HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Liposuction for surgical therapy of lipoedema

Systematic Review

AIHTA Decision Support Document: 125 | ISSN-online: 1998-0469

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

Liposuction for surgical therapy of lipoedema

Systematic Review

Vienna, March 2021

Project Team
Project leader: Melanie Walter, PhD EU-MSc
Authors: Melanie Walter, PhD EU-MSc
Lucia Gassner, MSc

Project Support
Systematic literature search: Tarquin Mittermayr, BA(Hons), MA
Abstract screening: Gregor Goetz, MSSc MPH
External Review: Ao.Univ.-Prof. Dr.med.univ. Kornelia Böhler,
Department for Dermatology, Medical University of Vienna
Internal Review: Priv.-Doz. Dr. phil. Claudia Wild

Correspondence: Melanie Walter, melanie.walter@aihta.at

This report should be referenced as follows:
Walter, M. and Gassner, L. Liposuction for surgical therapy of lipoedema. AIHTA Decision Support Documents No. 125; 2021. Vienna: Austrian Institute for Health Technology Assessment GmbH.

Conflict of interest
All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer
The external reviewers did not co-author the scientific report and did not necessarily all agree with its content. Only the AIHTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the AIHTA.

The HTA Core Model®, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: HTA Core Model®, Version 4.2. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided using the Model.

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

IMPRINT
Publisher:
HTA Austria – Austrian Institute for Health Technology Assessment GmbH
Garnisongasse 7/Top 20 | 1090 Vienna – Austria
https://www.aihta.at/

Responsible for content:
Priv.-Doz. Dr. phil. Claudia Wild, managing director

AIHTA Decision Support Documents do not appear on a regular basis and serve to publicise the research results of the Austrian Institute for Health Technology Assessment.

AIHTA Decision Support Documents are only available to the public via the Internet at http://eprints.aihta.at/view/types/hta_report.html.

AIHTA Decision Support Documents No.: 125

ISSN online 1998-0469

Content

List of figures

List of tables

List of abbreviations

AE.....Adverse events
AWMF .....Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.
BMASK.....Bundesministerium für Arbeit, Soziales, Gesundheit und Konsumentenschutz
BMI .....Body mass index
CDT .....Combined (complex) decongestive therapy
CT.....Controlled trial
DVT.....Deep vein thrombosis
FU .....Follow-up
G-BA.....Gemeinsamer Bundesausschuss
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
ICD .....International Statistical Classification of Diseases and Related Health Problems
ICU.....Intensive care unit
IHE.....Institute of Health Economics
m.....Mean
NA .....Not available/not applicable
NR .....Not reported
NRCT.....Non-randomised controlled trial
NRS .....Non-randomised study
WAL.....Water jet-assisted liposuction
p.....p-value
PAL .....Power-assisted liposuction
Pat .....Patient*innen
Pkt .....Punkt(e)
pts.....Patients
QoL .....Quality of life
RCT.....Randomised controlled trial
RoB.....Risk of bias
SAE.....Serious adverse events
SD.....Standard deviation
TAL .....Tumescent anaesthesia liposuction
VAEV .....Verwaltung von Änderungs- und Ergänzungsvorschlägen zum Leistungskatalog des BMASK
VAS .....Visual Analogue Scale
VAL .....Vibration-assisted liposuction
WAL.....Water jet-assisted liposuction

Executive Summary

Introduction

liposuction as surgical intervention for lipoedema (painful disproportional fat distribution disorder) compared to conservative treatment

Lipoedema is a chronic and progressive fat distribution disorder characterised by a symmetrical disproportional increase of adipose tissue on the extremities. The disorder is most commonly associated with pain, oedemas, increased tendency of bruising, as well as sensory dysfunctions on the affected limbs, resulting in severely reduced quality of life (QoL) for exclusively female patients. According to current clinical guidelines, conservative treatment of lipoedema consists of manual lymphatic drainage, compression garments, or both combined as complex decongestive therapy (CDT). If conservative therapy does not result in sufficient improvement of symptoms, a surgical intervention, in the form of liposuction under tumescence anaesthesia, may be indicated.

synthesis of evidence for comparative clinical effectiveness and safety

This systematic review aims to assess the clinical effectiveness and safety of liposuction in patients with lipoedema (stage I-III) in comparison to any conservative treatment, concerning patient-relevant outcomes, as reduction of pain, reduction in the size of extremities, improvement of QoL, and procedure-related adverse events.

Methods

systematic literature search, qualitative data analysis, methodological quality of the studies

A systematic literature search was conducted in December 2020 in five databases to answer customised research questions on clinical effectiveness and safety-related outcomes, yielding in overall 294 potentially relevant hits. One additional hit was identified by hand search. The study selection, data extraction, and assessment of the methodological quality of the studies were performed by two independent researchers.

Results

6 prospective (+1 retrospective) single-arm before/after studies

A total of six prospective and one retrospective single-arm before/after studies were eligible for inclusion in the current report. Overall, data on safety and clinical effectiveness were evaluated in 492 and 467 female patients of all three lipoedema stages, respectively. The post-operative follow-up ranged from six months to twelve years.

Clinical effectiveness

no controlled studies were identified

Due to the lack of controlled trials, no conclusions on the comparative clinical effectiveness of liposuction for lipoedema could be made. Therefore, data from the prospective single-arm studies comparing patient-reported complaints before and after the liposuction were analysed.

statistically significant before vs after improvements in patient complaints on pain and QoL, reduction in size of extremities

All six prospective studies reported statistically significant improvements in pain outcomes pre- vs post-liposuction. These effects were reported beginning at a six-month follow-up but also up to twelve years after the intervention. Reduced sizes of patients' extremities before-and-after liposuction were reported in three of the included studies, in terms of reduced leg volume and circumference of lower extremities. Statistically significant changes in lipoedema-related QoL outcomes were reported by four studies. Further, reduction in complaints about oedema/swelling, bruising and sensory dysfunctions were reported in some of the included studies.

Safety

overall 17 post-operative adverse events in 492 pts

Concerning safety outcomes, 17 (in 492 pts; 3.5%) post-operative adverse events occurred overall. Five of these patients were affected by serious adverse events. Other reported procedure-related adverse events comprise, e.g. post-operative wound infections and bleedings.

Upcoming evidence

1 ongoing RCT (450 pts)

Concerning upcoming evidence, one ongoing study (NCT04272827), a large multi-centre RCT with 450 patients from Germany, could be identified. Primary completion is expected in July 2024.

Reimbursement

currently not reimbursed in Austria

Currently, liposuction for lipoedema therapy is not reimbursed by the Austrian health care system.

Discussion

strength of evidence for clinical effectiveness not estimable; "very low" strength of evidence for safety outcomes

Overall, the strength of evidence on clinical effectiveness cannot be determined. For safety outcomes, the strength of evidence is "very low" according to the GRADE scheme.

The overall risk of bias was considered moderate to high due to the uncontrolled design of the studies, the single-centred setup, no information about exclusion criteria, lack of blinding of the investigators, and patients entering the studies during different stages of the disease.

evidence gaps: robust RCTs, sub-analyses depending on lipoedema stages, comparison of surgical techniques, comorbidities, consequences on society

The included uncontrolled studies demonstrate that liposuction may potentially reduce lipoedema-associated clinical symptoms and improve the quality of life of affected patients. Still, in addition to the need for robust randomised controlled trials (RCTs), evidence gaps concern more detailed stratified analyses. These analyses depend on the stages of lipoedema, direct comparisons of different liposuction techniques (e.g., power-assisted and water jet-assisted liposuction), (sub-)analyses of comorbidities, and quantified consequences of lipoedema for society (e.g., occupational restrictions or full disability to work). An assessment of effect sizes comparing inpatient vs outpatient settings, especially in terms of safety, is likewise of interest.

In terms of external validity, the data are considered generalizable to the Austrian context, as the countries of recruitment were Germany and Switzerland.

Conclusion

currently not recommended to include in the catalogue of benefits

The current evidence is not sufficient to prove that liposuction is more effective and equally safe or equally effective but safer than conservative therapy for lipoedema. Consequently, inclusion in the hospital benefit catalogue is currently not recommended.

Zusammenfassung

Einleitung

Das Lipödem ist eine chronisch fortschreitende Fettverteilungsstörung, die durch eine symmetrische, disproportionale Vermehrung des subkutanen Fettgewebes der Extremitäten, hauptsächlich an den Beinen, gekennzeichnet ist. Die Erkrankung geht meist mit Schmerzen, Schwellungen, einer starken Neigung zu Blutergüssen sowie Sensibilitätsstörungen an den betroffenen Gliedmaßen einher und führt bei den ausschließlich weiblichen Patienten zu einer stark reduzierten Lebensqualität (quality of life; QoL). Schätzungsweise sind bis zu 10 % der weiblichen Bevölkerung betroffen. Genaue Prävalenzen, auch Österreich-spezifische, sind allerdings nicht verfügbar.

Liposuktion als chirurgische Intervention im Vergleich zu konservativen Therapiemaßnahmen (u. a. kombinierte physikalische Entstauungstherapie) für die schmerzhafte disproportionale Fettverteilungstörung Lipödem

Die Pathophysiologie des Lipödems sowie mögliche Risikofaktoren sind noch weitgehend unbekannt. Viele Patientinnen weisen eine positive Familienanamnese mit ebenfalls betroffenen Verwandten auf, was auf genetische Risikofaktoren schließen lässt. Hiervon könnte der Östrogenhaushalt der Patientinnen betroffen sein, da sich ein Lipödem in der Regel in Zeiten hormoneller Veränderungen wie Pubertät, Schwangerschaft oder Menopause manifestiert.

Nach den aktuellen klinischen Leitlinien besteht die konservative Therapie des Lipödems u. a. aus manueller Lymphdrainage und Kompressionstherapie, bzw. einer Kombination dieser in Form der komplexen Entstauungstherapie (complex decongestive therapy; CDT). Führt diese nicht zu einer ausreichenden Besserung der Symptome und Beschwerden, kann ein operativer Eingriff in Form einer Liposuktion in Tumeszenz-Anästhesie (TAL) indiziert sein.

laut klin. Leitlinien: Liposuktion nur, wenn konservative Therapie keine Erfolge erzielt

Die TAL ist eine sowohl in der ästhetischen Chirurgie als auch in der Behandlung des Lipödems lange etablierte chirurgische Methode. Hierbei werden mehrere Liter einer Tumeszenz-Flüssigkeit in das Unterhautgewebe infiltriert und anschließend zusammen mit den gelösten Fettzellen mittels Mikrokanülen wieder abgesaugt. Verschiedenste technische Weiterentwicklungen der TAL befinden sich auf dem Markt, u. a. die Power-assistierte Liposuktion (PAL, vibrationsassistierte Liposuktion) sowie die Wasserstrahl-assistierte Liposuktion (WAL).

verschiedene Techniken: Power-assistierte Liposuktion und Wasserstrahl-assistierte Liposuktion

Methoden

Ziel der vorliegenden systematischen Übersichtsarbeit war es, den Einsatz von Liposuktion bei Patientinnen mit Lipödem (Stadium I-III) im Vergleich zu konservativen Therapien (z. B. CDT) zu untersuchen. Die Forschungsfrage war, ob die Liposuktion wirksamer und gleich sicher bzw. gleich wirksam, aber sicherer hinsichtlich Patientinnen-relevanter klinischer Endpunkte, wie Schmerzreduktion, Reduktion des Umfangs der Extremitäten und Verbesserung der Lebensqualität ist. Dies wurde angelehnt an die Bewertungselemente des „EUnetHTA Core Model® for Rapid Assessment of Relative Effectiveness“ beantwortet.

Ziel: Synthese der Evidenz für vergleichende klin. Wirksamkeit und Sicherheit

Eine systematische Literatursuche wurde im Dezember 2020 in fünf Datenbanken durchgeführt (Medline via Ovid, Embase, The Cochrane Library, CRD [DARE, NHS-EED, HTA], HTA-INAHTA). Die Suche beschränkte sich auf kein Publikationsjahr oder Studiendesign, jedoch auf Artikel, die in englischer oder deutscher Sprache veröffentlicht wurden.

systematische Suche in 5 Datenbanken: insgesamt 295 Treffer nach Deduplizierung,

Suche in den Registern für klinische Studien nach laufenden Studien: 14 potenzielle Treffer

Insgesamt wurden hierbei 399 Treffer mit einbezogen. Zusammen mit einem Artikel, der über die Handsuche gefunden wurden, betrug die Gesamtzahl der identifizierten Zitate nach Deduplizierung 295. Eine Suche nach laufenden Studien in drei klinischen Studienregistern (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) wurde im Januar 2021 durchgeführt. Diese Suche ergab einen potentiell relevanten Treffer (von 14 gesamt).

RoB- und GRADE-Bewertung

Die Studienauswahl, Datenextraktion und Bewertung der methodischen Qualität der Studien wurde von zwei unabhängigen Personen durchgeführt. Das Risiko einer Verzerrung (risk of bias; RoB) der eingeschlossenen Studien wurde systematisch mit Hilfe der IHE-Checkliste für Fallserien bewertet. Darüber hinaus wurden, falls möglich, die Daten zu jeder ausgewählten Endpunktkategorie studienübergreifend nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet.

Klinische Wirksamkeit

Endpunkte für Empfehlung hinsichtlich der Wirksamkeit

Zur Bewertung der klinischen Wirksamkeit wurden die Patientinnen-relevanten entscheidenden Endpunkte Schmerz, QoL und die Verringerung des Umfangs der Extremitäten für eine Empfehlung herangezogen.

Sicherheit

Endpunkte für Empfehlung hinsichtlich der Sicherheit

Zur Bewertung der Sicherheit wurden die entscheidenden Endpunkte schwerwiegende unerwünschte Ereignisse (serious adverse events; SAE) sowie generelle postoperative (Verfahrens-bedingte) unerwünschte Ereignisse (adverse events; AE) für eine Empfehlung herangezogen.

Ergebnisse

Verfügbare Evidenz

keine kontrollierten Studien verfügbar; 6 prospektive einarmige Vorher-Nachher-Studien; +1 retrospektive

Im Rahmen der Suchstrategie wurden keine vergleichenden Studien identifiziert, daher besteht die Evidenzbasis zur Bewertung der Liposuktion bei Lipödem aus einarmigen Vorher-Nachher-Studien. Insgesamt wurden sechs prospektive Studien und zusätzlich eine retrospektive Studie, die in insgesamt elf Publikationen veröffentlicht wurden, eingeschlossen.

467 weibliche Pat. (6 Studien) für vorher vs. nachher Vergleich; alle Lipödem Stadien vertreten; FU zwischen 6 Monaten und 12 Jahren

zusätzliche 25 Pat. für Sicherheit (1 Studie)

In den prospektiven Studien, welche für die Evaluierung der klinischen Wirksamkeit herangezogen wurden, waren insgesamt 467 Patientinnen, die für mindestens eine postoperative Nachuntersuchung zur Verfügung standen, eingeschlossen. Weitere 25 Patientinnen der retrospektiven Studie wurden für die Evaluierung der Sicherheits-Endpunkte herangezogen. Die Patientinnen verteilten sich über alle Schweregrade des Lipödems (Stadium I-III) und wurden zwischen sechs Monaten und zwölf Jahren nach der Liposuktion nachuntersucht. Bei den angewandten Fettabsaugungstechniken, die alle in Tumeszenz-Lokalanästhesie durchgeführt wurden (mit Ausnahme der retrospektiven Studie), handelte es sich meist um die power- oder wasserstrahl-assistierte Liposuktion. Je nach Schweregrad ihres Lipödems wurden die Patientinnen in bis zu sieben Liposuktions-Sitzungen behandelt.

Klinische Wirksamkeit

klinische Wirksamkeit: keine Vergleiche zwischen Liposuktion und konservativer Therapie möglich

Aufgrund des Fehlens kontrollierter Studien können keine Aussagen zur vergleichenden klinischen Wirksamkeit der Liposuktion bei Lipödem getroffen werden. Nichtsdestotrotz zeigen die Daten der prospektiven einarmigen Vorher-Nachher-Studien einen möglichen positiven Effekt hinsichtlich entscheidender klinischer Endpunkte.

Alle sechs prospektiven Studien berichteten über eine statistisch signifikante Schmerzreduktion nach der Liposuktion. Dieser Effekt konnte nach einem kurzen Follow-up von sechs Monaten, bis hin zu zwölf Jahren nach dem letzten Eingriff, beobachtet werden, was auf mögliche positive Langzeiteffekte der Liposuktion bei Lipödem hinweist. Über eine Reduktion der Größe der betroffenen Extremitäten vor und nach der Liposuktion wurde in drei der eingeschlossenen Studien berichtet und über statistisch signifikante Verbesserungen der Lipödem-bezogenen Lebensqualität in vier Studien.

alle Studien (n=6) zeigen eine statistisch signifikante Reduktion der Pat.-Beschwerden bzgl. Schmerzen;
3 Studien berichten eine Reduktion des Beinumfangs/-volumen;
4 Studien berichten eine statistisch signifikante Reduktion der Pat.-Beschwerden bzgl. Lebensqualität

Darüber hinaus wurden in einigen der eingeschlossenen Studien eine Verringerung der Patientinnen-Beschwerden bezüglich Schwellungen, Blutergüssen sowie eine Milderung von Sensibilitätsstörungen (z. B. Berührungsempfindlichkeit, Spannungsgefühle und „schwere Beine“) berichtet. Auch verbesserten sich Lipödem-assoziierte Bewegungseinschränkungen postoperativ, welche von allen sechs eingeschlossenen prospektiven Studien berichtet wurden.

Sicherheit

In Abwesenheit von Daten aus kontrollierten Studien konnten auch für die Bewertung der Sicherheitsendpunkte keine Vergleiche von Liposuktion mit konservativen Therapieoptionen durchgeführt werden.

Sicherheit:
keine Vergleiche der Endpunkte möglich

Alle sieben eingeschlossenen Studien berichteten über das (Nicht-)Vorkommen von unerwünschten Ereignissen. Bei den 492 Patientinnen, die für die Sicherheitsanalyse in Frage kamen, traten insgesamt 17 (3,5 %) postoperative unerwünschte Ereignisse auf. Fünf dieser Patientinnen waren von schwerwiegenden unerwünschten Ereignissen betroffen: ein epileptischer Anfall, eine einmalige postoperative Anämie, welche eine Bluttransfusion erforderte, eine mikroskopische pulmonale Fettembolie, ein akutes Lungenödem, das eine erneute Aufnahme auf der Intensivstation erforderte, und eine Patientin mit einem Abszess, welcher einen erneuten Krankenhausaufenthalt erforderte. Andere Verfahrens-bedingte unerwünschte Ereignisse waren meist postoperative Wundinfektionen oder Blutungen.

insgesamt
17 postoperative unerwünschte Ereignisse in 492 Pat. (7 Studien)

Kostenerstattung

Zum Zeitpunkt der Berichtverfassung werden die Kosten für eine Liposuktion zur Therapie des Lipödems in Österreich nicht erstattet. In Deutschland hingegen, wird der Eingriff bei Patientinnen mit Lipödem Stadium III unter bestimmten Bedingungen rückvergütet.

in Ö derzeit keine Kostenerstattung

Laufende Studien

Es konnte eine laufende Studie zur Liposuktion bei Lipödem identifiziert werden. Die sogenannte LIPLEG-Studie (NCT04272827) ist ein in Deutschland durchgeführtes multizentrisches RCT, welches den Endpunkt Schmerzreduktion nach Liposuktion im Vergleich zur alleinigen CDT evaluiert. Die Rekrutierung von 450 Patientinnen aller Lipödem-Stadien ist bereits abgeschlossen und das geschätzte primäre Abschlussdatum wird mit Juli 2024 angegeben.

1 laufendes RCT in D (450 Pat.)

Diskussion

Stärke der Evidenz für klinische Wirksamkeit nicht bestimmbar; sehr geringe Stärke der Evidenz für Sicherheitsendpunkte

Das Ziel des vorliegenden Berichts war es, die klinische Wirksamkeit und Sicherheit der Liposuktion bei Lipödem im Vergleich zu konservativen Maßnahmen zu bewerten. Insgesamt kann die Stärke der Evidenz für die klinische Wirksamkeit jedoch nicht bestimmt werden, da keine kontrollierten Studien zur Beurteilung dieser identifiziert werden konnten. Für die Sicherheitsendpunkte wurde die Evidenzstärke als „sehr gering" eingestuft.

Bias-Risiko: moderat bis hoch; hauptsächlich wegen des unkontrollierten Studiendesigns und Pat.-berichteter Endpunkte

Das Verzerrungsrisiko wurde als moderat bis hoch eingestuft, in erster Linie aufgrund des unkontrollierten Studiendesigns, aber auch wegen des monozentrischen Settings, der teilweise fehlenden Informationen über Ausschlusskriterien, fehlender Verblindung, aber auch weil die Patientinnen in verschiedenen Stadien der Erkrankung in die Studien eintraten und es keine stratifizierten Analysen gab. Zusätzlich basieren die Ergebnisse der eingeschlossenen Studien fast ausschließlich auf subjektiven Angaben (z. B. Schmerz), was ebenfalls zu einer möglichen Verzerrung der Ergebnisse führen kann.

