lasting treatment for lipoedema to date. While all patients' symptoms noticeably improved as a result of the

Main Study Findings	Authors' Conclusion
Sensitivity to pressure • The mean (SD) sensitivity to pressure score decreased significantly from a preoperative value of 2.88 (1.01) to 0.94 (0.95) at the last postoperative follow-up assessment (effect size 1.92, P<0.001). 0 **Edema/Swelling** • The mean (SD) edema score decreased significantly from a preoperative value of 3.07 (0.06) to 1.34 (0.92) at the last postoperative follow-up assessment (effect size 1.73, *P*<0.001). (**Bruising** • The mean (SD) bruising score decreased significantly from a preoperative value of 2.91 (1.10) to 1.46 (1.17) at the last postoperative follow-up assessment (effect size 1.28, *P*<0.001). **Restriction in movement** The mean (SD) restriction in movement score decreased significantly from a preoperative value of 2.11 (1.30) to 0.53 (0.69) at the last postoperative follow-up assessment (effect size 1.51, *P*<0.001) **Cosmetic impairment** • The mean (SD) cosmetic impairment score decreased significantly from a preoperative value of 3.32 (0.89) to 1.40 (1.07) at the last postoperative follow-up assessment (effect size 1.96, *P*<0.001) **Reduction in quality of life** • The mean (SD) reduction in QoL in score decreased significantly from a preoperative value of 3.35 (0.84) to 0.94 (1.00)at the last postoperative follow-up assessment (effect size 2.59, P<0.001). **Overall impairment** • The mean (SD) cosmetic impairment score decreased significantly from a preoperative value of 2.78 (0.7.2) to 1.00 (0.66) at the last postoperative follow-up assessment (effect size 2.58, P<0.001) **Changes in conservative treatment after liposuction** • Of the 85 patients surveyed in at the last postoperative follow-up assessment, 47 (55%) underwent CDT before liposuction. • Fourteen patients (30%) no longer needed to undergo CDT, and 28 patients (60%) had fewer CDT, and five	liposuction, only one-third of the patients were completely free of symptoms. For this reason, conservative treatment – as an additional treatment – continues to play a significant role in lipoedema."[12] p.7

Main Study Findings	Authors' Conclusion
patients (10%) continued CDT with the same extent as before.	
Schmeller et al., 2012[9]	
The average followed-up duration at the time of assessment was 35 months (range: 8 months to 82 months) **Circumference of extremities** • Mean reductions of 8 cm (range: 1 to 23) in the thighs (inguinal region) and of 4 cm (1 to 11) in the middle of the lower legs (calves) were achieved. • Clothing size reductions of one, two and three were reported by 38%, 25%, and 11% of the patients, respectively. 23% of the patients did not notice any change and 2% experienced an increase of one size. **Improvement of complaints** Complaint outcomes were assessed on a 5-point scale as follows: 0, none; 1, minor; 2, medium; 3, strong; 4, very strong. The results were considered exploratory because the statistical analysis was performed without alpha adjustments. Thus, the term "significant" as denoted by P-values < 0.05 was given only as a description of differences. **Spontaneous pain** • The mean (SD) spontaneous pain score decreased significantly from a preoperative value of 1.88 (1.33) to 0.37 (0.60) at postoperative assessment (effect size 1.36; P<0.001). **Pain due to pressure** • The mean (SD) pain because of pressure score decreased significantly from a preoperative value of 2.91 (1.06) to 0.91 (0.92) at postoperative assessment (effect size 2.01; P<0.001). **Edema** • The mean (SD) edema score decreased significantly from a preoperative value of 3.06 (1.02) to 1.27 (0.88) at postoperative assessment (effect size 1.88; P<0.001). **Bruising** • The mean (SD) bruising score decreased significantly from a preoperative value of 3.01 (1.03) to 1.26 (1.11) at postoperative assessment (effect size 1.63; P<0.001).	• "In conclusion, tumescent liposuction in lipoedema is a highly effective method with long-term benefit concerning body shape, together with a significant improvement of pain, oedema, bruising and restriction of movement. The obvious reduction in the need for further conservative treatment and the remarkable increase in the quality of life are important positive aspects of this therapy. Because often large amounts of TLA solution are needed and extensive volumes of subcutaneous fat have to be removed, a considerable degree of experience is required; therefore, the procedure should be performed in specialized centres only."[9] p. 167 • "In agreement with others, we can confirm that liposuction with exclusively TLA according to the existing guidelines is a safe procedure with no serious and only a few minor side-effects."[9] p. 164