Evidenzlücken: vor allem RCTs nötig; stratifizierte Analyse nach Lipödem-Stadien; Vergleich verschiedener Liposuktions-Techniken

Neben dem Bedarf an robusten randomisierten kontrollierten Studien (RCTs) bestehen noch weitere Evidenzlücken in Bezug auf detailliertere stratifizierte Analysen in Abhängigkeit von den Stadien des Lipödems, direkte Vergleiche verschiedener Liposuktionstechniken (z. B. Power-assistierte und Water-Jet-assistierte Liposuktion), (Sub-)Analysen von Komorbiditäten und die Quantifizierung möglicher Folgen des Lipödems für die Gesellschaft (z. B. berufliche Einschränkungen oder vollständige Arbeitsunfähigkeit der betroffenen Frauen). Eine Bewertung von Effektgrößen im Vergleich stationärer vs. ambulanter Settings, insbesondere im Hinblick auf die Sicherheit, ist ebenfalls von Interesse.

unerwünschte Ereignisse sollten auch basierend auf der Zahl der durchgeführten Liposuktionen (pro Pat.) erhoben werden

Im Rahmen der Interpretation der Sicherheitsergebnisse sollten die unerwünschten Ereignisse immer zusätzlich anhand der Zahl durchgeführten Liposuktions-Sitzungen und nicht nur der Zahl der eingeschlossenen Patientinnen erhoben werden. Da diese meist Verfahrens-abhängig sind erhöht sich das Risiko von Komplikationen mit der Zahl der Eingriffe welche die jeweilige Patientin für eine erfolgreiche chirurgische Lipödem-Therapie benötigt.

Daten sind auf den österreichischen Kontext übertragbar

Hinsichtlich der externen Validität sind die Daten auf den österreichischen Kontext übertragbar. Die Rekrutierung der Patientinnen wurde in Deutschland und der Schweiz durchgeführt.

Empfehlung

Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen

Die derzeitig vorliegende Evidenz ist nicht ausreichend, um zu belegen, dass die untersuchte Intervention Liposuktion bei Patientinnen mit Lipödem effektiver und gleich sicher (oder gleich effektiv und sicherer) ist als die konservative Therapie. Daher wird eine Aufnahme in den Leistungskatalog derzeit nicht empfohlen.

ohne kontrollierte Studien keine Schlussfolgerungen über Wirksamkeit und Sicherheit möglich

Die limitierte Evidenz der eingeschlossenen unkontrollierten Studien deutet dennoch darauf hin, dass die Liposuktion einen möglichen klinischen Nutzen in Bezug auf die signifikante Reduktion von Lipödem-assoziierten Symptomen bietet. Eine derzeit laufendes robustes RCT könnte die positiven Befunde der Liposuktions-assoziierten Schmerzlinderung und anderer Patientinne-relevanter Endpunkte der bestehenden einarmigen vorher-/nachher Studien unterstützen. Daher wird eine Re-Evaluierung nach Abschluss dieses RCTs, voraussichtlich im Jahr 2025, empfohlen.

Re-Evaluierung für 2025 empfohlen

1 Background

1.1 Overview of the disease, health condition, and target population[1]

Lipoedema is a chronic, painful fat distribution disorder, which is found almost exclusively in women. Its progressive and incurable course is characterised by a marked disproportional fat distribution between patients' extremities and trunk [1, 2] [2].

Lipödem ist eine chronisch fortschreitende, schmerzhafte Fettverteilungsstörung

Lipoedema almost exclusively affects women with onset in puberty, pregnancy, or menopause. Diagnoses in men are rarely described in single case reports, and often associated with hormonal therapies, hormonal disorders, or in combination with liver cirrhosis [1][3]. There is a paucity of objective criteria to confirm the diagnosis of lipedema. This might lead to underdiagnosis but as well to overdiagnosis [1, 3]. Exact data on the prevalence of lipedema in the female population is in the range of 10% [4]. Austria-specific prevalence data are not available[4].

ausschließlich Frauen betroffen

Prävalenz: ~10 % der erwachsenen Frauen, Zahl der Diagnosen in Ö nicht bekannt

In contrast to the clinical picture of obesity, often a mismatch between Body Mass Index (BMI) and waist-hip ratio is described in lipoedema patients. The symptomatic increase in subcutaneous adipose tissue always affects the lower limbs and sometimes also the arms. Sometimes parts of the trunk are also affected. Different types can be classified based on the localisation of the lipoedema [2, 5]:

Missverhältnis zwischen BMI und Taille/Hüften-Verhältnis; Klassifizierung anhand der Lokalisation:

- Type I: Buttocks and saddlebags
- Type II: Thighs (to the knee)
- Type III: Entire lower limb
- Type IV: Arms (often associated with type II or III)
- Type V: Calves only

Typ I-V

Feet and hands are not affected by the disproportions; the pathognomic so-called cuff phenomena occurs at knees, ankles, elbows, and wrists. Lipoedema fat is unresponsive to traditional weight-loss interventions such as physical activities or dietary measures. Further, there exists a marked tendency for bruising and oedemas [1, 3, 6].

Füße und Hände sind nicht betroffen, Neigung zu Hämatombildung, Ödeme

Lipoedema is a chronic progressive disorder, which manifests in different morphological stages [1][5]:

- **Stage I:** Smooth skin surface, evenly thickened, homogeneous subcutis with small nodules
- **Stage II:** Uneven skin surface, nodular structured in thickened subcutis
- **Stage III:** A marked increase in size of extremities, disfiguring fat deposits

drei Stadien beschreiben Schweregrad der Erkrankung

---

[1] This section addresses the EUnetHTA Core Model® domain CUR.

[2] A0001 – For which health conditions, and for what purposes is liposuction used?

[3] A0007 – What is the target population in this assessment?

[4] A0023 – How many people belong to the target population?

[5] A0004 – What is the natural course of lipoedema?

ICD-10-GM: E88.2 Lipödem

In the current German ICD-10 catalogue (ICD-10-GM-Version 2021) [7] lipoedema is listed as *E88.20 lipoedema, stage I, E88.21 lipoedema, stage II, E88.22 lipoedema, stage III,* and *E88.28 other or unspecified lipoedema*[6].

Patientinnen leider unter Druckschmerz, Berührungsempfindlichkeit, Spannungsgefühl, „schweren" Beinen, psychologischen Beeinträchtigungen

Besides these clinical symptoms, the disease has a great impact on the QoL of the affected individuals. Patients suffer from pain upon pressure, touch sensitivity, and a feeling of heaviness and tension in the affected limbs. These symptoms worsen over the course of the day and especially after prolonged standing or sitting, and in warm weather. In some cases, there may also be severe spontaneous pain [1, 2]. Aesthetic impairments may impact psychological health, lowered self-esteem, and emotional disturbance [2][7].

Bewegungseinschränkungen, orthopädische Komplikationen

Furthermore, the increase in the extremities' volume and the disproportion between trunk and extremities may result in restrictions on movement, scouring effects, and gait dysfunctions with axial misalignment of the legs and orthopaedic complications [1]. These complications may result in (partial) occupational incapacity of the affected women[8].

genetische Veränderungen/ Vererbung als mögliche Risikofaktoren

Ätiologie und genaue Pathomechanismen noch ungeklärt

The aetiology and pathophysiology of lipoedema are still undiscovered and remains on various hypotheses [1, 2]. It is reported that 60% of the patients have a positive family history and affected first-degree relatives, which suggest inheritance as a risk factor [2, 5][9]. These genetic factors may influence the patients' oestrogen status, as lipoedema usually first manifests in periods of hormonal change such as puberty, pregnancy, or menopause. Another unclear aspect is if, in lipoedema, the subcutaneous adipocytes of the affected areas become more numerous (hyperplasia) or grow in size (hypertrophy). Further, the pathophysiological hypothesis of primary microvascular dysfunction in the lymphatic and blood capillaries may cause easy bruising. The increased capillary permeability of proteins into the extracellular compartment leads to tissue oedema. Lastly, the lipoedema-typical increased perception of pain may be caused by dysregulation of loco-regional sensory nerve fibres through an inflammatory mechanism [2].

1.2 Current clinical practice[1]

zwei klinische Leitlinien: AWMF und Niederlande

Currently, two clinical guidelines for diagnosis and treatment options of lipoedema, one from Germany [1] and one from the Netherlands [3][10], are published. The consensus-based guideline of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF) for 'S1-Leitlinie Lipödem'[11] is also applied as guidance in Austria. Further, in a very recent publication in the *Deutsche Ärzteblatt International*, the current standard of care, including diagnostic and treatment pathway, in Germany is described [2].

---

[6] In the international WHO ICD-10 catalogue (Version 2019) lipoedema does not yet have a registered diagnosis. Whereas, in the upcoming WHO ICD-11 system (Version 09/2020) it will be listed as EF02.2 Lipoedema.

[7] A0005 – What is the burden of disease for the patients with lipoedema?

[8] A0006 – What are the consequences of lipoedema for the society?

[9] A0003 – What are the known risk factors for lipoedema?

[10] Systematic search for evidence, but recommendation based on expert consensus.

[11] Please note: Guideline is expired as of 30.06.2020, currently under revision and expected to be updated in late 2021.

klinische Untersuchung inklusive Anamnese, Inspektion und Palpation

The standard diagnostic evaluation of lipoedema via an extensive clinical examination comprises anamnesis (including family history), inspection, and palpation, including the following diagnostic criteria (see 1.1):

- Onset of disease in puberty, during pregnancy, or menopause
- Bilateral, symmetrical, disproportional fatty tissue hypertrophy on the limbs
- Sparing of hands and feet
- Sensory symptoms as 'heavy' legs and tension in the affected limbs
- Spontaneous pain, pain upon pressure, and touch sensitivity
- Stable limb circumference with weight reduction or caloric restriction
- Worsening of symptoms over the course of the day

Staging nach Schweregrad des Lipödems: Stadium I-III

Patients with lipoedema show a negative Stemmer sign (positive Stemmer sign in case of secondary lymphoedema: the skin fold on the dorsum of the second and third toe is thickened and cannot be lifted) [1, 2][12]. The Dutch guideline's working group assembled a list of clinical symptoms to calculate a diagnostic score [3]. Following the clinical assessment, a staging of severity and morphology of lipoedema is performed according to the aforementioned stages and ICD-10-GM codes (see 1.1). However, symptoms and the subjective degree of suffering may not always correlate with the disease stage [2].

Differentialdiagnosen: Lipohypertrophie, Adipositas, Lymphödem

Laboratory testing of renal and hepatic dysfunctions, hypothyroidism, pathological lipid profiles, and insulin resistance should be performed to assess differential diagnoses. Ancillary diagnostic testing, such as imaging procedures and lymphography, which requires special equipment, is usually only used to rule out other diagnoses [2].

The most relevant differential diagnoses of lipoedema include lipohypertrophy, obesity, and non-lipoedema-associated lymphoedema [1, 3]. Their clinical characteristics in comparison to lipoedema are shown in Table 1-1.

Verlaufskontrolle anhand von Gewicht, BMI, Taille/Hüfte-Verhältnis Umfang der Extremitäten empfohlen

Standardised anthropometric measures should be part of routine clinical follow-ups to assess the spontaneous course of lipoedema and to monitor the response to treatments. These follow-ups include weight, BMI, waist-hip ratio, waist-height ratio, and limb circumference and volume. Especially in patients with difficult differential diagnosis, lipoedema vs obesity, these measures can support diagnosing lipoedema (absent reduction of size of the extremities despite a reduction in total weight and trunk fat) [1, 3]. Additional assessment of pain perception in regular intervals is recommended [2] and should be performed using a Visual Analogue Scale (VAS), and a questionnaire assessing patients' complaints developed by Schmeller et al. [8][13].

[12] A0024 – How is lipoedema currently diagnosed according to published guidelines and in practice?

[13] A0025 – How is the lipoedema condition currently managed according to published guidelines and in practice?

Table 1-1: Differential diagnoses of lipoedema. Sources: [1, 2]

	Lipoedema	Lipohypertrophy	Obesity	Lymphoedema
Sex	female	female/male	female/male	female/male
Family history	++	(+)	+++	primary ++ secondary Ø
Symmetry	+++	(+)	+++	(+)
Swollen feet	Ø	(+)	(+)	+++
Increased fatty tissue	+++	+++	+++	(+)
Disproportion	+++	+++	(+)	+
Oedema	depending on stage Ø/+++	Ø	(+)	+++
Tenderness	+++	Ø	Ø	Ø
Haematoma tendency	+++	(+)	Ø	Ø
Influence of diet	(+)	Ø	+++	Ø

+ to +++ – present, (+) – possible, Ø – absent

Therapieziele: Beseitigung oder Linderung von Beschwerden (Schmerz oder Bewegungseinschränkungen), Vermeidung von Fortschreiten der Krankheit

Due to the fact that the cause of lipoedema remains unknown, there is currently no curative therapy available. Treatment is primarily focused on reducing patients' complaints, disability, and functional limitations to improve QoL and prevent disease progression [3, 6]. The German AWMF S1 guideline defined lipoedema therapy's major goals in more detail: removal or improvement of symptoms and complaints (especially pain, oedema, and disproportion) and prevention of complications, which may occur with a progressive manifestation of the disease, particular with an increase in leg volume. This leg volume may further increase the risk of dermatological (e.g., macerations, infections), lymphatic (e.g., erysipelas, lymphoedema), and orthopaedic complications (e.g., gait problems) [1]. In Table 1-2, an overview of therapy goals and corresponding current options of treatments is provided.

konservative Therapie vs. chirurgischer Eingriff

In general, recommended treatment options for lipoedema, should be adopted in an individual, stage-specific manner. These options can be divided into conservative treatments (wearing of compression garments, manual lymphatic drainage, education of patients, weight control, dietary modifications, complex decongestive therapy [CDT], psychological therapy) and surgical interventions – mainly liposuction [1-3][13].

umfassende Information der Patientinnen als Voraussetzung

Patient education presents the first step in lipoedema management, including comprehensive information on the nature of the disease and its chronic progression. Patients should be adequately educated on the different treatment options, especially CDT; information material and contact data of patients' organisations should be provided [2].

Table 1-2: Overview of therapy goals and corresponding options of treatment. Sources: [1, 2]

Goal	Therapy options
Reduction of oedema	Compression Manual lymphatic drainage Instrumental intermitting compression Movement Liposuction
Pain relief	Compression Manual lymphatic drainage Instrumental intermitting compression Liposuction
Reduction of bruising	Manual lymphatic drainage Instrumental intermitting compression Liposuction
Reduction of pathologically increased subcutaneous fatty tissue	Liposuction
Prevention/elimination of mechanical complications	Compression Liposuction Other plastic surgical interventions
Reduction of possible concomitant obesity	Movement Dietary modifications Guideline-based obesity therapy (interdisciplinary)

Weight control and dietary modifications represent further initial steps in lipoedema treatment. Common accompanying obesity has to be treated, according to clinical guidelines.

Gewichtskontrolle und Ernährungsumstellung, um eventuelle Adipositas zu verhindern oder zu mildern

The increased subcutaneous fat depots in lipoedema are considered to be diet-resistant [2]. Therefore, dietary modifications are mandatory in patients with accompanying obesity and should be focussed on hypocaloric nutrition, aiming to reduce non-lipoedema fat tissue [1].

Combined (or Complex) decongestive therapy (CDT) comprises the elements of manual lymphatic drainage, compression therapy (garments), exercise therapy, and skincare, aiming at the reduction of pain and size of oedema.

kombinierte physikalische Entstauungstherapie: Lymphdrainage, Kompression, Bewegungstherapie und Hautpflege

Compression therapy includes dressings and special garments (stockings, sleeves). Due to the size of extremities, lipoedema patients often require customised, flat-knit compression garments. In addition to manual lymphatic drainage, but not as a substitute, instrumental intermitting compression may help in improving lipoedema symptoms. CDT has to be applied on a regular basis, with an individually adapted intensity and frequency to achieve treatment success. Reduction of oedema should be measured regularly to control the success of treatment [1]. CDT most often takes place in an outpatient setting, but if patients do not benefit from CDT, hospitalisation in specialised lymphological units may be indicated [2]. The Dutch guideline recommends compression therapy if an oedema component is present. It does not recommend manual lymphatic drainage, as lipoedema has no lymphological impairment (except secondary lymphoedema) [3].

Exercise therapy, especially water activities (e.g., swimming, aqua jogging, aqua aerobic, aqua cycling), are recommended. These activities relieve joints, and the pressure underwater may have a lymphatic drainage effect [1].

körperliche Aktivität, besonders Sport im Wasser

unterstützende Psychotherapie falls benötigt

Psychotherapy is recommended in the presence of coexisting eating disorders and other lipoedema-associated psychological symptoms, such as reduced self-esteem and signs of depression [1].

häufig: Liposuktion

Liposuction is the primary surgical intervention for lipoedema, and its clinical effectiveness and safety in comparison to conservative treatment is the topic of the present assessment. Liposuction, in detail, will be described in the following section (see 1.3).

selten: Dermolipektomie bei sehr fortgeschrittenem Lipödem

Surgical debulking (dermato-fibro-lipectomy) is only indicated in patients with highly advanced lipoedema stages accompanying lymphoedema and strongly fibrotic tissue [2].

1.3 Features of the intervention[14]

Lipopsuktion als etablierte Therapie für Lipödem

Liposuction is an established therapeutic option for lipoedema recommended by current clinical guidelines [1, 2][2]. Its superiority in clinical effectiveness for lipoedema therapy compared to conservative treatments (e.g., CDT) is evaluated in this report.

Tumeszenzliposuktion (TAL) mit Kanülen

It is a surgical procedure in which parts of the subcutaneous fatty tissue are suctioned off with the help of cannulas. Over the years, **tumescent anaesthesia liposuction (TAL)** has emerged from various cosmetic liposuction techniques as the preferred procedure, called the 'wet-technique'. The outdated 'dry-technique' liposuction under general anaesthesia without infiltration substrate, is not subject of this assessment[15].

TAL für Lipödem seit 2006 etabliert

TAL was invented and first performed in 1987 [9]. Currently¸ TAL is widely utilised around the world and is the standard for liposuctions in aesthetic surgery, showing a sufficient safety profile with a low risk of complications [10, 11]. Surgical therapy of lipoedema using lymph-sparing liposuction in tumescent anaesthesia was initially described in [12] in 2006. Since then, it is established in the standard treatment of lipoedema [1, 3][16].

Infiltrations-Phase mit Einspritzung der Tumeszenz-Lösung

The technical procedure can be divided into two phases: infiltration and liposuction. During the infiltration phase, several litres of a tumescent fluid are infiltrated into the subcutaneous tissue using an infiltration device. This causes the interstitial tissue to swell and the blood vessels to constrict. Typically, this watery solution consists of an isotonic carrier (buffer), a local anaesthetic (e.g., lidocaine, prilocaine), and a vaso-constrictive agent (often adrenaline).

Absauge-Phase: unterschiedliche unterstützende Techniken

After a waiting period, the actual liposuction, the removal of the adipocyte/tumescent fluid mixture, is performed using microcannulas. Different types of cannulas should be used depending on the suction area, the thickness of the subcutaneous fatty tissue layer, and the consistency of the adipocytes. The cannulas may differ in diameter (2-6 mm) and the shape of their ends (sharp vs blunt cannulas; multi-hole cannulas; holes on one side or circular cannulas) [13].

---

[14] This section addresses the EUnetHTA Core Model® domain TEC.

[15] B0001 – What is liposuction?

[16] B0003 – What is the phase of development and implementation of liposuction?

Vibrations-unterstützte und Wasserstrahl-unterstützte Liposuktion häufig angewandt bei Lipödem

Different variations of this technique exist. **Power-assisted liposuction** (PAL, vibration-assisted liposuction) using vibrating microcannulas is the most common. Further, techniques differ according to the different amounts of liquid used (e.g., super-wet technique, **water jet-assisted liposuction** [WAL]) or the use of different types of energy sources (mechanical, laser, and ultrasound) to destroy the fat cells before suction [14].

In liposuction for lipoedema, all these techniques are utilised, but PAL and WAL are of particular importance. Cannulas with supplementary water jets or vibration functions cause the adipocytes to detach from the cell composite more easily and prevent suction and adhesion of the surrounding tissue to the cannulas. Therefore, PAL and WAL allow a reduction of procedure time [15, 16].

chirurgische Lipödem-Therapie kann mehrere einzelne Liposuktionsinterventionen beinhalten

A completed liposuction treatment most often comprises several separate interventions. In the course of a single session, liposuction may be performed on one or several limbs [15]. Especially high-volume liposuctions should be performed in multiple sessions; patients from whom more than three litres of pure adipose tissue have been aspirated should remain under post-operative-care for at least twelve hours after the procedure [2, 15, 17].

methodische Unterschiede zu Liposuktion im rein ästhetischen Bereich

In contrast to liposuction in an aesthetic context (e.g., local lipohypertrophy), technical differences are present when performed for lipoedema. Typically, liposuction for lipoedema includes more extensive areas, larger volume fat removals, circumferential treatments in multiple sessions, and more extended downtimes [5].

Liposuktion soll zusätzlich das pathologische Fettgewebe entfernen und Langzeiterfolge erzielen

The claimed benefit of liposuction for lipoedema, especially in contrast to CDT, is that it is the only available technique to correct lipoedema-specific pathologically increased fat deposits. Liposuction for lipoedema may yield long-term improvements to the typical symptoms. Compression therapy and manual lymphatic drainage cannot reduce the abnormal fatty tissue themselves. They only aim to reduce the painful feeling of tension and pressure, the tendency to form haematomas, and sequelae of lipoedema [2, 3][17]. Furthermore, the aim of liposuction for lipoedema is that the patient does not have to continue with conservative therapy, which otherwise usually has to be administered for the rest of the patient's life.

Liposuktion nur nach erfolgloser konsequent durchgeführter kombinierter physikalischer Entstauungstherapie

Liposuction can be considered as second-line or add-on therapy. It is only recommended if conservative therapy measures failed, i.e., complaints are insufficiently alleviated by other means or the disease still progresses [1, 2, 15]. Liposuction should not be performed in patients at any stage of the disease whose weight exceeds 120 kg or whose BMI exceeds 32 kg/m^2. They should be treated for obesity before the potential indication for liposuction is considered [1, 2][18].

normalerweise in lokaler Anästhesie (Tumeszenz-Anästhesie), aber auch unter Vollnarkose möglich

Usually, tumescent liposuction is performed under local anaesthesia, which, in addition to the absence of the risks of general anaesthesia, has a lower risk of thrombosis. Moreover, local anaesthesia enables active cooperation in positioning and immediate intraoperative control of the findings for possible fine corrections [1, 15, 17]. Nevertheless, liposuction for lipoedema can also be performed under general anaesthesia; this does not require the addition of lidocaine or prilocaine to the tumescent fluid, as for liposuction under local anaesthesia [17].

---

[17] B0002 – What is the claimed benefit of liposuction in relation to conservative therapy?

[18] B0008 – What kind of special premises are needed to use liposuction?

in D Kostenerstattung nur bei Einhaltung von Mindestmengen für Ärzt*innen, ambulant oder stationär durchführbar

In general, liposuction for lipoedema should only be performed by experienced specialists. In Germany, a directive stipulates that all physicians performing at the expense of the statuary health insurances must have independently carried out liposuction for lipoedema in 50 or more cases prior to the guidelines' publication [15]. However, physicians can be from different fields, such as dermatology, phlebology, and vascular surgery. Moreover, specialists from other surgical areas are authorised, above all, aesthetic surgeons, who perform liposuctions for lipoedema in large numbers [15]. The setting can be inpatient or outpatient[19].

konservative Therapie auch bei Hausarzt

Conservative therapy measures (e.g., CDT) may be initiated and controlled by general practitioners in primary care and specialists in the fields of lymphology, phlebology, angiology, and dermatology [15][19].

CE Kennzeichen für die gängigen Liposuktions-Geräte vorhanden

In Table 1-3, a selection of currently available liposuction devices (and manufacturers) used in the surgical therapy of lipoedema is listed. Tumescence liposuction devices, such as PAL or WAL, have been utilised for decades in aesthetic surgery and lipoedema therapy [12]. All devices listed received CE marking under the European Medical Device Directive (MDD) 93/42/EEC. In the scope of the new European Medical Devices Regulation (MDR) 2017/745, cosmetic and aesthetic products (as liposuction devices) must implement a quality management system according to the EN ISO 13485:2016. All listed devices fulfil this regulation[20].

Table 1-3: Selections of liposuction devices used in lipoedema, information retrieved from manufacturers' websites[21]

Product	Manufacturer	Technology	Clearance
Vibrasat® power (Liposat® power) (Vacusat® power)	Möller Medical GmbH, Germany	Power-assisted liposuction	CE mark
LipoSurg® (Vacuson 60®)	Nouvag, Switzerland	Power-assisted liposuction	CE mark
PAL® Liposuction System	MicroAire Surgical Instruments, United States	Power-assisted liposuction	CE mark
Body-jet®	Human Med, Germany	Water jet-assisted liposuction	CE mark
Vaser Lipo®	Solta Medical, United States	Ultrasound-assisted liposuction	CE mark

Supplies needed are liposuction systems (infiltration device, suction device, aspirator, microcannulas), additional disposable instruments and tumescent agents of choice. Post-operatively, patients have to wear flat-knit compression garments for up to six weeks[22].

in Ö ca. 5.000 Liposuktionen bei Lipödem jährlich

Based on the information given by the VAEV, the estimated annual utilisation of liposuction for surgical therapy of lipoedema in the submitting hospital is around 150. The estimated annual utilisation in all of Austria is about 5,000 surgeries[23].

[19] B0004 – Who administers liposuction and conservative therapy and in what context and level of care are they provided?

[20] A0020 – For which indications has liposuction received marketing authorisation or CE marking?

[21] List is not intended to be exhaustive.

[22] B0009 – What supplies are needed to use liposuction?

[23] A0011 – How much is liposuction for lipoedema utilised?

in D wird die Liposuktion unter bestimmten Voraussetzungen rückerstattet; aber nur bis Ergebnisse eines RCTs vorliegen (2024)

In Germany, liposuction has been reimbursable as of January 2020 under special premises: stage III lipoedema, at least six months of prior conservative treatment and BMI<35 kg/m^2 (or BMI 35-40 kg/m^2 with accompanying guideline-based treatment of obesity). This reimbursement ends in December 2024 due to upcoming results of a large-scale, prospective, multi-centre randomised controlled trial (RCT; sponsored by the German Joint Federal Committee, G-BA), investigating long-term therapeutic benefits [14, 15, 18]. Further information on the current German lipoedema management, reimbursement, and upcoming evidence is discussed in Chapter 6.

in Ö ist die Liposuktion bei Lipödem derzeit nicht im LKF Katalog abgebildet

Currently, liposuction for lipoedema is not included in the Austrian DRG system (Leistungsorientierte Krankenanstaltenfinanzierung/LKF) [19]. Still, the Austrian health insurances grant individual approval and reimbursement (according to the information given by the VAEV)[24].

[24] A0021 – What is the regulatory and reimbursement status of liposuction for lipoedema?

2 Objectives and Scope

2.1 PICO question

PIKO-Frage

Is liposuction in comparison to conservative treatment, such as combined decongestive therapy, in patients with lipoedema (stage I-III) more effective and equally safe concerning the reduction of pain, reduction in the size of extremities, and improvement of quality of life?

2.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 2-1.

Table 2-1: Inclusion criteria

Population	Patients with painful ■ lipoedema (also lipedema) at stage I, II, or III ■ lipolymphoedema (patients with lipoedema and secondary lymphoedema) with disproportional fat distribution disorder and consistent conservative therapy did not lead to symptom relief or pain reduction. **ICD-10-GM:** E88.20, E88.21, E88.22, E88.24 **MeSH:** Lipoedema [C17.300.451], Connective Tissue Diseases [C17.300], Lymphedema [C15.604.496]
Intervention	Liposuction – 'wet technique' ■ tumescent liposuction ■ tumescent local anaesthesia liposuction ■ power- (vibration-) assisted liposuction ■ vibrating micro-cannula liposuction ■ laser-assisted liposuction ■ water jet-assisted liposuction NOT: 'dry technique' **Product names:** e.g., PAL® Liposuction System, Liposat® Power, Vibrasat® Power **MeSH:** Lipectomy [E02.218.530, E04.062.937]
Control	Conservative therapy: ■ wrapping/compression ■ lymphatic drainage ■ combined (or complex) decongestive therapy (e.g., lymphatic drainage and wearing compression garments) **Rationale:** According to clinical guidelines, wrapping, drainage, or combined (or complex) decongestive therapy are standard of care interventions in therapeutic management of patients with lipoedema [1, 3].

Outcomes	
Efficacy	Primary: ■ pain ■ reduction in size of extremity ■ quality of life Others: ■ restrictions to movement ■ bruising ■ swelling/oedema ■ reduction of feeling of tension ■ sensitivity to pressure ■ use of combined (or complex) decongestive therapy **Rationale:** Appropriate clinical outcomes have been chosen according to ongoing clinical studies and clinical guidelines. They reflect key clinical claims that liposuction for lipoedema can improve symptoms of pain and quality of life and reduce the risk for dermatological, lymphatic, and orthopaedic complications due to increased size of extremities [1, 3, 18].
Safety	Serious adverse events (SAEs): ■ e.g., intervention-related death, hospitalisation All other procedure-related adverse events (AEs), including post-operative complications such as ■ bleeding ■ infections
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials In absence of controlled trials: prospective case series
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case series Retrospective case series

3 Methods

3.1 Research questions

Forschungsfragen nach EUnetHTA

Assessment elements from the EUnetHTA Core Model® for the production of Rapid Relative Effectiveness Assessments (Version 4.2) were customised to the specific objectives of this assessment [20].

Table 3-1: Research questions concerning the health problem and current use

Element ID	Research question
A0001	For which health conditions, and for what purposes is liposuction used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for lipoedema?
A0004	What is the natural course of lipoedema?
A0005	What is the burden of disease for the patients with lipoedema?
A0006	What are the consequences of lipoedema for the society?
A0024	How is lipoedema currently diagnosed according to published guidelines and in practice?
A0025	How is lipoedema currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Table 3-2: Research questions concerning the description of the technology

Element ID	Research question
B0001	What is the technology and the comparator(s)?
A0020	For which indications has liposuction received marketing authorisation or CE marking?
B0002	What is the claimed benefit of liposuction in relation to conservative therapy?
B0003	What is the phase of development and implementation of liposuction and conservative therapy?
B0004	Who administers liposuction and conservative therapy and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use liposuction and conservative therapy?
B0009	What supplies are needed to use liposuction and conservative therapy?
A0021	What is the reimbursement status of liposuction for lipoedema?

Table 3-3: Research questions concerning clinical effectiveness

Element ID	Research question
D0005	How does the technology affect symptoms and findings (severity, frequency) lipoedema?
D0006	How does the technology affect progression (or recurrence) of lipoedema?
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of liposuction on disease-specific quality of life?
D0017	Was the use of liposuction worthwhile?

Table 3-4: Research questions concerning safety

Element ID	Research question
C0008	How safe is liposuction in comparison to conservative therapy?
C0002	Are the harms related to dosage or frequency of applying liposuction?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of liposuction?
C0007	Are liposuction and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of liposuction and the comparator?

3.2 Clinical effectiveness and safety

3.2.1 Systematic literature search

systematische Literatursuche in 5 Datenbanken

The systematic literature search was conducted on the 4th of December 2020 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)
- HTA-INAHTA

deutsche und englische Literatur insgesamt 295 Publikationen identifiziert

The systematic search was not limited to the year of publication or the study design, but articles published in English or German. After deduplication, 294 citations were included. The specific search strategy employed can be found in the Appendix.

By hand-search, one additional publication was found, resulting in 295 hits overall.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 12th of January 2021 resulting in 14 potentially relevant hits.

3.2.2 Flow chart of study selection

Overall, 295 hits were identified after deduplication; thereof seven studies were included in this assessment. The references were screened by two independent researchers (abstracts: MW, GG; full texts: MW, LG), and in case of disagreement, a third researcher was involved in solving the differences. The selection process is displayed in Figure 2-1.

Literaturauswahl: 7 relevante Studien (in 11 Publikationen)

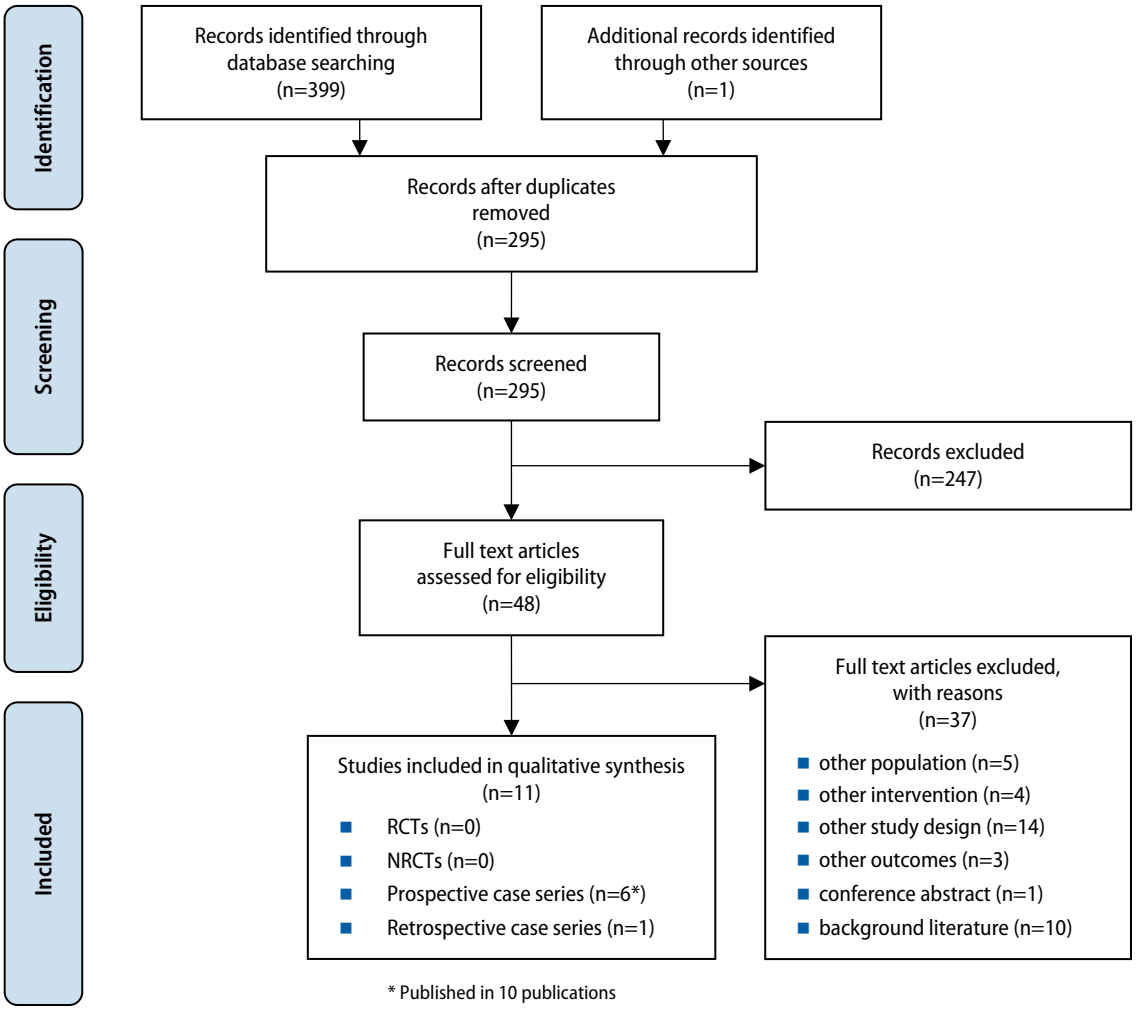

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

3.2.3 Analysis

Datenextraktion

The data retrieved from the selected studies (see Section 3.2.2) were systematically extracted into data-extraction-tables (see Appendix Table A-1 and Table A-2). No further data processing (e.g., indirect comparison) was applied.

Bewertung des Verzerrungsrisikos (RoB) mit IHE-Checkliste

The studies were systematically assessed for internal validity and risk of bias (RoB) by two independent researchers (MW, LG) using the Institute of Health Economics (IHE) Risk of Bias checklist for case series [21] presented in the Appendix (see Table A-3). Overall RoB was assessed using a predefined point score (range: 0–20; Table 3-5): a high score indicates a low RoB and a low score indicates a higher RoB. Detailed thresholds are presented in Table 3-6.

Table 3-5: Overall risk of bias (RoB) point scores for RoB assessment of case series

Answers to specific questions of the IHE-20 checklist	Points
No	0
Partial	0.5
Unclear	0.5
Yes	1

Table 3-6: Cut-off criteria for the risk of bias (RoB) assessment of overall RoB of case series

Criteria	Points
Low risk	> 18
Moderate risk	14.5 to 18
High risk	≤ 14

3.2.4 Synthesis

Verwendung von GRADE zur Synthese der Evidenz (sofern anwendbar)

Based on the data extraction tables (see Appendix Table A-1 and Table A-2), data on each selected outcome category were, if applicable, synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [22]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Table 5-1).

4 Results: Clinical effectiveness and Safety

4.1 Outcomes

4.1.1 Outcomes clinical effectiveness

Entscheidungs-relevante Endpunkte für die Wirksamkeit: Schmerz, Umfang der Extremitäten, Lebensqualität

The following outcomes were defined as *crucial* to derive a recommendation:

- Pain
- Reduction in size of extremity
- Quality of life (QoL)

The outcomes defined as *crucial* to derive a recommendation are considered the most relevant to lipoedema patients. They reflect key clinical claims that liposuction for lipoedema can improve symptoms of pain and QoL, as well as reduce the risk for dermatological, lymphatic, and orthopaedic complications due to increased size of extremities [1, 3, 18].

Schmerz mit nicht validierten Lipödem-spezifischen Patienten-Fragebögen erhoben (6 Studien)

Pain is one of the main symptoms patients with lipoedema suffer from [1, 3, 18]. Patient-reported pain intensity changes, pain relief, or pain sensitivity were measured in all included studies using different non-validated instruments. In [8, 23-26], spontaneous pain and pain upon pressure were assessed using a self-report questionnaire before the first liposuction, after the last one, and at two further follow-ups. Quantification was performed on a five-point Likert scale (0, none; 1, minor; 2, medium; 3, strong; 4, very strong). Another study measured pain and pain upon pressure on a Visual Analogue Scale (VAS)[25] of self-assessed complaint criteria ranging from 0 to 9, with 0 'not present' and 9 'very pronounced' [13]. A VAS (range 0 to 10, increments of 1) was used for the self-assessment of pain symptoms in [27], [28], [29], and in [30] assessed during interviews by a clinician, not a self-reported questionnaire.

Umfang der Extremitäten mit Maßband (2 Studien) und 3D-Bildgebung (1 Studie) erhoben

Reduction in size of extremity is a major goal of lipoedema therapy as stated by the AWMF S1 guideline [1]: As the volume of the leg increases during the progression of lipoedema, the risk of dermatological (e.g. macerations, infections), lymphatic (e.g. erysipelas, lymphoedema), and orthopaedic complications (e.g., gait disturbances, axial malpositions) increases. Two studies report on the reduction of circumference of extremities in cm: thighs (inguinal region) and middle of the lower legs (calves) in [8, 26], and limb circumference on thighs assessed with a tape measure in [30]. Another study reports reducing size extremity via the leg volume (in litres) using 3D-imaging for assessment [27].

Lebensqualität mit nicht validierten Lipödem-spezifischen Fragebögen erhoben (4 Studien)

Quality of life (QoL) is a further goal of lipoedema therapy concerning the improvement of lipoedema-related patients' complaints. The Dutch guideline on lipoedema [3] recommends using the SF36 health condition questionnaire to assess the generic health-related QoL; but none of the included studies assessed QoL with this instrument. Further, there exists no validated instrument to measure lipoedema-(disease-) specific QoL. But, if applicable, it was evaluated as a patient-reported questionnaire item, similar to the above-described scales (Likert scale and VAS) concerning the *pain* outcome [8, 13, 23-28].

[25] The VAS is a preference-based method, not involving a choice but asking to reveal the relative value of health states on a thermometer-like scale. From: https://eunethta.eu/methodology-guidelines/

weitere wichtige Endpunkte für die Wirksamkeit:

Bedarf an konservativer Therapie, Bewegungseinschränkungen, Neigung zu Hämatomen, Ödeme und Schwellungen, sensorische Körperfunktionen (Spannungsgefühl, Juckreiz, …)

Further outcomes were defined as *important*, but not *crucial* to derive a recommendation:

- Reduction of conservative therapy (e.g. CDT)
- Restrictions to movement
- Bruising
- Oedema/swelling
- Sensory body functions (e.g. feeling of tension, itchy legs)

Reduction of conservative therapy is measured as the number (or proportion) of patients, who require no or less lymphatic drainage, compression, or CDT, compared to the baseline. One study [31] reported on this outcome in the form of a CDT score, which was calculated as the sum of the number of manual lymphatic drainage sessions per month and the number of hours spent wearing compression garments per day [26].

Restrictions to movement, bruising, oedema (swelling), and **sensory body functions** (e.g., feeling of tension, itchy legs) were assessed via patient-reported questionnaire items, included in the aforementioned scales (Likert scale and VAS) concerning pain outcomes. Restrictions to movement were assessed as running impairments in [29]. The study [30] reports on the post-operative reduction of bruising and the post-operative improvement of mobility measured on a three-point scale: 0 – no improvement, 1 – minor to medium improvement, 3 – marked improvement or no impairment.

Mortalität kein relevanter Endpunkt

Since lipoedema is not life-threatening, mortality was not considered as a *crucial* or *important* outcome for clinical effectiveness to derive a recommendation. However, procedure-related mortality can be found in the safety domain (see 4.1.2).

minimale klinisch-relevante Unterschiede nicht berichtet

No study reported minimal clinically important differences for any of the assessed outcomes.

4.1.2 Outcomes safety

Entscheidungs-relevante Endpunkte für die Sicherheit:

The following outcomes were defined as *crucial* to derive a recommendation:

- Serious adverse events (SAEs)
- Procedure-related adverse events (AEs)

schwerwiegende unerwünschte Ereignisse (UE)

Serious adverse events (SAEs) comprise any adverse event with serious medical consequences, including post-operative mortality, complications that resulted in substantial morbidity or disability, an increase in the level of care (e.g. ICU), admission to the hospital, or substantial prolongation of the hospital stay [32].

Verfahrens-bedingte UE, wie Infektionen oder Blutungen

Procedure-related adverse events (AEs) are complications associated with the intervention. Possible procedure-related complications are events related to anaesthesia, post-operative infections or bleeding, or the occurrence of blood clots (e.g., thrombosis) [10, 11].

Post-operative bruising (haematomas), swelling, or local indurations were not considered as adverse events or complications. They are general symptoms following liposuction procedures.

[26] Due to the retrospective assessment of these pre-operative outcomes, the mentioned study was excluded in evaluating clinical effectiveness outcomes and was only considered for safety.

4.2 Included studies

4.2.1 Included studies clinical effectiveness and safety

To evaluate liposuction's clinical effectiveness and safety for lipoedema, we considered RCTs and non-randomised controlled trials (CT) comparing liposuction to conservative interventions (e.g., CDT), as well as prospective single-arm studies reporting on before versus after intervention outcomes.