Main Study Findings	Authors' Conclusion
Restriction of movement • The mean (SD) restriction of movement score decreased significantly from a preoperative value of 2.03 (1.36) to 0.28 (0.68) at postoperative assessment (effect size 1.58; P<0.001). **Cosmetic impairment** • The mean (SD) cosmetic impairment score decreased significantly from a preoperative value of 3.33 (0.88) to 1.08 (0.91) at postoperative assessment (effect size 2.25; P<0.001). **Reduction in quality of life** • The mean (SD) reduction in quality of life score decreased significantly from a preoperative value of 3.36 (0.86) to 0.76 (0.91) at postoperative assessment (effect size 2.95; P<0.001). **General impairment (total score)** • The mean (SD) general impairment score (i.e. the summary score) decreased significantly from a preoperative value of 2.81 (0.70) to 0.86 (0.63) at postoperative assessment (effect size 2.93; P<0.001). **Reduction of conservative therapy** The post-operative assessment of 67 patients who used combined physical therapy (manual lymphatic drainage and compression) before liposuction found that, • 13 patients (19.4%) needed manual lymphatic drainage and compression as often as before; • 20 patients (29.9%) also continued with physical decongestive therapy, but less often; • 13 patients (19.4%) still used compression garments; • six patients (9%) declared that they only needed manual lymphatic drainage from time to time; • 15 patients (22.4%) reported that they no longer required conservative therapy. **Adverse events** • Postoperative wound infections occurred in five patients (4.5%). Four patients (3.6%) with erysipelas were treated at home with oral antibiotics, whereas one patient (0.9%) with an abscess of the lower leg was treated in hospital. • Postoperative bleeding occurred in one patient (0.9%) with one liposuction, although the incident did not repeat in three subsequent operations.	
Rapprich et al., 2011[11]	

Main Study Findings	Authors' Conclusion
Circumference of extremities • Six months after liposuction, a mean (SD) reduction in leg volume of 18.0 (3.8) L to 16.8 (3.5) L was observed using 3D imaging, corresponding to an average reduction of 6.9%. **Improvement of complaints** Complaint outcomes were assessed on a 0-10 VAS from none to very severe. The average follow-up duration was six months after the last procedure. **Pain** • The mean (SD) pain score reduced significantly from 7.2 (2.2) preoperative to 2.1 (2.1), indicating a significant improvement ($p < 0.001$). **Sensitivity to pressure** • There was also a significant improvement in sensitivity to pressure, with VAS score decreasing from a preoperative value of 6.4 to 1.9 six months after liposuction ($p < 0.001$) **Bruising** • The VAS score for bruising easily decreased from 7.9 before liposuction to 4.2 six months after the operation, indicating significant improvement ($p < 0.001$). **Reduction in quality of life impairment** • Results showed a reduction in mean (SD) score from 8.7 (1.7) before liposuction to 3.6 (2.5) six month after the procedure, representing significant improvement ($p < 0.001$). **Total impairment score** • Of a possible highest impairment score of 150 for 15 symptom parameters, the mean (SD) score six months after the procedure was 39.0 (23.2), corresponding 58% improvement over the baseline score of 92.0 (21.3), ($p < 0.001$). **Reduction of conservative therapy** • Two-thirds (66%) of patients were treated with manual lymph drainage and compression prior to liposuction. Six months after the last liposuction session, 8 % of patients reported that they required MLD less frequently, and 16% reported occasionally or regularly	"When performed by an experienced practitioner, tumescent liposuction is a safe and effective method of treatment for lipedema. The results of therapy are better in younger patients with early-stage disease compared with more severe disease in older patients. CPT, before and after liposuction, is an important part of therapy."[11] p.7

Main Study Findings	Authors' Conclusion
wearing compression stockings. **Adverse events or complications** • One patient (4.0%) with a previous history of DVT of the lower leg, experienced DVT of the lower leg one week after the liposuction. The complication was treated promptly and there were no further complications or worsening of the condition.	

AE = adverse event; CDT = combined decongestive therapy; CI = confidence interval; DVT = deep vein thrombosis; MLD = manual lymph drainage; SD = standard deviation, QoL = quality of life; VAS = visual analog scale.

Table 7: Summary of Recommendations in Included Guideline

Recommendations	Strength of Evidence and Recommendations
First Dutch Guidelines on Lipedema – Halk , 2017[2]	
1. Tumescent liposuction is the treatment of choice for patients with a suitable health profile and/or inadequate response to conservative and supportive measures. 2. Before using tumescent liposuction, associated deteriorating components, such as edema, obesity, unhealthy lifestyle, lack of physical activity, lack of knowledge about the disease, and psychosocial distress, should be addressed. 3. After liposuction, patients generally require conservative therapy, and weight normalization should remain a goal. 4. Tumescent liposuction requires specialized skills of the healthcare deliverer and should only be performed at a specialized center.	Not reported

* Recommendations reported here are limited to the use of liposuction the treatment of lipedema. Recommendations on diagnosis and conservative treatment were not of interest to this review and have not been reported.

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Appendix 5: Additional References of Potential Interest

Guidelines with Unclear Methodology

Reich-Schupke S, Schmeller W, Brauer WJ, et al. S1 guidelines: Lipedema. J. 2017 Jul;15(7):758-767.
PubMed: PM28677175

Wounds UK. Wounds UK. Best practice guidelines: the management of lipoedema. London (UK): Wounds UK; 2017: https://www.lipoedema.co.uk/wp-content/uploads/2017/05/WUK_Lipoedema-BPS_Web.pdf. Accessed 2019 May 28.