Einschlusskriterien: RCTs, CTs und prospektive unkontrollierte Studien

No comparative studies were identified. Therefore, the evidence is based on prospective single-arm studies. A total of six single-arm, single-centred, before-and-after studies published between 2011 and 2020 in ten publications were identified [8, 13, 23-30]. All studies, except one from Switzerland [13], were conducted in Germany.

6 prospektive unkontrollierte vorher/nachher Studien eingeschlossen

A total of 737 female patients were assessed pre-operatively, whereof 467 were eligible for at least one post-operative follow-up and, therefore, included in the before versus after analyses. Mean age ranged from 37.2 to 38.0 years [8, 13, 23-28], and median age ranged from 35 to 44 years [29, 30]. One study did not report on the age of the included patients [28].

Studienpopulation: 467 Frauen in vorher vs. nachher-Untersuchung eingeschlossen

Three studies reported on the clinical stages of lipoedema, resulting in 78 patients overall in stage I, 170 patients in stage II, and 50 patients in stage III [8, 23-26, 29, 30]. Three studies did not report on lipoedema stages [13, 27, 28]. Further baseline criteria, such as mean weight [8, 13, 24, 26, 29] and mean BMI [13, 29], were reported in some studies, ranging from 72.5 to 81.9 kg and 26.6 to 28.4, respectively. One study reported patients' distribution to different BMI classes (Table A-1) [8, 26].

3 Studien (insg. 298 Pat.) berichten Lipödem-Stadien: Stadium I 78 Pat., Stadium II 170 Pat, Stadium III 50 Pat.

The mean (or median) follow-up of the studies ranged from 6 to 35.9 months. One study reported outcomes over a long-term follow-up of 4, 8, and 12 years [8, 23-26]. Losses to follow-up between pre-operative assessment to the latest post-operative assessment ranged from 0 [30], to 52 % [29].

mittlerer FU zwischen 6 Monaten und 12 Jahren nach Liposuktion

Inclusion criteria differed slightly between studies. In some studies, patients were eligible for inclusion if they had conservative therapy (e.g., CDT) for at least six months [30] (or several years [8, 23-26]) without adequate response or improvement of symptoms. Other inclusion criteria were: completed surgical therapy with at least six months since the last intervention or the exclusion of other lymphatic diseases or eating disorders. For detailed information, see the Appendix (Table A-1 and Table A-2).

häufiges Einschlusskriterium: erfolglose konservative Therapie über min. 6 Monate

In this assessment, we included all types of 'wet-technique' liposuctions. In all included studies, liposuction was conducted under tumescent local anaesthesia, requiring no general anaesthesia. Liposuction with vibrating micro-cannulas was performed in three of the included studies [8, 23-28]; and in two other studies, water jet-assisted devices were used [13, 29]. In one study [30], liposuction was performed using a mechanical or laser-assisted device.

alle Studien Tumeszenzliposuktion in Lokalanästhesie

Depending on disease severity, patients were treated in multiple liposuction sessions, ranging from one to seven per patient. Two studies did not report on the number of liposuction sessions per patient [29, 30].

mehrere Liposuktions-Einheiten (1-7) abhängig v. Schweregrad des Lipödems

Study characteristics and results of included studies are displayed in Table A-1 and Table A-2, and the evidence profile in Table A-6.

4.2.2 Additionally included studies safety

zusätzlich: 1 retrospektive vorher/nachher-Studie für Sicherheits-Endpunkte eingeschlossen

In addition to RCTs, non-randomised CTs, and prospective single-arm studies, retrospective single-arm studies were also considered to evaluate the safety of liposuction for lipoedema.

We identified one retrospective single-arm study reporting on before versus after liposuction outcomes [31]. This study was classified as retrospective, because the authors state in their limitations that data for the pre-operative period were collected in a retrospective manner.

zusätzliche 25 Pat.: Stadium I 1 Pat., Stadium II 11 Pat., Stadium III 13 Pat.

In this study, a total of 25 female patients were pre- and post-operatively assessed at two follow-ups. The median age was 45 years, ranging from 23 to 64 years. One of the patients was diagnosed with stage I, eleven with stage II, and 13 with stage III lipoedema. The mean BMI of the patients was 35.3, ranging from 24.5 to 50.6.

letztes FU nach 37 Monaten im Mittel

The last follow-up was 37 months (mean) post-surgery (range 25 to 56 months, respectively, and a loss to follow-up of 24%.

Einschlusskriterium: erfolglose konservative Therapie für min. 6 Monate

Patients were eligible for inclusion if they had a clinically confirmed lipoedema diagnosis by a lymphologist. Furthermore, conservative therapy (e.g., CDT) for at least six months without adequate response or improvement of symptoms was required [31].

Tumeszenzliposuktion unter Vollnarkose

In contrast to the identified prospective single-arm studies included in the evaluation of clinical effectiveness, the study by [31] performed tumescence liposuction without local but under general anaesthesia, using either a vibration- or water jet-assisted device. Depending on lipoedema severity, patients were treated in multiple liposuctions sessions, ranging from one to seven per patient.

Study characteristics and results of included studies are displayed in Table A-1, Table A-2, and the evidence profile in Table 5-1.

4.3 Results

In the absence of data from controlled trials (CTs), no comparisons can be made between the intervention liposuction and any conservative therapy (e.g., CDT) for treatment of patients with lipoedema.

kein Vergleich mit konservativer Therapie möglich

Lipoedema stage-specific analyses were not performed in the included studies concerning the *crucial* or *important* outcomes.

keine Analysen getrennt nach Lipödem-Stadien

4.3.1 Results clinical effectiveness

Morbidity

The *crucial* outcomes of *pain* and *reduction in size of extremities* and the outcomes *bruising* and *oedema/swelling* were considered when answering the research question on how liposuction affects symptoms (severity, frequency) of lipoedema[27].

Pain

All six prospective studies reported statistically significant reductions in pain outcomes pre- vs post-liposuction (see Table 4-1).

Schmerz (6 Studien)

In one study [8, 23-26] (60 patients), *spontaneous pain* was reported pre-operatively and after three follow-ups (4-, 8-, and 12-year follow-up); improvements were shown in all eligible patients. The mean (SD) reduction of the *spontaneous pain* score[28] decreased from pre-operatively 1.76 (1.41) to 0.33 (0.55), 0.31 (0.51), and 0.37 (0.49) twelve years after the last liposuction. Although, there is an increase of the pain score between the 8-year follow-up to the 12-year follow-up, the effect size of the pre-operative *spontaneous pain* assessment, compared to the last follow-up decreased statistically significant by 1.04 points ($p<0.001$).

1 Studie (60 Pat.) spontaner Schmerz: Verbesserung um 1 Pkt. auf 5-Pkt. Likert Skala, zu 3 Messzeitpunkten (4, 8, 12 Jahre FU)

The median[29] *pain* score on a 10-point VAS (interviewer-assessed) reduced from 7.8 (2.1) pre-operatively to 2.2 (1.3) post-operatively ($p<0.3$)[30], with a median follow-up of 24 months after the last liposuction in one study [30] (111 patients). A statistically significant reduction of the mean *pain* score (SD; 10-point VAS) was reported in [27] (25 patients) and [28] (85 patients), both after a six-month follow-up (7.2 [2.2] pre to 2.1 [2.1] post-operatively; and 6.5 [3.0] to 2.1 [2.0], respectively; both $p<0.001$). Similarly, in [29] (63 patients) the mean *pain* score (SD; 10-point VAS) decreased statistically significantly from pre-operatively 6.47 (2.05) to 1.39 (1.66) at a median follow-up of 21.5 months ($p<0.001$).

4 Studien (insg. 284 Pat.) Schmerz: Verbesserung auf 10-Pkt. VAS um -4,4 bis -5,6 Pkt.

One study [13] (71 patients) also assessed the change of mean *pain upon pressure* score (SD not reported; 0 to 9-point VAS) before liposuction and at a mean follow-up of 35.9 months of 6.0 to 2.9 ($p<0.05$).

1 Studie (71 Pat.) Schmerz bei Druck: Verbesserung auf 0-9 Pkt. VAS um -3,7 Pkt.

[27] D0005 – How does liposuction affect symptoms and findings (severity, frequency) of lipoedema?

[28] On a 5-step Likert scale.

[29] Study reports on median values, but further provides SDs, which are not calculable for median estimates.

[30] A p-value of less than 0.5 was considered as statistically significant by the authors.

Table 4-1: Summary of crucial outcome pain

Study (No. patients)	Patients' complaints score, mean (p-value)	Diff. pre- vs post-liposuction	Tool	Duration of follow-up(s)
Spontaneous pain				
[8, 23-26] (60)[31]	1.76, 0.33, 0.31 to 0.37 (p<0.001)	-1.04[32]	5-step Likert scale	4, 8, 12 years
Pain				
[30] (111)	7.8 to 2.2 (p<0.3)	-5.6	10-point VAS	24 months
[27] (25)	7.2 to 2.1 (p<0.001)	-5.1	10-point VAS	6 months
[28] (85)	6.5 to 2.1 (p<0.001)	-4.4	10-point VAS	6 months
[29] (63)	6.47 to 1.39 (p<0.001)	-5.08	10-point VAS	21.5 months
Pain upon pressure				
[13] (71)	6.0 to 2.9 (p<0.05)	- 3.1	0 to 9-point VAS	35.9 months

Abbreviations: p – p-value, VAS – Visual Analogue Scale

Reduction of limb circumference

3 Studien (insg. 248 Pat.) Reduktion des Beinumfangs: Oberschenkel: -6cm/-8cm (2 Studien) Unterschenkel: -4 cm (1 Studie); Beinvolumen: -2,2 Liter/0,9% (1 Studie)

The study [8, 26] (112 patients) reports a mean *reduction of circumference of extremities* of 8 cm (range: 1 to 23 cm) in the thighs (inguinal region) and 4 cm (range: 1 to 11 cm) in the middle of the lower legs (calves) after the first follow-up four years after the last liposuction (mean 35 months). Similarly, a median *reduction of limb circumference* of 6 cm (SD: 1.6 cm[29]) post-operatively was reported in [30] (111 patients) after a median follow-up of 24 months. After a follow-up of six months, a mean (SD) reduction in *leg volume* of 18.0 (3.8) to 16.8 (3.5) litres was observed by [27] (25 patients) using 3D imaging. This corresponds to an average decrease of 1.2 (1.0) litres or 6.9%. The average duration of follow-ups at the time of assessment was six months after the last procedure.

1 Studie (71 Pat.): Reduktion (ohne Angabe von cm/%)

In the study [13] (71 patients), a reduction of circumference and normalisation of all patients' body proportions after the liposuction procedure was mentioned, but quantitative data were not provided.

Oedema and swelling

Ödeme und Schwellungen (5 Studien)

Significant comparative complaint scores for *oedema* or *swelling* before and after liposuction were reported by five studies.

1 Studie (60 Pat.) Ödeme: Verbesserung um -1,5 Pkt. auf 5-Pkt. Likert Skala, zu 3 Messzeitpunkten (4, 8, 12 Jahre FU)

In the study [8, 23-26] (60 patients), patients' *oedema* complaints were reported pre-operatively and in three follow-ups (4-, 8-, and 12-year follow-up): the mean reduction of *oedema* score (SD; a 5-step Likert scale) decreased from 3.05 (1.06) to 1.42 (0.91), to 1.51 (0.93), and 1.35 (0.88) at twelve years after the last liposuction. The pre-operative *oedema* assessment's effect size compared to the last follow-up was reported as a statistically significant decrease of 1.49 points (p<0.001).

1 Studie (71 Pat.) Neigung zu Schwellungen: Verbesserung (VAS) um -3 Pkt.

A statistically significant decrease of *swelling tendency* before and after liposuction was reported in [13] (71 patients), with a reduction of a mean score (SD not reported; 0 to 9-point VAS) of 6.5 to 3.5 at a mean follow-up of 35.9 months (p<0.05).

[31] Including patients eligible for all three follow-ups.

[32] As reported by study authors, pre-operative vs 12-year follow-up.

A further three studies reported on statistically significant changes of mean *swelling* complaints (SD; 10-point VAS) pre- 6.9 (NA) to post-operatively 3.3 (NA) [27] in 25 patients ($p<0.001$); 6.3 (3.2) to 3.2 (2.5) [28] in 85 patients ($p<0.001$); and 6.75 (2.41) to 1.52 (1.65) [29] in 63 patients ($p<0.001$). These data were collected at a six-month follow-up [27, 28] and a median of 21.5 months after the last liposuction [29].

3 Studien (insg. 173 Pat.) Schwellungen: Verbesserung -3,1 bis -5,2 Pkt. auf 10-Pkt. VAS

Bruising

All six included studies reported complaint scores for *bruising* tendencies before and after liposuction among lipoedema patients.

Neigung zu Hämatomen (6 Studien)

In one study [8, 23-26] (60 patients), patients' complaints on *bruising tendencies* improved pre-operatively and in three follow-ups (4, 8, and 12 years post-operatively). The mean *bruising* score (SD; 5-step Likert scale) decreased from mean 3.04 (0.98) to 1.16 (0.98), to 1.47 (1.23), and 1.40 (1.08) at an average of twelve years after the last liposuction. The effect size of the pre-operative bruising assessment, compared to the last follow-up, was reported as a statistically significant decrease of 1.27 points ($p<0.001$).

1 Studie (60 Pat.) Hämatome: Verbesserung um -1,3 Pkt. auf 5-Pkt. Likert Skala, zu 3 Messzeitpunkten (4, 8, 12 Jahre FU)

The study [13] (71 patients) found that the mean *bruising* score (SD not reported; 0 to 9-point VAS) decreased from 5.9 (pre-operative) to 3.7 (mean follow-up 35.9 months) points. Three studies reported on statistically significant reduction of mean (SD) *bruising* scores of 7.9 (NA) before liposuction to 4.2 (NA) afterwards [27] (25 patients; $p<0.001$); 8.1 (2.2) to 4.3 (31.1[33]) [28] (85 patients; $p<0.001$), and 7.18 (1.93) to 2.45 (2.62) [29] (63 patients; $p<0.001$), at a six-month follow-up [27, 28], respectively, and at a median of 21.5 months after the last liposuction [29].

4 Studien (insg. 244 Pat.) Hämatome: Verbesserung um -3,7 bis -4,7 Pkt. auf 10-Pkt. VAS; -2.2 Pkt. auf 0-9 Pkt. VAS

Bruising after minor trauma improved 'somewhat' in 20.9% and 'completely or almost completely' in 29.1% of patients after a median follow-up of 24 months in [30] (111 patients; $p<0.5$).

1 Studie (111 Pat.) Hämatome: Verbesserungen

Reduction of conservative therapy

The outcome *reduction of conservative therapy* was considered by answering the research question on how liposuction affects progression (or recurrence) of lipoedema[34].

Reduktion der konservativen Therapie (5 Studien)

Five studies reported that lipoedema patients who underwent liposuction had a reduced need for conservative therapy (e.g., lymphatic drainage, compression, or CDT) compared to the baseline.

In one study [8, 23-26] (60 patients), the need for *conservative therapy* was reported pre-operatively compared to three follow-ups (4, 8, and 12 years pre-operatively): 37 patients needed CDT (manual lymphatic drainage and compression) before the liposuction interventions. Thereof, 20 (54%) patients still required CDT as before, seven (19%) patients required less, and ten (27%) patients required no more conservative therapy. The second study [13] (71 patients) found that after a mean follow-up of 35.9 months, 23.4% of patients needed less and 5.3% no more conservative therapy after liposuction. Another study [30] (111 patients) reported that 16.4% of the patients did not need conservative therapy after liposuction.

3 Studien (insg. 242 Pat.): komplexe physikalische Therapie (KPT) wie zuvor: 54 % (1 Studie); weniger als zuvor: 19 %/23 % (2 Studien); keine KPT mehr nötig: 5-27 % (3 Studien)

[33] Potential error in reporting, as VAS of 0-10 points was used for assessment.

[34] D0006 – How does liposuction affect progression (or recurrence) of lipoedema?

2 Studien (insg. 88 Pat.): Kompressions-Therapie vorher 76 %/95 % vs. nachher 16 %/32 %; manuelle Lymphdrainage vorher 60 %/89 % vs. nachher 8 %/40 %

Of the 25 lipoedema patients analysed in [27], 19 (76%) required pre-operative compression therapy and 15 (60%) lymphatic drainage. After the intervention, four (16%) and two (8%) of them still needed conservative therapy at the six-month follow-up. Similarly, in the study [29] (63 patients), 60 (95.2%) patients required pre-operative compression, and afterwards, 20 (31.7%) of them were still in compression therapy. Respectively, 56 (88.9%) patients received lymphatic drainages pre-operatively; 25 (39.7%) were still in drainage therapy afterwards. This resulted in 34 patients who post-operatively did not require any conservative therapy after 21.5 months (mean) follow-up.

Function

The outcomes *restrictions to movement* and *sensory body functions* were considered to answer the research question on the effect of liposuction on patients' body functions[35].

Restrictions to movement

Bewegungseinschränkungen (6 Studien)

In all six included studies, pre- and post-operative mobility functions were reported, most often by means of *restrictions to movement*.

1 Studie (60 Pat.) Bewegungseinschränkungen: Verbesserung um -1,3 Pkt. auf 5-Pkt. Likert Skala, zu 3 Messzeitpunkten (4, 8, 12 Jahre FU)

In one study [8, 23-26] (60 patients), *restrictions to movements* were reported pre-operatively and in three follow-ups (4, 8, and 12 years post-operatively), showing significant improvements in all eligible patients. The mean *restrictions to movement* score (SD; 5-step Likert scale) decreased from 2.13 (1.32) to 0.20 (0.40), to 0.59 (0.71), and 0.52 (0.81) at an average of twelve years after the last liposuction. The effect size of the pre-operative restriction of movement assessment, compared to the last follow-up, decreased by 1.29 points ($p<0.001$).

3 Studien (insg. 181 Pat.) Bewegung: Verbesserung um -3,0 und -2,9 Pkt. auf 10-Pkt. VAS; -1,9 auf 0-9 Pkt. VAS

In another study [13] (71 patients), the mean *restrictions to movement* score (SD not reported; 0-to-9-point VAS) decreased statistically significantly from a pre-operative value of 3.7 to 1.8, after a mean follow-up of 35.9 months ($p<0.05$). Similarly, a statistically significant reduction of the mean *restrictions to movement* score (SD; 10-point VAS) was reported in [27] (25 patients) and [28] (85 patients), both after a six-month follow-up: 4.6 (NA) pre-operatively to 1.6 (NA); and 4.1 (3.5) to 1.2 (1.9) both with $p<0.001$.

1 Studie (63 Pat.) Einschränkungen b. Laufen: Verbesserung um -4,8 Pkt. auf 10-Pkt. VAS

In [29] (63 patients), mobility functions are reported in terms of patient-reported mean (SD) *running impairment* scores. A statistically significant reduction of 5.25 (3.04) points before liposuction to 0.6 (1.11) points afterwards could be observed at a mean follow-up of 21.5 months ($p<0.001$).

1 Studie (111 Pat.) Bewegung: 86 % starke Verbesserung/ keine Einschränkungen

Finally, in the study [30] (111 patients), all included patients achieved post-operative *improvements in movement*, with 86% of them reporting marked improvement or complete loss of impairment, and 14% reporting minor to medium enhancements (median follow-up of 24 months).

Sensory body functions

Sensorische Körperfunktionen (6 Studien), z. B. Berührungsempfindlichkeit, ...

Five of the included studies reported on outcomes concerning *sensory body functions* (see Table 4-2), including:

- Sensitivity to pressure or touch [8, 13, 23-29]
- Feeling of tension [13, 27-29]

[35] D0011 – What is the effect of liposuction on patients' body functions?

- Feeling of heavy or tired legs [13, 27-29]
- Feeling of cold or warmth [27, 28]
- Feeling of itchy legs [27-29]

... Spannungsgefühle, Juckreiz

Five studies reported significantly reduced patients' complaints after the liposuction procedure concerning *sensitivity to pressure* or *touch sensitivity*. In one study [8, 23-26] (60 patients), *sensitivity to pressure* was reported pre-operatively and after three follow-ups (4-, 8-, and 12-year follow-up); improvements were shown in all eligible patients. The mean reduction of the *sensitivity to pressure* score (SD; 5-step Likert scale) decreased from pre-operatively 2.88 (1.06) to 0.88 (0.91), to 1.02 (1.03), and 0.98 (0.94) twelve years after the last liposuction. The effect size of the pre-operative sensitivity to pressure assessment, compared to the last follow-up, statistically significantly decreased by 1.46 points ($p<0.001$). The studies [27] (25 patients) and [28] (85 patients) both showed a statistically significant reduction in mean (SD; 10-point VAS) *sensitivity to pressure* score from 6.4 (NA) pre-operatively to 1.9 (NA) and 6.5 (3.0) to 2.4 (2.4), six months after the last liposuction, respectively (both $p<0.001$). In one study [13] (71 patients), the mean reduction in *touch sensitivity* score (SD not reported; 0 to 9-point VAS) decreased statistically significantly from a pre-operative value of 5.8 to 3.2 after a mean follow-up of 35.9 months ($p<0.05$). Similarly, in [29] (63 patients), patient-reported mean *touch sensitivity* scores (SD; 10-point VAS) decreased statistically significantly from 7.14 (1.9) to 1.55 (1.79) points at a mean follow-up of 21.5 months ($p<0.001$).

Berührungsempfindlichkeit (6 Studien): Verbesserung, Details in Table 4-2

Before-and-after liposuction lipoedema-related *feeling of tension* scores were reported in four studies. In one study [13] (71 patients), the mean reduction in *feeling of tension* score (SD not reported; 0 to 9-point VAS) decreased statistically significantly from a pre-operative value of 5.7 to 2.6 after a mean follow-up of 35.9 months ($p<0.05$). Two studies, [27] (25 patients) and [28] (85 patients), showed a statistically significant reduction in mean *feeling of tension* scores (SD not reported; 10-point VAS) from 7.7 pre-operatively to 2.3 six months after the last liposuction, 6.9 to 2.6, respectively (both $p<0.001$). In study [29] (63 patients), a decrease of mean *feeling of tension* score (SD; 10-point VAS) of 7.56 (1.72) points before to 1.42 (1.78) points was observed after a mean follow-up of 21.5 months ($p<0.001$).

Spannungsgefühle (4 Studien, insg. 244 Pat.): Verbesserung, Details in Table 4-2

Table 4-2: Summary of important outcomes of sensory body functions

Study (No. patients)	Patients' complaints score, mean (p-value)	Diff. pre- vs post-intervention	Tool	Duration of follow-up(s)
Sensitivity to pressure or touch sensitivity				
[8, 23-26] (60)[36]	2.88, 0.88, 1.02, to 0.98 (p<0.001)	-1.46[37]	5-step Likert scale	4, 8, 12 years
[27] (25)	6.4 to 1.9 (p<0.001)	-4.5	10-point VAS	6 months
[28] (85)	6.5 to 2.4 (p<0.001)	-4.1	10-point VAS	6 months
[29] (63)	7.14 to 1.55 (p<0.001)	-5.59	10-point VAS	21.5 months
[13] (71)	5.8 to 3.2 (p<0.05)	-2.6	0 to 9-point VAS	35.9 months

[36] Including patients eligible for all three follow-ups.

[37] As reported by study authors, pre-operative vs 12-year follow-up.

Study (No. patients)	Patients' complaints score, mean (p-value)	Diff. pre- vs post-intervention	Tool	Duration of follow-up(s)
Feeling of tension				
[27] (25)	7.7 to 2.3 (p<0.001)	-5.4	10-point VAS	6 months
[28] (85)	6.9 to 2.6 (p<0.001)	-4.3	10-point VAS	6 months
[29] (63)	7.56 to 1.42 (p<0.001)	-6.14	10-point VAS	21.5 months
[13] (71)	5.7 to 2.6 (p<0.05)	-3.1	0 to 9-point VAS	35.9 months
Feeling of heavy legs				
[27] (25)	8.4 to 3.6 (p<0.001)	-4.8	10-point VAS	6 months
[28] (85)	7.8 to 3.1 (p<0.001)	-4.7	10-point VAS	6 months
[29] (63)	8.42 to 1.55 (p<0.001)	-6.87	10-point VAS	21.5 months
[13] (71)	6.7 to 3.1 (p<0.05)	-3.6	0 to 9-point VAS	35.9 months
Feeling of tired legs				
[27] (25)	8.4 to 3.5 (p<0.001)	-4.9	10-point VAS	6 months
[28] (85)	7.4 to 3.1 (p<0.001)	-4.3	10-point VAS	6 months
Feeling of cold				
[27] (25)	3.8 to 2.1 (p<0.120, diff. n.s.)	-1.7	10-point VAS	6 months
[28] (85)	3.4 to 1.6 (p<0.001)	-1.8	10-point VAS	6 months
Feeling of warmth				
[27] (25)	3.0 to 1.4 (p<0.001)	-1.6	10-point VAS	6 months
[28] (85)	2.8 to 1.2 (p<0.001)	-1.6	10-point VAS	6 months
Itching				
[27] (25)	4.2 to 1.9 (p<0.001)	-2.3	10-point VAS	6 months
[28] (85)	2.8 to 1.3 (p<0.001)	-1.5	10-point VAS	6 months
[29] (63)	4.0 to 0.8 (p<0.001)	-3.2	10-point VAS	21.5 months

schwere und müde Beine (4 Studien, insg. 244 Pat.): Verbesserung, Details in Table 4-2

The same four studies reported on patient-reported scores of *feeling of heavy* or *tired legs*, too. Here, one study [13] (71 patients) found a significantly mean decrease in *feeling of heavy legs* score (SD not reported; $p<0.05$; 0 to 9-point VAS) from pre-operatively 6.7 to 3.1 at a mean follow-up of 35.9 months. In one study [29] (63 patients), significant before vs after scores for *feeling of heavy legs* (SD; $p<0.001$; 10-point VAS) of 8.42 (1.80) to 1.55 (1.66) points were reported at a mean follow-up of 21.5 months. In another two studies, [27] (25 patients) and [28] (85 patients), significant reductions in mean *feeling of heavy legs* score (SD not reported; $p<0.001$; 10-point VAS) from 8.4 pre-operatively to 3.6 six months after the last liposuction were observed, 7.8 to 3.1, respectively. Further, these two studies reported a significant reduction of mean scores *of feeling of tired legs* from 8.4 to 3.5 and 7.4 to 3.1.

Kälte-/Wärmegefühl (2 Studien, insg. 110 Pat.): Verbesserung, Details in Table 4-2

Sensory *feelings of cold* or *warmth* were assessed in two studies prior to and six months after liposuctions amongst lipoedema patients using self-reported questionnaires. Both studies [27, 28] (25 and 85 patients) showed a statistically significant reduction in mean *feeling of warmth* scores (SD not reported; 10-point VAS) from 3.0 to 1.4 ($p<0.008$), 2.8 to 1.2 ($p<0.001$), respectively. A decrease of mean scores of *feeling of cold* of 3.8 to 2.1 ($p<0.120$, diff. n. s.), and 3.4 to 1.6 was reported ($p<0.001$).

Improvement in before-and-after liposuction lipoedema-related *itching* was reported by three studies. The studies [27] (25 patients) and [28] (85 patients) both showed a statistically significant reduction in mean *feeling of itchy legs* complaint scores (SD not reported; 10-point VAS) from 4.2 points to 1.9 points and 2.8 to 1.3 points six months after the last liposuction, respectively (both $p<0.001$). Furthermore, in one study [29] (63 patients), mean complaints of *itching* (SD; 10-point VAS) decreased from 4.0 (3.3) before liposuction to 0.8 (1.3) after a mean follow-up of 21.5 months ($p<0.001$).

Juckreiz (3 Studien, insg. 173 Pat.): Verbesserung, Details in Table 4-2

No evidence was found to answer the research question on how liposuction affects daily living activities[38].

keine Daten zu Aktivitäten des täglichen Lebens

Health-related quality of life

The *crucial* outcome of *QoL* was considered when answering the research question on the effect of liposuction on disease-specific quality of life[39].

Reduction in QoL

Four prospective studies reported statistically significant improvements in *reduction in QoL* scores after liposuction compared to pre-operative assessed values.

gesundheitsbezogene Lebensqualität (4 Studien)

In one study [8, 23-26] (60 patients), improvement of *QoL* was reported pre-operatively and after three follow-ups (4, 8, and 12 years after the last liposuction). The mean reduction of the *QoL* score (SD; 5-step Likert scale) decreased from pre-operatively 3.49 (0.77) to 0.69 (0.81), 1.00 (1.04), and 0.96 (0.90) at twelve years after the last liposuction. The effect size of the pre-operative QoL assessment, compared to the last follow-up, decreased by 2.18 points ($p<0.001$).

1 Studie (60 Pat.) Lebensqualität: Verbesserung um -2.2 Pkt. auf 5-Pkt. Likert Skala, zu 3 Messzeitpunkten (4, 8, 12 Jahre FU)

One study [13] (71 patients) assessed the change of *QoL* score (SD not reported; 0 to 9-point VAS) before liposuction and at a mean follow-up of 35.9 months of 6.3 to 2.6 ($p<0.05$). A further two studies, [27] (25 patients) and [28] (85 patients), showed a statistically significant reduction in *QoL* mean scores (SD; 10-point VAS) from 8.7 (1.7) to 3.6 (2.5); and 8.5 (2.0) to 3.3 (2.8), both six months after the last liposuction (both $p<0.001$).

3 Studien (insg. 181 Pat.) Lebensqualität: Verbesserung um -5,1 und -5,2 Pkt. auf 10-Pkt. VAS; -3,7 auf 0-9 Pkt. VAS

No evidence was found to answer the research question on the effect of liposuction on generic health-related quality of life[40].

Patient satisfaction

No evidence was found to answer the research question on whether the use of liposuction was worthwhile[41].

keine Daten zu Zufriedenheit der Patientinnen

Although all studies included patient-reported outcomes assessed via questionnaires, they were focused on patients' complaints and symptoms. Patients' satisfaction was not assessed directly.

[38] D0016 – How does the use of liposuction affect activities of daily living?

[39] D0013 – What is the effect of liposuction on disease-specific quality of life?

[40] D0012 – What is the effect of liposuction on generic health-related quality of life?

[41] D0017 – Was the use of liposuction worthwhile?

4.3.2 Results safety

Patient safety

kein Vergleich mit konservativer Therapie möglich

In the absence of data from CTs, no comparisons can be made between liposuction and any conservative therapy (e.g., CDT). Only procedure-related complications can be considered to analyse safety because the effects directly attributable to the intervention can be analysed without a control group[42].

7 Studien berichten über Sicherheit der Liposuktion bei Lipödem

All included studies reported on the occurrence of SAEs or (procedure-related) post-operative AEs. Wherein, in [8, 23-26], with a follow-up of 4, 8, and 12 years safety was reported solely in the publications of the 4-year follow-up [8, 26].

insgesamt 17 unerwünschte Ereignisse (UE) in 492 Pat.

Overall, adverse events occurred in 17 out of 492 patients included in the assessment of safety across all the studies (3.5%)[43].

Serious adverse events

5 schwerwiegende UE in 492 Pat., davon:

SAEs occurred in five out of 492 patients included in the assessment of safety across all the studies (1.0%)[43].

1 Abszess mit Hospitalisierung, 1 epileptischer Anfall, 1 Anämie mit Bluttransfusion, 1 pulmonale Fettembolie, 1 akutes Lungenödem mit Intensivaufnahme

One study reported on one patient with an abscess of the lower leg, who was hospitalised for one week in her home town[44] [8, 26]. In a second study [30], in 1.2% of the liposuction procedures,[45] SAEs were observed; temporary met-haemoglobinemia[46] occurred in all patients. An epileptic attack was observed during the procedure in a 34-year-old female without known comorbidities. The epileptic attack caused a fall with subsequent subgaleal hematoma. In the following liposuction procedures, no further epileptic attack occurred in this patient. In the same study, a 67-year-old female had a single episode of post-surgical anaemia requiring a blood transfusion. A 46-year-old female developed a microscopic pulmonary fat embolism two days after release from the hospital after her first liposuction. The following liposuction procedures were well-tolerated with perioperative, low-molecular heparin prophylaxis. One patient, a 52-year-old female, developed acute pulmonary oedema about 24 hours after liposuction that needed intensive care admission [30].

keine Todesfälle nach Liposuktionen berichtet

Procedure-related death did not occur in any of the included studies.

Procedure-related adverse events

Postoperative Wundinfektionen: 5 Pat. mit Erysipel und Behandlung mit Antibiotika

Post-operative wound infections were reported in five out of 492 patients included in the assessment of safety across all studies (1.0%)[43]. In one study, five patients with post-operative wound infections were reported, wherein one patient required hospitalisation and was classified as SAE. The remaining four patients (1.2% of 349 liposuction procedures in 112 patients at 4-year follow-up) with erysipelas were treated at home with oral antibiotics [8, 26]. A further patient (1.4% of 72 liposuction procedures in 25 patients) with erysipelas requiring antibiotic treatment was reported in [31].

---

[42] C0008 – How safe is liposuction in comparison to conservative therapy?

[43] The proportion of (S)AEs of all liposuction procedures performed cannot be assessed. Not all studies reported how many liposuctions were actually performed in the study population.

[44] Furthermore, it is reported that this patient did not follow post-operative care as instructed.

[45] Exact number of liposuction procedures was not reported.

[46] Met-haemoglobinemia that was treated by intravenous injection of toluidine blue.

Post-operative bleeding was reported in two out of 492 patients included in the assessment of safety across all studies (0.4%)[43]. One patient (0.3% of 349 liposuction procedures in 112 patients) suffering from post-operative bleeding with one liposuction was reported in [8, 26]. The incident did not repeat in three subsequent sessions. Another patient suffering from post-operative bleeding was reported in [30].

Postoperative Blutungen bei 2 Pat.

Other post-operative adverse events were reported in five out of 492 patients included in the assessment of safety across all studies (1.0%)[43]. Three patients with mild arm-vein phlebitis (1.8%) were reported in two studies [28, 30], and one patient needed treatment of post-operative seroma [28]. One patient 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 reported in [27]. The incident was treated promptly, and there were no further complications or worsening of the condition.

5 andere postoperative UEs: 3 milde Infektionen der Armvenen, 1 Serom, 1 Thrombose in den Beinvenen

Two studies reported that in 141 patients[47] (who received a total of 202 liposuctions), respectively in 130 patients[47], no adverse events or complications occurred [13, 29].

2 Studien (141 Pat.): keine UE aufgetreten

As the adverse events and complications of liposuction for lipoedema are procedure-related, each intervention poses a potential risk of post-operative harms. Therefore, the assessment of safety should not only be based on the number of patients but also on the performed number of liposuction procedures. Three studies reported adverse events and complications of overall performed interventions [8, 26, 28, 31][48]. Furthermore, the number of performed liposuctions per patients may depend on the severity of disease (stage of lipoedema), respectively, the total amount of fat that is planned to be removed. Occurring adverse events were not reported with respect to the patients' stage of lipoedema[49].

Pat. mit mehreren Liposuktions-Einheiten wahrscheinlich unter höherem Risiko f. UE

Only one event (erysipelas) of the above reported overall AEs (n=17) occurred after liposuction under general anaesthesia [31].

No evidence was found to answer the research questions on how the frequency or severity of harms change over time or in different settings and if liposuction and the conservative therapy of lipoedema are associated with user-dependent harms[50].

keine Evidenz für Benutzer-verschuldete Schäden und Komplikationen

Investments and tools required

Concerning data needed to monitor the use of liposuction: Some studies state that robust RCT data are needed to establish the efficacy of liposuction for surgical therapy of lipoedema, as well as information on the prevalence of lipoedema in general[51].

robuste RCTs nötig

[47] At baseline, not all of them were eligible for post-operative assessment of clinical effectiveness outcomes.

[48] C0002 – Are the harms related to frequency of applying liposuction?

[49] C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of liposuction?

[50] C0004 – How does the frequency or severity of harms change over time or in different settings? C0007 – Are liposuction and conservative therapy of lipoedema associated with user-dependent harms?

[51] B0010 – What kind of data/records and/or registry is needed to monitor the use of liposuction or conservative therapy for lipoedema?

5 Quality of evidence

Risk of Bias (RoB) mit IHE Checkliste bewertet

Risk of bias (RoB) for individual studies was assessed with the IHE checklist for single-arm studies [21] and is presented in Table A-3 in the Appendix. Across the seven included single-arm studies, overall RoB ranged from moderate to high, with four studies being ranked as moderate [8, 23-27, 29, 30] and three studies as high [13, 28, 31].

moderates bis hohes RoB in den eingeschlossenen Studien

The main reasons for downgrading were the single-centred set up of the studies, no information about exclusion criteria, lack of blinding of the investigators, and patients entering the studies during different stages of the disease. Moreover, reasons were uncertainties in using appropriate statistical tests. In some studies, the distribution of data was not reported, and estimates of random variability in the data analysis of relevant outcomes were partially not reported.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme [22] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement, a third researcher was involved in solving the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [22].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

Qualität der Evidenz der klinischen Wirksamkeit konnte aufgrund fehlender kontrollierter Studien nicht untersucht werden

The ranking, according to the GRADE scheme for the research question, can be found in the evidence profile below in Table 5-1.

The strength of evidence on clinical effectiveness of liposuction for surgical therapy of lipoedema in comparison to conservative treatment could not be assessed due to the lack of trials with a comparative treatment arm (single-arm study design).

Overall, the strength of evidence for the safety of liposuction for surgical therapy of lipoedema in comparison to conservative treatment is very low.

Table 5-1: Evidence profile: efficacy and safety of liposuction for surgical therapy of lipoedema

Certainty assessment							Impact	Certainty (importance)
No. of studies (patients)	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		
Efficacy								
Due to the lack of a controlled group, no data on efficacy outcomes can be compared and synthesised.								
Safety								
Serious adverse events								
7 (492) [a]	single-arm before-after NRS	very serious[b]	serious[c]	not serious	not serious	none	SAEs across all studies in 5/492 pts ■ abscess of lower leg, hospitalisation in 1/112 pts [8, 26] ■ epileptic attack occurred in 1/111 pts [30] ■ postsurgical anaemia in 1/111 pts [30] ■ microscopic pulmonary fat embolism in 1/111 pts [30] ■ acute pulmonary oedema in 1/111 pts [30]	⊕◯◯◯ VERY LOW (crucial)
Post-operative wound infections								
7 (492) [a]	single-arm before-after NRS	very serious[b]	serious[c]	not serious	not serious	none	Post-operative wound infections across all studies in 5/492 pts ■ erysipelas in 5/184 pts [8, 26, 31]	⊕◯◯◯ VERY LOW (crucial)
Post-operative bleedings								
7 (492) [a]	single-arm before-after NRS	very serious[b]	serious[c]	not serious	not serious	none	Post-operative bleedings across all studies in 2/492 pts [8, 26, 30]	⊕◯◯◯ VERY LOW (crucial)
Other post-operative adverse events								
7 (492) [a]	single-arm before-after NRS	very serious[b]	serious[c]	not serious	not serious	none	Other post-operative AEs across all studies in 5/492 pts ■ DVT in 1/25 pts [27] ■ thrombophlebitis 1/85 pts [28] ■ seroma in 1/85 pts [28] ■ mild arm vein phlebitis in 2/111 pts [30]	⊕◯◯◯ VERY LOW (crucial)

Comments:

[a] *Including six prospective and one retrospective single-arm before-after NRS.*

[b] *Using the IHE RoB checklist (three studies with high and four with moderate RoB). Very serious limitations are given, due to the lack of a controlled study design.*

[c] *Reporting of adverse events and complications was inconsistent across included studies as some studies reported on events per liposuction procedures and others solely on events per pts.*

Abbreviations: *AE – adverse event, DVT – deep vein thrombosis, ICU – intensive care unit, IHE – Institute of Health Economics, NRS – non-randomised studies, pts – patients, RoB – risk of bias, SAE – serious adverse event*

6 Discussion

Lipoedema is a chronic and progressive fat distribution disorder characterised by a symmetrical disproportional increase of adipose tissue on the extremities, mainly on legs but also on arms. The disorder is most commonly associated with pain, oedemas, an increased tendency of bruising, as well as sensory dysfunctions on the affected limbs, resulting in severely reduced quality of life (QoL) for the almost exclusively female patients. Secondary lymphoedema may occur in an advanced severe stage. This results in movement restrictions due to the increased leg volume, which may lead to dermatological and orthopaedic complications. According to current clinical guidelines, the conservative treatment of lipoedema consists of manual lymphatic drainage and compression therapy, combined as complex decongestive therapy (CDT); if necessary, supported by weight control, dietary modifications, and psychotherapy. If conservative therapy does not result in sufficient improvement of symptoms, a surgical intervention, in the form of liposuction under tumescence anaesthesia, may be indicated.

Liposuktion als chirurgische Intervention im Vergleich zu konservativen Therapiemaßnahmen (u. a. kombinierte physikalische Entstauungstherapie) für die schmerzhafte disproportionale Fettverteilungstörung Lipödem

This report aimed to assess the clinical effectiveness and safety of liposuction in patients with lipoedema (stage I-III) in comparison to conservative treatment (e.g., CDT), concerning patient-relevant outcomes, as reduction of pain, reduction in the size of extremities, and improvement of QoL.

Ziel: Synthese der Evidenz für vergleichende klin. Wirksamkeit und Sicherheit

Summary of evidence

Prior to our systematic search for primary studies concerning liposuction for lipoedema, we identified two evidence syntheses from international HTA institutions; one from Germany conducted in 2015 [33], and the other, a more recent one from Canada conducted in 2019 [6]. In contrast to these, our assessment includes further evidence from the last five years, as well as German literature.

Evidenzsynthesen aus Deutschland (2015) und Kanada (nur englische Literatur)

Hence, our systematic search was not limited to a specific time period, but to publications in English or German and specific study designs – only randomised controlled trials (RCTs), non-randomised CTs, and prospective observational studies were included in order to assess outcomes on clinical effectiveness. Concerning safety outcomes, we further considered retrospective studies. Even though liposuction has been clinically used for more than 15 years [12], we identified no controlled trial concerning liposuction for surgical therapy of lipoedema compared to conservative treatment. Therefore, the evaluation of clinical effectiveness and safety is based on six prospective single-arm before-and-after studies [8, 13, 23-30] and one additional retrospective single-arm before-and-after study for safety only [31].

systematische Suche nach (randomisierten) kontrollierten Studien und prospektiven Beobachtungstudien: 6 prospektive unkontrollierte vorher/nachher Studien; +1 retrospektive Studie

A total of 737 female patients were assessed prior to their first liposuction, with 467 of them eligible for at least one post-operative follow-up and therefore included in the before versus after analyses. An additional 25 patients were included in the safety analysis. Patients were included across all three severity stages of lipoedema (stage I-III) and the mean (or median) follow-up of the studies was between six to 35.9 months. One study reported the outcomes over a long-term follow-up of 4, 8, and 12 years. The performed liposuction techniques, all in tumescence local anaesthesia (except for the included safety-only study), were mainly power-assisted and water jet-assisted liposuction, but mechanical or laser-assisted devices were also used. Depending

Studien klin. Wirksamkeit: 467 weibliche Pat. für vorher/nachher Vergleich; alle Lipödem Stadien vertreten; FU zwischen 6 Monaten und 12 Jahren

on the severity of their lipoedema, patients were treated in multiple sessions of liposuctions ranging from one to seven sessions per patient.

kein Vergleich zwischen konservativer Therapie und Liposuktion möglich

Due to the lack of any controlled trial, no conclusions on the comparative clinical effectiveness of liposuction for lipoedema can be made. Nonetheless, the data from the prospective single-arm studies show a potential beneficial effect concerning *crucial* and *important* outcomes.

klinische Wirksamkeit: alle Studien (n=6) zeigen eine statistisch signifikante Reduktion der Pat.-Beschwerden bzgl. Schmerzen; 3 Studien berichten eine Reduktion des Beinumfangs/-volumens; 4 Studien berichten eine statistisch signifikante Reduktion der Pat.-Beschwerden bzgl. Lebensqualität

All six prospective studies reported significant improvement of pain outcomes pre- vs post-liposuction. The individual tools and scores for pain measurements are further explained in the results chapter (see Section 4.3) and the extraction tables (see Appendix Table A-1 and Table A-2). A decrease of post-operative pain complaints was reported beginning at a six-month follow-up [27, 28]. Still, up to a mean of twelve years after the last intervention, pain reduced significantly [24], indicating beneficial long-term effects of liposuction in lipoedema. Reduced sizes of patients' extremities before-and-after liposuction were reported in three of the included studies in terms of before and after leg volume (3D imaging technique; -6.9%) [27] and circumference of lower extremities (4-8cm) [8, 26] 30]. Four prospective studies reported on improvement in QoL assessed with the same non-validated patient complaint scores as for the pain outcome [8, 23-26], [13], [27], [28]. All of them report significantly reduced complaints about QoL after liposuction compared to pre-operative assessed values. Some of the included studies also reported a significant reduction of patients' complaints about oedema or swelling and bruising. Furthermore, significant decrease in patients' complaints about sensory dysfunctions, like sensitivity to pressure or touch, a feeling of tension, or itching, was reported, and lipoedema-associated mobility impairment improved post-operatively. The individual results are further described in the results chapter (see Section 4.3).

Sicherheit: insgesamt 17 postoperative unerwünschte Ereignisse in 492 Pat.

In terms of safety, not all of the included studies reported procedure-related adverse events based on the interventions performed, as the majority of included patients received several liposuction sessions, but instead on the patients enrolled. So, concerning the 492 patients eligible for safety analyses, 17 (3.5%) post-operative adverse events occurred overall. Five of these patients were affected by serious adverse events: one epileptic attack, a single episode of postsurgical anaemia requiring a blood transfusion, one microscopic pulmonary fat embolism, one acute pulmonary oedema requiring intensive care admission, and one patient with an abscess, requiring hospitalisation [8, 26, 30]. Other procedure-related adverse events reported were: post-operative wound infections, post-operative bleedings, mild arm vein phlebitis, a deep vein thrombosis and a post-operative seroma.

Internal and external validity

Qualität der Evidenz nur für Sicherheit: sehr niedrig

Overall, the strength of evidence for clinical effectiveness outcomes was not assessed due to the lack of controlled studies. Regarding the safety of liposuction, the quality of evidence was very low.

moderates bis hohes Risiko für Bias, besonders aufgrund des unkontrollierten Studiendesigns

When interpreting the results of our evidence summary, several limitations related to the risk of bias (RoB) and to study design have to be considered: Above all, the key limitation is that all of the studies are highly prone to bias due to their uncontrolled before-and-after study design.

Another major limitation is that almost all of the clinical outcomes were patient-reported. Only one study assessed the outcomes via an investigator-guided interview, the others via self-reported questionnaires. The only objectively assessed outcome was the size of the extremities, which was assessed in three studies; still, the investigators were not blinded. Although the questionnaires used to assess patients' symptoms are very similar, they were most often only standardised within the same study; the instruments used (e.g., VAS) were not validated for lipoedema. In any case, it should be noted that a guideline from the Netherlands published recommendations for validated measurement instruments for lipoedema symptoms in 2016 [3].

viele Endpunkte sind subjektiv von Pat. berichtet mittels nicht validierter Instrumente

Further concerns were the single-centred setup of the studies, no information about exclusion criteria, lack of blinding of the investigators, and patients entering the studies during different stages of the disease. Moreover, there are some concerns regarding uncertainties in appropriate statistical methods: In some studies, data distribution was not analysed (or, if done, not reported). Therefore, it is not possible to evaluate whether the statistical test used was appropriate. In some cases, estimates of random variability in the data analysis of relevant outcomes were not reported. Here, it must also be mentioned that none of the studies had performed a sample size calculation.

weitere Risiken für Bias: Pat. mit unterschiedlichem Lipödem-Schweregrad eingeschlossen, keine Berechnungen des Stichprobenumfangs

Concerning safety, adverse events were partly counted according to different denominators (numbers were given either per liposuction session or per patient). The low numbers of included participants across the studies could have influenced the occurrence of very rare adverse events.

seltene unerwünschte Ereignisse möglicherweise aufgrund geringer Pat.-Zahl nicht erfasst

In terms of external validity, the data is considered generalizable to the Austrian context, as the countries of recruitment were Germany and Switzerland. Moreover, in the included studies, liposuction was performed in the inpatient and the outpatient setting; this also applies to the Austrian clinical practice. More detailed information on external validity is provided in Table A-4.

externe Validität: Daten auf österreichischen Kontext übertragbar

Evidence gaps and ongoing studies

First and foremost, before evaluating the clinical benefit and safety of liposuction for lipoedema, it would be essential to know how many potentially affected patients exist. No lipoedema prevalences for Austria could be identified within the scope of this report. German or other internationally reported prevalences (around 10% of the total female population) are also based solely on estimates from individual clinics [4]. Still, it is also believed that lipoedema is often confused with other diseases and is ultimately rather rare [34].

genaue Zahl der betroffenen Pat. nicht bekannt (Lipödem-Prävalenz)

Evidence gaps concern more detailed stratified analyses depending on the stages of lipoedema. The question of when is the right time for the liposuction is here of main interest. In the early stage, the differentiation from lipohypertrophy is difficult, but stage III liposuction may be too late. Also comparisons of different tumescence anaesthesia techniques, e.g., power-assisted and water jet-assisted liposuction are of interest. As lipoedema is often associated with other comorbidities like obesity, hypertension, or hypothyreosis, those should not only be assessed (e.g., in [29]), but also included in the (sub-)analysis of clinical effectiveness. Another focus could be placed on outcomes concerning the consequences of lipoedema for society, like occupational restrictions or full disability to work. An assessment of effect sizes comparing inpatient vs outpatient settings, especially in terms of safety, is likewise of interest.

neben kontrollierten Studien auch nötig: Subgruppen-Analyse nach Lipödem-Schweregrad (Stadium), Vergleich versch. Liposuktions-Methoden, Sicherheit in unterschiedlichen klin. Settings

In the course of a more valid assessment of lipoedema-related symptoms and endpoints, minimal clinically important differences should be defined. However, one study reported that a magnitude of change of the assessed effect sizes >0.50 is classified as medium and a value >0.80 as a strong effect. The clinical relevance for the patients was not described [8, 26].

Lipödem keine lebensbedrohliche Erkrankung, Liposuktion lange etabliert (nicht experimentell) → hochqualitative Studien nötig

As lipoedema is not a life-threatening disease, other therapeutic options are available, and a high prevalence of around 10% in the female population is estimated, high-quality evidence to assess liposuction's superiority would be required to evaluate the comparative clinical effectiveness and safety. Furthermore, liposuction, including tumescent anesthesia liposuction, is an established intervention that has been used for a long time. The devices are on the market for decades and, in principle, conducting RCTs would not have been unethical and could have been possible by now.

vorhandene Evidenz nicht ausreichend für Evaluierung der vergleichenden klin. Wirksamkeit/Sicherheit zwischen Liposuktion und konservativen Maßnahmen

Thus, the identified low quality of evidence, based upon uncontrolled studies, is insufficient to evaluate comparative clinical effectiveness and safety. However, we identified one ongoing study which might show effects of liposuction for lipoedema with a higher quality of evidence (Table A-5). Conducted in Germany, the large multi-centre RCT evaluates the primary outcome of successful pain reduction between liposuction compared to CDT alone. Enrolment of 450 female patients of all lipoedema stages already finished, and the estimated primary completion date of the so-called LIPLEG study (NCT04272827) is expected in July 2024.

robustes RCT in Deutschland (450 Pat.), erste Ergebnisse 2024 erwartet

in D Liposuktion unter bestimmten Vorrausetzungen befristet erstattungsfähig

The LIPLEG study was commissioned by the German Joint Federal Committee (Gemeinsamer Bundesauschuss, G-BA) following the suspension of an assessment for liposuction for lipoedema due to insufficient evidence of clinical effectiveness in 2017 [33], and the subsequent preparation of an *Erprobungsrichtline* in 2019 [14, 35]. Since then (January 2020), liposuction is temporarily reimbursable under special premises, which comprise patients with stage III lipoedema, at least six months of prior conservative treatment, and BMI <35 kg/m^2 (or BMI 35-40 kg/m^2 with accompanying guideline-based treatment of obesity). Reimbursement for surgical treatment of stage I and II lipoedema remains restricted and must generally be decided upon by the health insurances on a case-by-case basis [2, 15, 35].

Limitations to this report

retrospektive Studien nur für Sicherheits-Endpunkte

First of all, retrospective studies for the evaluation of clinical effectiveness were excluded. Additional evidence – though of lower quality – on liposuction for lipoedema could have thereby been missed.

kein Vergleich zwischen Liposuktion und konservativer Therapie möglich

Furthermore, due to the single-arm design of the identified studies, the comparative quality of evidence of clinical effectiveness outcomes could not be assessed. Therefore, only procedure-related safety outcomes based on narrative descriptions could be analysed within the GRADE scheme.

ästhetische/kosmetische Beschwerden nicht betrachtet

The pre-specified *crucial* or *important* outcomes for decision-making represent measures of the most important clinical therapeutic goals. However, other patient-relevant outcomes, such as aesthetic impairment, were not evaluated in this assessment.

Conclusion

ohne kontrollierte Studien keine Schlussfolgerungen über bessere Wirksamkeit und gleiche Sicherheit möglich

In the absence of comparative data, it is difficult to ascertain the relative risk and benefit of liposuction for lipoedema in comparison to conservative therapy, such as lymphatic drainage, compression garments, and combined decongestive therapy. Therefore, without any control, we cannot conclude that liposuction might be more effective and equally safe or safer than its comparators.

weitere robuste Studien (RCTs) könnten erste Anzeichen für erhöhte Wirksamkeit der Liposuktion unterstützen

However, based on the limited evidence of the included uncontrolled studies, it appears that liposuction provides potential benefit in terms of the significant reduction of lipoedema-associated clinical symptoms. An ongoing randomised controlled study may support the beneficial findings of liposuction-associated pain relief and other outcomes in lipoedema patients of the existing single-arm studies. Concerning safety, procedure-related adverse events are rare overall. A comparison to the safety profile of conservative therapy was not possible.

7 Recommendation

In Table 7-1, the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlungsschema

Table 7-1: Evidence-based recommendation

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is **currently not recommended**.
	The **inclusion in** the catalogue of benefits is **not recommended**.

Reasoning:

The current evidence is not sufficient to prove that the assessed intervention liposuction is more effective and equally safe (or equally effective and safer) for lipoedema therapy than the comparator conservative treatment, which includes manual lymphatic drainage, compression garments, and combined decongestive therapy.

Aufnahme in den Leistungskatalog derzeit nicht empfohlen

However, based on the limited evidence of the included uncontrolled studies, liposuction may potentially reduce lipoedema-associated clinical symptoms and improve the quality of life of affected patients. New study results based on the German LIPLEG study (NCT04272827), a high-quality multi-centre RCT including 450 females, will potentially influence the effect estimates considerably.

Evidenz unzureichend, aber großes RCT schon in Durchführung

The re-evaluation is recommended after the completion of this ongoing RCT, expected in 2025.

Re-Evaluierung für 2025 empfohlen

8 References

[1] Reich-Schupke S., Schmeller W., Brauer W. J., Cornely M. E., Faerber G., Ludwig M., et al. S1 guidelines: Lipedema. J Dtsch Dermatol Ges. 2017;15(7):758-767. Epub 2017/07/06. DOI: 10.1111/ddg.13036.

[2] Kruppa P., Georgiou I., Biermann N., Prantl L., Klein-Weigel P. and Ghods M. Lipedema-Pathogenesis, Diagnosis, and Treatment Options. Dtsch Arztebl Int. 2020;117(22-23):396-403. Epub 2020/08/09. DOI: 10.3238/arztebl.2020.0396.

[3] Halk A. B. and Damstra R. J. First Dutch guidelines on lipedema using the international classification of functioning, disability and health. Phlebology. 2017;32(3):152-159. Epub 2016/04/15. DOI: 10.1177/0268355516639421.

[4] Marshall M. and Schwahn-Schreiber C. Prävalenz des Lipödems bei berufstätigen Frauen in Deutschland. Phlebologie. 2011;40:127-134.

[5] Sandhofer M., Hanke C. W., Habbema L., Podda M., Rapprich S., Schmeller W., et al. Prevention of Progression of Lipedema With Liposuction Using Tumescent Local Anesthesia: Results of an International Consensus Conference. Dermatol Surg. 2020;46(2):220-228. Epub 2019/07/30. DOI: 10.1097/dss.0000000000002019.

[6] Peprah K. and MacDougall D. CADTH Rapid Response Reports. Liposuction for the Treatment of Lipedema: A Review of Clinical Effectiveness and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health 2019.

[7] Deutsches Institut für Medizinische Dokumentation und Information (DIMDI). ICD-10-GM Version 2021. 2021 [cited 12.01.2021]. Available from: https://www.dimdi.de/static/de/klassifikationen/icd/icd-10-gm/kode-suche/htmlgm2021/block-e70-e90.htm.

[8] Schmeller W., Hüppe M. and Meier-Vollrath I. Long-term results following liposuction in lipedema. Lymphologie in Forschung und Praxis. 2010;14(2):69-80.

[9] Klein J. A. The Tumescent Technique for Lipo-Suction Surgery. The American Journal of Cosmetic Surgery. 1987;4(4):263-267. DOI: 10.1177/074880688700400403.

[10] Boeni R. Safety of Tumescent Liposuction under Local Anesthesia in a Series of 4,380 Patients. Dermatology. 2011;222(3):278-281. DOI: 10.1159/000327375.

[11] Habbema L. Safety of liposuction using exclusively tumescent local anesthesia in 3,240 consecutive cases. Dermatol Surg. 2009;35(11):1728-1735. Epub 2009/08/08. DOI: 10.1111/j.1524-4725.2009.01284.x.

[12] Schmeller W. and Meier-Vollrath I. Tumescent liposuction: a new and successful therapy for lipedema. J Cutan Med Surg. 2006;10(1):7-10. Epub 2007/01/24. DOI: 10.1007/7140.2006.00006.

[13] Münch D. Wasserstrahlassistierte Liposuktion zur Therapie des Lipödems. Journal für Ästhetische Chirurgie. 2017;10(2):71-78. DOI: 10.1007/s12631-017-0083-6.

[14] Gemeinsamer Bundesausschuss. Abschlussbericht Beratungsverfahren nach § 135 Absatz 1, § 137c und § 136 Absatz 1 Satz 1 Nummer 2 SGB VLiposuktion bei Lipödem im Stadium III. 2019 [cited 14.01.2021]. Available from: https://www.g-ba.de/downloads/40-268-6048/2019-09-19_MVV-RL_Liposuktion-Lipoedem-III_ZD.pdf.

[15] Gemeinsamer Bundesausschuss. Qualitätssicherungs-Richtlinie zur Liposuktion bei Lipödem im Stadium III/QS-RL Liposuktion. 2020 [cited 14.01.2021]. Available from: https://www.g-ba.de/downloads/62-492-2243/QS-Ma%C3%9Fnahmen_Liposuktion-Lipoedem_2020-06-18_iK-2020-09-16.pdf.

[16] Schmeller W. and Meier-Vollrath I. Lipödem. Gefässchirurgie. 2009;14(6):516. DOI: 10.1007/s00772-009-0747-4.

[17] Ghods M. and Kruppa P. Operative Behandlung des Lipödems. Handchir Mikrochir Plast Chir. 2018;50(06):400-411.

[18] Gemeinsamer Bundesausschuss. Abschlussbericht, Beratungsverfahren über eine Richtlinie zur Erprobung gem. § 137e SGB V, Liposuktion bei Lipödem. 2018 [cited 14.01.2021]. Available from: https://www.g-ba.de/downloads/40-268-4769/2018-04-10_Erp-RL_Liposuktion_ZD.pdf.

[19] Austrian Ministry of Health. Leistungsorientierte Krankenanstaltenfinanzierung (LKF). Leistungskatalog BMGF 2018. 2018 [cited 06.12.2018]. Available from: https://www.bmgf.gv.at/cms/home/attachments/8/6/4/CH1166/CMS1128332460003/leistungskatalog_bmgf_2018_-_stationaer_verpflichtend.pdf.

[20] European Network for Health Technology Assessment (EUnetHTA Work Package WP5). HTA Core Model for the production of Rapid Relative Effectiveness Assessments (version 4.2). 2015 [cited 27.11.2020]. Available from: https://eunethta.eu/wp-content/uploads/2018/06/HTACoreModel_ForRapidREAs4.2-3.pdf.

[21] Moga C., Guo B., Schopflocher D. and Harstall C. Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique. Edmonton AB: Institute of Health Economics. 2012. Available from: https://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about.

[22] Guyatt G., Oxman A. D., Akl E. A., Kunz R., Vist G., Brozek J., et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-394. Epub 2011/01/05. DOI: 10.1016/j.jclinepi.2010.04.026.

[23] Baumgartner A., Hüppe M. and Schmeller W. How long do patients with lipedema benefit from liposuction? A follow-up study performed an average of 4 and 8 years after surgery. Lymphologie in Forschung und Praxis. 2015;19(1):8-14.

[24] Baumgartner A., Hueppe M., Meier-Vollrath I. and Schmeller W. Improvements in patients with lipedema 4, 8 and 12 years after liposuction. Phlebology. 2020:268355520949775.

[25] Baumgartner A., Hueppe M. and Schmeller W. Long-term benefit of liposuction in patients with lipoedema: a follow-up study after an average of 4 and 8 years. British Journal of Dermatology. 2016;174(5):1061-1067.

[26] Schmeller W., Hueppe M. and Meier-Vollrath I. Tumescent liposuction in lipoedema yields good long-term results. British Journal of Dermatology. 2012;166(1):161-168.

[27] Rapprich S., Dingler A. and Podda M. Liposuction is an effective treatment for lipedema-results of a study with 25 patients. Journal der Deutschen Dermatologischen Gesellschaft. 2011;9(1):33-40.

[28] Rapprich S., Baum S., Kaak I., Kottmann T. and Podda M. Treatment of lipoedema using liposuction: Results of our own surveys. Phlebologie. 2015;44(3):121-132.

[29] Witte T., Dadras M., Heck F. C., Heck M., Habermalz B., Welss S., et al. Water-jet-assisted liposuction for the treatment of lipedema: Standardized treatment protocol and results of 63 patients. Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS. 2020;73(9):1637-1644.

[30] Wollina U. and Heinig B. Treatment of lipedema by low-volume micro-cannular liposuction in tumescent anesthesia: Results in 111 patients. Dermatologic Therapy. 2019;32(2):e12820.

[31] Dadras M., Mallinger P. J., Corterier C. C., Theodosiadi S. and Ghods M. Liposuction in the Treatment of Lipedema: A Longitudinal Study. Archives of Plastic Surgery. 2017;44(4):324-331.

[32] Chou R., Aronson N., Atkins D., Ismaila A. S., Santaguida P., Smith D. H., et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the effective health-care program. J Clin Epidemiol. 2010;63(5):502-512. Epub 2008/10/01. DOI: 10.1016/j.jclinepi.2008.06.007.

[33] Gemeinsamer Bundesausschuss. Zusammenfassende Dokumentation, Beratungsverfahren nach §§ 135 Absatz 1, 137c SGB V, Liposuktion bei Lipödem. 2017 [cited 14.01.2021]. Available from: https://www.g-ba.de/downloads/40-268-4515/2017-07-20_KHMe-RL_Liposuktion_ZD.pdf.

[34] Shavit E., Wollina U. and Alavi A. Lipoedema is not lymphoedema: A review of current literature. Int Wound J. 2018;15(6):921-928. Epub 2018/06/30. DOI: 10.1111/iwj.12949.

[35] Gemeinsamer Bundesausschuss. Nr 12/2019, Methodenbewertung – Erprobungsstudie soll offene Frage des Nutzens der Liposuktion bei Lipödem beantwor-ten: G-BA beauftragt wissenschaftliche Institution mit Studienbegleitung. 2019 [cited 24.01.2021]. Available from: https://www.g-ba.de/downloads/34-215-795/12_2019-04-18_Vergabe%20uwl_Liposuktion.pdf.

[36] Austrian Institute for Health Technology Assessment. Methodenhandbuch für Health Technology Assessment, Version 1.2012. 2012. Available from: https://aihta.at/uploads/tableTool/UllCmsPage/gallery/methodenhandbuch-aihta1.pdf.

[37] EUnetHTA Joint Action 2. Internal validity of non-randomised studies (NRS) on interventions. 2015. Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/2015-07-06_Non-RCT_Assessment_WP7_SG3_Guideline_final.pdf.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Liposuction for surgical therapy of lipoedema: Results from observational studies (part 1)

Author (year)	Schmeller et al. (2010, 2012) [8, 26], Baumgartner et al. (2015, 2016) [23, 25][52], Baumgartner et al. (2020) [24][53]	Dadras et al. (2017) [31]	Münch (2017) [13]
Country	Germany	Germany	Switzerland
Sponsor	None reported	None reported	None reported
Study design	Single-center, single-arm, before-and-after NRS	Single-center, single-arm, before-and-after NRS	Single-center, single-arm, before-and-after NRS
Conducted in	01/2003-early 2019	07/2010-07/2013	07/2010-07/2016
Indication	Female patients with lipoedema	Female patients with lipoedema	Female patients with lipoedema
Intervention	Tumescent local anaesthesia liposuction with blunt vibrating microcannulas (power-assisted liposuction) Median No. of sessions: 2 (range: 1-7) Average fat removed/session: 3,077 mL (range: 450-7,000 mL)	Tumescent liposuction (vibration-assisted or water jet-assisted device) was performed using saline with epinephrine (1:1,000,000) under general anaesthesia Median No. of sessions: 3 (range: 1-7) Average fat removed/session: 3,106 mL (range: 1,450-6,600 mL)	Tumescent local anaesthesia water jet-assisted liposuction (Body-Jet Evo® device) No. of sessions: 2 in 61 pts; 1 in 80 pts[54] Average fat removed/session: NR
Comparator	None	None	None
Number of pts at baseline (pre-operative)	165	33	141
Number of pts analysed (n liposuction procedures)	4y follow-up: 112 (349) 8y follow-up: 85 (NA) 12y follow-up: 60 (NA)	25 (27)	71 (NA)
Inclusion criteria	Completed surgical therapy At least 6 months have passed since last intervention, conservative therapy over several years did not result in adequate response	Lipoedema diagnosis had been clinically confirmed by a lymphologist, ruling out other lymphatic diseases At least 6 months conservative therapy with no adequate response and improvement	NA

[52] 8-year follow-up of Schmeller et al. (2010, 2012).

[53] 12-year follow-up of Schmeller et al. (2010, 2012).

[54] Based on pts at baseline.

Author (year)	Schmeller et al. (2010, 2012) [8, 26], Baumgartner et al. (2015, 2016) [23, 25][52], Baumgartner et al. (2020) [24][53]	Dadras et al. (2017) [31]	Münch (2017) [13]
Exclusion criteria	NA	NA	NA
Clinical outcome measures	*Efficacy*: Change of bodyshape (circumference of extremities), improvement of complaints[55] (spontaneous pain, pain upon pressure, oedema, bruising, restriction of movement, cosmetic impairment, reduction in quality of life, general impairment), reduction of conservative therapy *Safety*: AE	*Efficacy*: Improvement of complaints[56] (spontaneous pain, sensitivity to pressure, feeling of tension bruising, cosmetic impairment, reduction in quality of life), CDT score[57] *Safety*: AEs	*Efficacy*: Pain, touch sensitivity, pain upon pressure, feeling of tension, feeling of heavy legs, oedema, bruising, restriction of movement, cosmetic impairment (bothersome body proportions), reduction in quality of life[58], reduction of conservative therapy *Safety*: AEs
Baseline patient characteristics			
Mean age, yrs (range)	4y follow-up: 38.8 (20-68) 8y follow-up: 40.1 (22-68) 12y follow-up: 41.9 (22-68)	Median: 45 (23-64)	37.2 (18-65; SD: 9.68)[59]
Stage of lipoedema, n	4/8/12y follow-up:		NA
Stage I	35/24/18	1	
Stage II	75/61/42	11	
StageIII	2/0/0	13	
Mean weight, kg (range)	4y follow-up: 79.3 (50-123) 8y follow-up: NA 12y follow-up: 79.7 (50-116)	NA	72.5 (47-136; SD: 13.96)[59]
BMI[60], m (range)	Reported at 4y follow-up [8, 26]:	35.3 (24.5-50.6)	26.6 (18.6-44.9; SD: 5.14)[59]
Underweight	1		
Normal weight	29		
Overweight	31		
Obese class I	32		
Obese class II	7		
Obese class III	12		

[55] Assessed with patients' questionnaire including seven items, quantification was performed on five-point-scales: 0, none; 1, minor; 2, medium; 3, strong; 4, very strong. Items were summarised to a total score named 'general impairment'.

[56] Visual Analogue Scale (VAS) of symptom severity ranging from 0 to 10 in increments of 0.5, with 10 being the most severe.

[57] CDT: sum of the number of manual lymphatic drainage sessions per month and the number of hours spent wearing compression garments per day.

[58] VAS based of self-assessed complaint criteria, ranging from 0 to 9, with 0 "not present" and 9 "very pronounced".

[59] No specification if pre- or post-operative.

[60] Body mass index (BMI; kg/m^2): Underweight: <18.5, Normal (healthy weight): 18.5-25; Overweight: 25-30; Obese Class I (Moderately obese): 30-35; Obese Class II (Severely obese): 35-40; Obese Class III (Very severely obese): >40.

Author (year)	Schmeller et al. (2010, 2012) [8, 26], Baumgartner et al. (2015, 2016) [23, 25][52], Baumgartner et al. (2020) [24][53]			Dadras et al. (2017) [31]	Münch (2017) [13]
Mean follow-up, months (range)	After last intervention:				35.9 (5-84; SD: 14.09) [61]
1st post-operative follow-up	4y follow-up: 35 (8-82)			16 (4-34)	
2nd post-operative follow-up	8y follow-up: 90 (56-130)			37 (25-56)	
3rd post-operative follow-up	12y follow-up: 148 (NA)				
Loss to follow-up, n (%)	Compared to baseline pts:			Compared to baseline pts:	Compared to baseline pts:
1st post-operative follow-up	4y follow-up: 53 (32)			8 (24)	70 (50)
2nd post-operative follow-up	8y follow-up: 27 (24)[62]			8 (24)	
3rd post-operative follow-up	12y follow-up: 52 (46)[62]				
Outcomes					
Efficacy					
Mean reduction of circumference of extremities, cm ±SD	Reported at 4y follow-up [8, 26]: Thighs (inguinal region): 8 (1–23) Middle of the lower legs (calves): 4 (1–11)			NA	NA[63]
Pain	NA			NA	
effect size (pre-operative vs last FU)					NA (p<0.05)
Pre-operative, m ±SD					6.0 ±NA
Post-operative, m ±SD					3.2 ±NA
Spontaneous pain	4y FU:	8y FU:	12y FU:		NA
effect size (pre-operative vs last FU)	1.36 (p< 0.001)[64]	1.50 (p< 0.001)[64]	1.04 (p< 0.001[64]	3.5 (95% CI: 2.83-4.17; p< 0.001)	
Pre-operative, m ±SD	1.88 ±1.33	1.86 ±1.33	1.76 ±1.41	7.20 ±1.46	
Post-operative 1, m ±SD	0.37 ±0.60	0.37 ±0.61	0.33 ±0.55	3.70 ±1.79	
Post-operative 2, m ±SD		0.37 ±0.57	0.31 ±0.51	4.28 ±2.10	
Post-operative 3, m ±SD			0.37 ±0.49		
Pain upon pressure	NA			NA	
effect size (pre-operative vs last FU)					NA (p<0.05)
Pre-operative, m ±SD					6.0 ±NA
Post-operative, m ±SD					2.9 ±NA

[61] Not mentioned if general follow-up or time till assessment with questionnaire.

[62] Compared to 112 pts analysed in 4-year follow-up of Schmeller et al. (2010, 2012).

[63] No quantitative values are provided, but mention of reduction of circumference and normalisation of body proportions of all patients.

[64] Effect size represents magnitude of change: value > 0.50 is classified as medium, a value > 0.80 may be classified as a strong effect. Pre-operative compared to 4 years post-operative, 8 years, or 12 years, respectively.

Author (year)	Schmeller et al. (2010, 2012) [8, 26], Baumgartner et al. (2015, 2016) [23, 25][52], Baumgartner et al. (2020) [24][53]			Dadras et al. (2017) [31]	Münch (2017) [13]
Sensitvity to pressure	4y FU:	8y FU:	12y FU:		NA
effect size (pre-operative vs last FU)	2.01 (p< 0.001)[64]	1.92 (p< 0.001)[64]	1.46 (p< 0.001)[64]	NA	
Pre-operative, m ±SD	2.91 ±1.06	2.88 ±1.01	2.88 ±1.06	7.38 ±1.79	
Post-operative 1, m ±SD	0.91 ±0.92	0.85 ±0.86	0.88 ±0.91	3.98 ±1.83	
Post-operative 2, m ±SD		0.94 ±0.95	1.02 ±1.03	4.42 ±2.08	
Post-operative 3, m ±SD			0.98 ±0.94		
Touch sensitivity		NA		NA	
effect size (pre-operative vs last FU)					NA (p<0.05)
Pre-operative, m					5.8 ±NA
Post-operative, m					3.2 ±NA
Feeling of heavy legs		NA		NA	
effect size (pre-operative vs last FU)					NA (p<0.05)
Pre-operative, m					6.7 ±NA
Post-operative, m					3.1 ±NA
Oedema	4y FU:	8y FU:	12y FU:	NA	
effect size (pre-operative vs last FU)	1.88 (p< 0.001)[64]	1.73 (p< 0.00)[64]	1.49 (p< 0.001)[64]		NA (p<0.05)
Pre-operative, m ±SD	3.06 ±1.02	3.07 ±0.06	3.05 ±1.06		6.5 ±NR
Post-operative 1, m ±SD	1.27 ±0.88	1.28 ±0.88	1.42 ±0.91		3.5 ±NR
Post-operative 2, m ±SD		1.34 ±0.92	1.51 ±0.93		
Post-operative 3, m ±SD			1.35 ±0.88		
Feeling of tension		NA			
effect size (pre-operative vs last FU)				NA	NA (p<0.05)
Pre-operative, m ±SD				7.52 ±1.36	5.7 ±NA
Post-operative 1, m ±SD				3.26 ±2.28	2.6 ±NA
Post-operative 2, m ±SD				4.06 ±2.18	
Bruising	4y FU:	8y FU:	12y FU:		
effect size (pre-operative vs last FU)	1.63 (p< 0.001)[64]	1.28 (p< 0.001)[64]	1.27 (p< 0.001)[64]	NA	NA (p<0.05)
Pre-operative, m ±SD	3.01 ±1.03	2.91 ±1.10	3.04 ±0.98	6.96 ±1.58	5.9 ±NA
Post-operative 1, m ±SD	1.26 ±1.11	1.12 ±1.02	1.16 ±0.98	4.36 ±1.91	3.7 ±NA
Post-operative 2, m ±SD		1.46 ±1.17	1.47 ±1.23	4.64 ±1.83	
Post-operative 3, m ±SD			1.40 ±1.08		

Author (year)	Schmeller et al. (2010, 2012) [8, 26], Baumgartner et al. (2015, 2016) [23, 25][52], Baumgartner et al. (2020) [24][53]			Dadras et al. (2017) [31]	Münch (2017) [13]
Restriction of movement	4y FU:	8y FU:	12y FU:	NA	
effect size (pre-operative vs last FU)	1.58 (p< 0.001)[64]	1.51 (p< 0.001)[64]	1.29 (p< 0.001)[64]		NA (p<0.05)
Pre-operative, m ±SD	2.03 ±1.36	2.11 ±1.30	2.13 ±1.32		3.7 ±NA
Post-operative 1, m ±SD	0.28 ±0.68	0.24 ±0.58	0.20 ±0.40		1.8 ±NA
Post-operative 2, m ±SD		0.53 ±0.69	0.59 ±0.71		
Post-operative 3, m ±SD			0.52 ±0.81		
Improvement of mobility, post-operative	NA			NA	NA
Marked improvement or complete loss of impairment, %					
Minor to medium improvement, %					
Cosmetic impairment	4y FU:	8y FU:	12y FU:		
effect size (pre-operative vs last FU)	2.52 (p< 0.001)[64]	1.96 (p< 0.001)[64]	1.43 (p< 0.001)[64]	NA	NA (p<0.05)
Pre-operative, m ±SD	3.33 ±0.88	3.32 ±0.89	3.46 ±0.91	8.98 ±0.81	8.5 ±NA
Post-operative 1, m ±SD	1.08 ±0.91	1.04 ±0.89	1.00 ±0.82	5.10 ±1.93	4.4 ±NA
Post-operative 2, m ±SD		1.40 ±1.07	1.46 ±1.15	7.36 ±1.66	(assessed as bothersome body proportions)
Post-operative 3, m ±SD			1.48 ±1.08		
Reduction in quality of life	4y FU:	8y FU:	12y FU:		
effect size (pre-operative vs last FU)	2.95 (p< 0.001)[64]	2.59 (p< 0.001)[64]	2.18 (p< 0.001)[64]	4.08 (95% CI: 3.12-5.04; p<0.001)	NA (p<0.05)
Pre-operative, m ±SD	3.36 ±0.86	3.35 ±0.84	3.49 ±0.77	8.38 ±1.06	6.3 ±NA
Post-operative 1, m ±SD	0.76 ±0.91	0.73 ±0.87	0.69 ±0.81	4.30 ±1.80	2.6 ±NA
Post-operative 2, m ±SD		0.94 ±1.00	1.00 ±1.04	5.16 ±1.60	
Post-operative 3, m ±SD			0.96 ±0.90		
Overall impairment	4y FU:	8y FU:	12y FU:	NA	NA
effect size (pre-operative vs last FU)	2.93 (p< 0.001)[64]	2.58 (p< 0.001)[64]	2.06 (p< 0.001)[64]		
Pre-operative, m ±SD	2.81 ±0.7	2.78 ±0.72	2.81 ±0.69		
Post-operative 1, m ±SD	0.86 ±0.63	0.81 ±0.56	0.84 ±0.58		
Post-operative 2, m ±SD		1.00 ±0.66	1.05 ±0.70		
Post-operative 3, m ±SD			0.99 ±0.66		

Author (year)	Schmeller et al. (2010, 2012) [8, 26], Baumgartner et al. (2015, 2016) [23, 25][52], Baumgartner et al. (2020) [24][53]			Dadras et al. (2017) [31]	Münch (2017) [13]
Reduction of conservative therapy	4y FU:	8y FU:	12y FU:	NA	
Pre-operative lymphatic drainage and compression, n (%)	67 (100) of 112	47 (100) of 85	37 (100) of 60		NA
Post-operative more conservative therapy, %	NA	NA 5 (10)	NA 20 (54)		NA
Post-operative lymphatic drainage and compression, as before, n (%)	13 (19.4)				NA
Post-operative less conservative therapy (drainage and compression), %	20 (29.9)	28 (60)	7 (19)		NA (23.4)
Post-operative only compression, n (%)	13 (19.4)	NA	NA		NA
Post-operative lymphatic drainage, n (%)	6 (9)	NA	NA		NA
Post-operative no conservative therapy, %	15 (22.4)	14 (30)	10 (27)		NA (5.3)
CDT score		NA			NA
Pre-operative, m ±SD				20.48 ±4.13[65]	
Post-operative 1, m ±SD				16.38 ±6.97	
Post-operative 2, m ±SD				13.90 ±7.32	
Safety					
Overall complications, n (%)	6 (1.7)[66]			1 (1.39)[67]	0 (0)[68]
Serious adverse events, n (%)	1 (0.3)			0 (0)	0 (0)
Post-operative wound infections, n (%)	4 (1.2)[69]			1 (1.39)[67]	0 (0)
Post-operative bleeding, n (%)	1 (0.3)			NA	0 (0)
Other post-operative complications, n (%)	NA			NA	NA

[65] Four patients were excluded who did not receive full CDT pre-operatively.

[66] In 349 liposuction procedures of 112 pts, adverse events were only reported in Schmeller et al (2010, 2012).

[67] In 72 liposuctions (of 25 pts) the complication rate was 1.39%, one patient with post-operative erysipelas, which required antibiotics.

[68] In 202 liposuction procedures (of 141 pts at baseline).

[69] Post-operative wound infections occurred in 5 pts, of that four patients with post-operative erysipelas, could be treated at home with further oral antibiotics, not classified as SAE. One patient with an abscess of the lower leg, treated in hospital in her home town, classified as SAE.

Table A-2: Liposuction for surgical therapy of lipoedema: Results from observational studies (part 2)

Author (year)	Rapprich et al. (2011) [27]	Rapprich et al. (2015) [28]	Witte et al. (2020) [29]	Wollina et al. (2019) [30]
Country	Germany	Germany	Germany	Germany
Sponsor	NA	NA	NA	NA
Study design	Single-center, single-arm, before-and-after NRS	Single-center, single-arm, before-and-after NRS	Single-center, single-arm, before-and-after NRS	Single-center, single-arm, before-and-after NRS
Conducted in	04/2006-07/2008	04/2003-02/2011	12/2016-01/2019	2007-2018
Indication	Patients with lipoedema	Patients with lipoedema	Patients with lipoedema	Female patients with lipoedema
Intervention	Tumescent local anaesthesia liposuction with vibrating microcannulas Median No. of sessions: 2 (range: 1-5) Average fat removed/session: 2,482 mL (SD: 968 mL)	Tumescent local anaesthesia liposuction with vibrating microcannulas Median No. of sessions: 3 (range: 1-6) Average fat removed/session: NA	Tumescent local anaesthesia water jet-assisted liposuction (body jet device) Median No. of sessions: NA Average fat removed/pts over all sessions: 12,922 mL (SD: 2,922 mL)	Tumescent local anaesthesia micro-cannula liposuction using classical mechanical liposuction or laser-assisted liposuction Median No. of sessions: NA Median fat removed/pts : 4,700 mL (range: 950-14,250 mL)
Comparator	None	None	None	None
Number of pts at baseline (pre-operative)	105	85	130	111
Number of pts analysed/eligible in postoperation follow-up (n liposuction procedures)	25 (NA)	85 (168)	63 (NA)	111 (334)
Inclusion criteria	NA	NA	Decongestive measure (consequent wearing of class II flatknit compression garments for at least 6 weeks pre-operatively, manual lymphatic drainage), weight should be approximated to normal BMI as much as possible in pts with coexistent obesity, pts with BMI >40 required pre-operative weight reduction, eating disorders or accompanying psychological morbidities required adequate treatment and psychological stability	CDT for at least 6 months without improvement or even deterioration of pain sensations and/or leg volume
Exclusion criteria	NA	NA	NA	NA

Author (year)	Rapprich et al. (2011) [27]	Rapprich et al. (2015) [28]	Witte et al. (2020) [29]	Wollina et al. (2019) [30]
Clinical outcome measures	*Efficacy*: Reduction of leg volume[70], self-assessed symptoms (pain, sensitivity to pressure, feeling of tension, bruising, feeling of heavy legs, feeling of cold, feeling of warmth, muscle cramps, skin involvement, feeling of itchy legs, feeling of tired legs, oedema, bruising, restriction of movement, cosmetic impairment, reduction in quality of life, total impairment[71, 72], reduction of conservative therapy *Safety*: AEs	*Efficacy*: Self-assessed symptoms (pain, sensitivity to pressure, feeling of tension, bruising, feeling of heavy legs, feeling of cold, feeling of warmth, muscle cramps, skin involvement, feeling of itchy legs, feeling of tired legs, oedema, bruising, restriction of movement, cosmetic impairment, reduction in quality of life, total impairment score[71, 72] *Safety*: AEs	*Efficacy:* Symptom severity (pain, sensitivity to touch, bruising, feeling of tension, feeling of heavy legs, swelling, itching, running impairment, occupational impairment, general impairment, aesthetic impairment)[73], need for conservative therapy *Safety*: AEs	*Efficacy*: Reduction of circumferences[74], pain[75], improvement of mobility and reduction of bruising[76] *Safety*: AEs
Baseline patient characteristics				
Mean age, yrs (range)	38 (22-65)	NA	Median: 35 (NA)	Median: 44 (20-81; SD: ±16.8)
Stage of lipoedema, n	NA	NA		
Stage I			18	7
Stage II			45	50
StageIII			0	48
Mean weight, kg (range)	NA	NA	81.9 (SD: 14.6)	NA
BMI, m (range)	NA	NA	28.4 (SD: 4.5)[77]	NA
Mean follow-up, months (range)	6 (NA)[78]	6 (NA)[78]	Median: 21.5 (NA)	Median: 24 (NA)[79]
Loss to follow-up, n (%)	80 (76)	0 (0)	67 (52)[80]	0 (0)

[70] Leg volume measurement using 3D imaging, results provided in Litres.

[71] Maximum 150 points.

[72] Self-assessment of symptoms was based on a modified quality of life survey for patients with lymphatic diseases including 15 criteria assed on a VAS of 0 to 10.

[73] Questionnaire of 11 symptoms/impairments on a VAS with range 0–10 and increments of 1.

[74] In cm, assessed with a tape measure.

[75] 10-point VAS, before the first and the last liposuction during an interview with the dermato-surgeon.

[76] 3-point scale: 0 – no improvement, 1 – minor to medium improvement, 3 – marked improvement or no impairment at all.

[77] In Table 1 of the publication SD of pre-operatively BMI is given as 4.5.

[78] No specification if mean or median.

[79] SD only provided in ±2.1 years. A follow-up between 5 and 7 years was available in 18 pts, none of these patients had a relapse of lipoedema.

[80] Compared to pre-operative number of patients (n=130).

Author (year)	Rapprich et al. (2011) [27]	Rapprich et al. (2015) [28]	Witte et al. (2020) [29]	Wollina et al. (2019) [30]
Outcomes				
Efficacy				
Mean reduction of circumference of extremities, cm (range)	NA	NA	NA	Median: 6.0 ±1.6
Leg volume, effect size ±SD (%) Pre-operative, m ±SD Post-operative, m ±SD	1.2 ±1.0 (6.9) 18.0 ±3.8 16.8 ±3.5	NA	NA	NA
Pain, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p<0.001) 7.2 ±2.2 2.1 ±2.1	NA (p< 0.001) 6.5 ±3.0 2.1 ±2.0	NA (p< 0.001) 6.47 ±2.05 1.39 ±1.66	Median: NA (p<0.3) 7.8 ±2.1 2.2 ±1.3
Spontaneous pain, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA	NA	NA	NA
Pain upon pressure, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA	NA	NA	NA
Sensitvity to pressure, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.001) 6.4 ±NR 1.9 ±NR	NA (p< 0.001) 6.5 ±3.0 2.4 ±2.4	NA	NA
Touch sensitivity, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA	NA	NA (p< 0.001) 7.14 ±1.9 1.55 ±1.79	NA
Feeling of heavy legs, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.001) 8.4 ±NR 3.6±NR	NA (p< 0.001) 7.8 ±NA 3.1 ±NA	NA (p< 0.001) 8.42 ±1.8 1.55 ±1.66	NA
Feeling of cold, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.120 diff. n. s.) 3.8 ±NA 2.1 ± NA	NA (p< 0.001) 3.4 ±NA 1.6 ±NA	NA	NA
Feeling of warmth, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.008) 3.0 ±NA 1.4 ±NA	NA (p< 0.001) 2.8 ±NA 1.2 ±NA	NA	NA
Skin involvement, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.001) 3.5 ±NA 1.3 ±NA	NA (p< 0.001) 3.2 ±NA 1.1 ±NA	NA	NA

Author (year)	Rapprich et al. (2011) [27]	Rapprich et al. (2015) [28]	Witte et al. (2020) [29]	Wollina et al. (2019) [30]
Muscle cramps, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.043) 2.7 ±NA 1.3 ±NA	NA (p< 0.001) 2.7 ±NA 1.3 ±NA	NA	NA
Feeling of itchy legs, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.001) 4.2 ±NA 1.9 ±NA	NA (p< 0.001) 2.8 ±NA 1.3 ±NA	NA	NA
Itching, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA	NA	NA (p< 0.001) 4.0 ± 3.3 0.8 ± 1.3	NA
Feeling of tired legs, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.001) 8.4 ±NA 3.5 ±NA	NA (p< 0.001) 7.4 ±NA 3.1 ±NA	NA	NA
Oedema/swelling, effect size Pre-operative, m ±SD Post-operative, m	NA (p< 0.001) 6.9 ±NA 3.3 ±NA	NA (p< 0.001) 6.3 ±3.2 3.2 ±2.5	NA (p< 0.001) 6.75 ±2.41 1.52 ±1.65	NA
Feeling of tension, effect size Pre-operative, m ±SD Post-operative, m	NA (p< 0.001) 7.7 ±NA 2.3 ±NA	NA (p< 0.001) 6.9 ±NA 2.6 ±NA	NA (p< 0.001) 7.56 ± 1.72 1.42 ±1.78	NA
Bruising, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.001) 7.9 ±NA 4.2 ±NA	NA (p< 0.001) 8.1 ±2.2 4.3 ±31.1[81]	NA (p< 0.001) 7.18 ±1.93 2.45 ±2.62	Post-operative improvement: somewhat: 20.9% completely or almost completely: 29.1% (p<0.5)
Restriction of movement, effect size Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.001) 4.6 ±NA 1.6 ±NA	NA (p< 0.001) 4.1 ±3.5 1.2 ±1.9	NA	NA
Improvement of mobility, post-operative Marked improvement or complete loss of impairment, % Minor to medium improvement, %	NA	NA	NA	 86 14
Cosmetic/aesthetic impairment Pre-operative, m ±SD Post-operative, m ±SD	NA (p< 0.001) 9.5 ±NA 5.0 ±NA	NA (p< 0.001) 9.5 ±NA 5.0 ±NA	NA (p< 0.001) 8.71 ±2.26 3.13 ±2.48	NA

[81] 31.1 reported, but scale of VAS 0-10.

Author (year)	Rapprich et al. (2011) [27]	Rapprich et al. (2015) [28]	Witte et al. (2020) [29]	Wollina et al. (2019) [30]
Reduction in quality of life, effect size	NA (p< 0.001)	NA (p< 0.001)	NA	NA
Pre-operative, m ±SD	8.7 ±1.7	8.5 ±2.0		
Post-operative, m ±SD	3.6 ±2.5	3.3 ±2.8		
Running impairment, effect size	NA	NA	NA (p< 0.001)	NA
Pre-operative, m ±SD			5.28 ±3.04	
Post-operative, m ±SD			0.6 ± 1.1	
Occupational impairment, effect size	NA	NA	NA (p< 0.001)	NA
Pre-operative, m ±SD			4.97 ±2.63	
Post-operative, m ±SD			0.77 ±1.72	
Overall (total/general) impairment	NA (p< 0.001)	NA (p< 0.001)	NA (p< 0.001)	NA
Pre-operative, m ±SD	92.0 ±21.3	86.2 ±NA	7.79 ±2.11	
Post-operative, m ±SD	39.0 ±23.2	36.8 ±NA	0.95 ±1.4	
Reduction of conservative therapy		NA		
Pre-operative compression, n (%)	19 (76)		60 (95.2) of 63	NA
Post-operative compression, n (%)	4 (16)		20 (31.7)	NA
Pre-operative lymphatic drainage, n (%)	15 (60)		56 (88.9)	NA
Post-operative lymphatic drainage, n (%)	2 (8)		25 (39.7)	NA
Post-operative no conservative therapy, n (%)	NA		34 (NA)	NA (16.4)
CDT score	NA	NA	NA	NA
Safety				
Overall complications, n (%)	1 (NA)	2 (1.2)	0 (0)	6 (NA)[82]
Serious adverse events, n (%)	0 (0)	0 (0)	0 (0)	4 (1.2)[83]
Post-operative wound infections, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Post-operative bleeding, n (%)	0 (0)	0 (0)	0 (0)	1 (0.3)
Other post-operative adverse events, n (%)	1 (NA)[84]	2 (1.2)[85]	0 (0)	2 (NA)[86]

Abbreviations: AE – adverse events, BMI – body mass index, CDT – combined decongestive therapy, FU – follow-up, m – mean, MD – mean difference, n – number, NA – not applicable, NRS – non-randomised study, p – p-value, pts – patients, SD – standard deviation, VAS – Visual Analogue Scale, yrs – years

[82] No information given on the number of liposuction procedures.

[83] One (0.3%) epileptic attack during met-hemoglobinemia. A single episode of postsurgical anaemia requiring a blood transfusion (0.3%). One microscopic pulmonary fat embolism 2 days after release from the hospital after first liposuction (0.3%). One patient with acute pulmonary oedema about 24 hrs after liposuction that needed intensive care admission (0.3%).

[84] In 1 of 25 patients (number of liposuction procedures not reported), deep vein thrombosis (DVT) of the lower leg one week after the procedure. This patient had already had DVT of the lower leg before.

[85] In 2 of 168 liposuction procedures (of 85 patients), 1 patient suffered from thrombophlebitis another patient required treatment of a seroma.

[86] Two cases (1.8% of all pts) of mild arm vein phlebitis.

Risk of bias table

Internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved in solving the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Manual of Methods of the AIHTA [36] and in the Guidelines of EUnetHTA [37].

Table A-3: Risk of bias – study level (case series), using the Institute for Health Economics appraisal tool [21]

Study reference/ID	Schmeller et al. (2010, 2012) [8, 26], Baumgartner et al. (2015, 2016) [23, 25][87], Baumgartner et al. (2020) [24][88]	Dadras et al. (2017) [31]	Münch (2017) [13]	Rapprich et al. (2011) [27]	Rapprich et al. (2015) [28]	Witte et al. (2020) [29]	Wollina et al. (2019) [30]
Study objective							
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design							
2. Was the study conducted prospectively?	Yes	No[89]	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	No	No	No	No	No
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
Study population							
5. Were the characteristics of the patients included in the study described?	Partial[90]	Partial[91]	Yes	Partial[92]	No	Yes	Partial[92]
6. Were the eligibility criteria (i.e., inclusion and exclusion criteria) for entry into the study clearly stated?	Partial[93]	Partial[93]	No	No	No	Partial[93]	Partial[93]
7. Did patients enter the study at a similar point in the disease?	No[94]	No[94]	Unclear	Unclear	Unclear	No[94]	No[94]

[87] 8-year follow-up of Schmeller et al. (2010, 2012).

[88] 12-year follow-up of Schmeller et al. (2010, 2012).

[89] The data for the pre-operative period were collected retrospectively, representing a possible bias.

[90] No information of mean weight and BMI provided in Baumgartner et al. (2015, 2016); no information on BMI provided in Baumgartner et al. (2020).

[91] No information on weight provided.

[92] No information of weight or BMI provided.

[93] Exclusion criteria not explicit defined.

[94] All stages of lipoedema included.

Study reference/ID	Schmeller et al. (2010, 2012) [8, 26], Baumgartner et al. (2015, 2016) [23, 25][87], Baumgartner et al. (2020) [24][88]	Dadras et al. (2017) [31]	Münch (2017) [13]	Rapprich et al. (2011) [27]	Rapprich et al. (2015) [28]	Witte et al. (2020) [29]	Wollina et al. (2019) [30]
Intervention and co-intervention							
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome measures							
10. Were relevant outcome measures established a priori?	Yes	Yes	Partial	Yes	Partial	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	No[89]	Yes	Yes	Yes	Yes	Yes
Statistical Analysis							
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Unclear[95]	Yes	Unclear[95]	Unclear[95]	Yes
Results and Conclusions							
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Partial	Partial	Partial	Yes	Partial[96]
18. Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Competing interests and sources of support							
20. Were both competing interests and sources of support for the study reported?	Yes	Partial[97]	Partial[97]	Partial[97]	No	Yes	Partial[97]
Overall Risk of Bias	**Moderate**	**High**	**High**	**Moderate**	**High**	**Moderate**	**Moderate**

[95] No information on distribution of data provided.

[96] SD provided for outcomes reduction of circumference and pain.

[97] Information on funding not given.

Applicability table

Table A-4: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	Since all studies were conducted in clinical routine, it can be assumed that the study population reflects the target population. All studies included exclusively female patients with lipoedema (stage I-III). Some of the studies reported on the distribution of the lipoedema stages across the patients, but overall patients of all clinical stages were included. A total of 467 patients (excl. patients only considered for assessment of safety) eligible for pre- and at least one post-intervention assessment, were available. The mean or median age was consistent across studies and ranged from 37.2 to 38.0, or 35 to 44 years. The inclusion criteria and the population in the studies seem to be in accordance with the intended patient population for the procedure. No patients with secondary lymphoedema (lipolymphoedema) were included in the studies.
Intervention	Since all studies were conducted in clinical practice, it can be assumed that the interventions applied also correspond to routine use. All of the included studies used tumescence liposuction ('wet-technique') under local anaesthesia (except for the additional safety study, general anaesthesia). Liposuction with vibrating micro-cannulas was performed in three of the included studies, two studies used a water jet-assisted device, and one study utilised mechanical or laser-assisted devices. Comparisons of these different liposuction methods were not performed. Depending on the stage and severity of lipoedema, one to seven sessions per patient were performed across the studies. 'Dry-technique' liposuction, which is associated with a worse safety profile, was not performed in any of the included studies.
Comparators	There were no comparators. To date, there are no published studies in which liposuction is compared to other or no treatment for lipoedema therapy.
Outcomes	The crucial clinical effectiveness outcomes pain, reduction in size of extremity, and quality of life were reported in all, three, and four of the overall six included studies. Except for reduction of extremity size, all outcomes were patient-reported complaints before and after the liposuction interventions. Further included outcomes, which are important for decision-making, were: restrictions to movement (in all studies), bruising (in all studies), oedema (in five studies), sensory restrictions (e.g., feeling of tension, sensitivity to touch, in overall five studies), and the need for conservative therapy (e.g., combined decongestive therapy, in five studies). Follow-ups ranged from six months to twelve years. Regarding safety outcomes, reporting of endpoints should also be based on the number of interventions performed, rather than solely on the number of patients included (patients received between one and seven liposuction sessions, each of which carries a risk of procedure-related complications).
Setting	All included studies were conducted in Germany and Switzerland, where health care systems are comparable and similar to Austria. Further, the clinical setting for liposuction in lipoedema comprise inpatient as well as outpatient setting among the included studies, this is again similar to the Austrian situation.

List of ongoing randomised controlled trials

Table A-5: List of ongoing randomised controlled trials of liposuction for surgical therapy of lipoedema

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT04272827 (LIPLEG-3806) Evaluation Between Surgical Therapy of the Lipoedema Compared to Complex Physical Decongestive Therapy (CDT) Alone (LIPLEG)	450 lipoedema pts female, age ≥18 years, lipoedema of the legs stage I, II, or III	Liposuction 'wet technique' depending on the amount of fat to be removed, if necessary in several sessions	Complex decongestive therapy alone	Successful pain reduction after 12 months	July 2024	Hautklinik Darmstadt, Zentrum für Klinische Studien Köln

Literature search strategies

Search strategy for Medline via Ovid

Search Name: Liposuction in Lipoedema (MEL 2021, DSD 125)	
Search date: 03.12.2020	
ID	Search
#1	exp Lipoedema/ (174)
#2	lip?edema*.mp. (477)
#3	lipolymph?edema*.mp. (26)
#4	lipo-lymph?edema*.mp. (16)
#5	lipohyperplasia*.mp. (45)
#6	lipo-hyperplasia*.mp. (0)
#7	painful fat*.mp. (20)
#8	fat* leg*.mp. (179)
#9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (721)
#10	exp Lipectomy/ (4292)
#11	lipectom*.mp. (4788)
#12	liposuction*.mp. (4249)
#13	lipo-suction*.mp. (10)
#14	lipoplast*.mp. (473)
#15	lipo-plast*.mp. (0)
#16	liposculture*.mp. (2)
#17	lipo-sculture*.mp. (0)
#18	10 or 12 or 13 or 14 or 15 or 16 or 17 (6493)
#19	((suction* or aspiration*) adj5 (fat* or lipolys* or lipo-lys* or adipos*)).mp. (803)
#20	exp Adipose Tissue/ (119910)
#21	(suction* or aspiration*).mp. (142750)
#22	20 and 21 (737)
#23	18 or 19 or 22 (7452)
#24	9 and 23 (109)
#25	Liposat*.mp. (2)
#26	Vibrasat*.mp. (0)
#27	SmartLipo*.mp. (15)
#28	Smart-Lipo*.mp. (41)
#29	PAL* liposuction.mp. (1)
#30	24 or 25 or 26 or 27 or 28 or 29 (168)
#31	remove duplicates from 30 (110)
#32	limit 31 to (english or german) (102)
Total hits: 102	

Search strategy for Embase

Search Name: Liposuction in Lipoedema (MEL 2021, DSD 125)	
Search date: 03.12.2020	
ID	Search
#38	#37 AND ([english]/lim OR [german]/lim)
#37	#31 OR #32 OR #33 OR #34 OR #35 OR #36
#36	'pal* lipo*':dn
#35	'smart-lipo*':ti,ab,kw,lnk,de,dn
#34	smartlipo*:ti,ab,kw,lnk,de,dn
#33	vibrasat*:ti,ab,kw,lnk,de,dn
#32	liposat*:ti,ab,kw,lnk,de,dn
#31	#14 AND #30
#30	#25 OR #26 OR #29
#29	#27 AND #28
#28	suction*:ti,ab,kw,lnk,de OR aspiration*:ti,ab,kw,lnk,de
#27	'adipose tissue'/exp
#26	((suction* OR aspiration*) NEAR/5 (fat* OR lipolys* OR 'lipo lys*' OR adipos*)):ti,ab,kw,lnk,de
#25	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#24	'lipo-sculture*':ti,ab,kw,lnk,de
#23	liposculture*:ti,ab,kw,lnk,de
#22	'lipo plast*':ti,ab,kw,lnk,de
#21	lipoplast*:ti,ab,kw,lnk,de
#20	'lipoplasty'/exp
#19	lipectom*:ti,ab,kw,lnk,de
#18	'lipectomy'/exp
#17	'lipo-suction*':ti,ab,kw,lnk,de
#16	liposuction*:ti,ab,kw,lnk,de
#15	'liposuction'/exp
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#13	'fat* leg*':ti,ab,kw,lnk,de
#12	'painful fat*':ti,ab,kw,lnk,de
#11	'lipo-hyperplasia*':ti,ab,kw,lnk,de
#10	lipohyperplasia*:ti,ab,kw,lnk,de
#9	'lipo-lymphoedema*':ti,ab,kw,lnk,de
#8	'lipo-lymphedema*':ti,ab,kw,lnk,de
#7	lipolymphoedema*:ti,ab,kw,lnk,de
#6	lipolymphedema*:ti,ab,kw,lnk,de
#5	'lipolymphedema'/exp
#4	'lipo-edema*':ti,ab,kw,lnk,de
#3	lipoedema*:ti,ab,kw,lnk,de
#2	lipoedema*:ti,ab,kw,lnk,de
#1	'lipoedema'/exp
Total hits: 241	

Search strategy for Cochrane

Search Name: Liposuction in Lipoedema (MEL 2021, DSD 125)	
Search date: 04.12.2020	
ID	Search
#1	MeSH descriptor: [Lipoedema] explode all trees
#2	(Lipoedema*) (Word variations have been searched)
#3	(Lipoedema*) (Word variations have been searched)
#4	(lipolymphedema*) (Word variations have been searched)
#5	(lipolymphoedema*) (Word variations have been searched)
#6	(lipohyperplasia*) (Word variations have been searched)
#7	(lipo-hyperplasia*) (Word variations have been searched)
#8	(painful fat*)
#9	(fat* leg*)
#10	#1 OR #2 OR #3 OR #5 OR #6 OR #7 OR #8 OR #9
#11	MeSH descriptor: [Lipectomy] explode all trees
#12	(lipectom*) (Word variations have been searched)
#13	(liposuction*) (Word variations have been searched)
#14	(lipo-suction*) (Word variations have been searched)
#15	(lipoplast*) (Word variations have been searched)
#16	(lipo-plast*) (Word variations have been searched)
#17	liposculture* (Word variations have been searched)
#18	(lipo-sculture*) (Word variations have been searched)
#19	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 (Word variations have been searched)
#20	((suction* OR aspiration*) NEAR (fat* OR lipolys* OR lipo-lys* OR adipos*))
#21	MeSH descriptor: [Adipose Tissue] explode all trees
#22	(suction* OR aspiration*) (Word variations have been searched)
#23	#21 AND #22 (Word variations have been searched)
#24	#19 OR #20 OR #23 (Word variations have been searched)
#25	#10 AND #24
#26	(Liposat*) (Word variations have been searched)
#27	(Vibrasat*) (Word variations have been searched)
#28	(SmartLipo*) (Word variations have been searched)
#29	(Smart-Lipo*) (Word variations have been searched)
#30	("Smart Lipo*") (Word variations have been searched)
#31	(PAL* liposuction) (Word variations have been searched)
#32	#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
Total hits: 27	

Search strategy for CRD

Search Name: Liposuction in Lipoedema (MEL 2021, DSD 125)	
Search date: 04.12.2020	
ID	Search
#1	MeSH DESCRIPTOR Lipoedema EXPLODE ALL TREES
#2	(Lipoedema*) IN HTA
#3	(Lipoedema*) IN HTA
#4	(Lipoedaema*) IN HTA
#5	(lipolymphedema*)
#6	(lipo-lymphedema*)
#7	(lipolymphoedema*)
#8	(lipo-lymphoedema*)
#9	(lipohyperplasia*)
#10	(lipo-hyperplasia*)
#11	(painful fat*)
#12	(fat* leg*)
#13	MeSH DESCRIPTOR Lipectomy EXPLODE ALL TREES
#14	(lipectom*)
#15	(liposuction*)
#16	(lipo-suction*)
#17	(lipoplast*)
#18	(lipo-plast*)
#19	(liposculture*)
#20	(lipo-sculture*)
#21	((suction* OR aspiration*) NEAR (fat* OR lipolys* OR lipo-lys* OR adipos*))
#22	MeSH DESCRIPTOR Adipose Tissue EXPLODE ALL TREES
#23	((suction* OR aspiration*))
#24	#22 AND #23
#25	(Liposat*)
#26	(Vibrasat*)
#27	(SmartLipo*)
#28	(Smart-Lipo*)
#29	(PAL* lipo*)
#30	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29
Total hits: 20	

Search strategy for HTA-INAHTA

Search Name: Liposuction in Lipoedema (MEL 2021, DSD 125)	
Search date: 04.12.2020	
ID	Search
#29	("PAL* lipo*") OR ("Smart-Lipo*") OR (SmartLipo*) OR (Vibrasat*) OR (Liposat*) OR (((suction* OR aspiration*)) AND ("Adipose Tissue"[mhe])) OR ((suction* OR aspiration*) NEAR (fat* OR lipolys* OR lipo-lys* OR adipos*)) OR ("lipo-sculture*") OR (liposculture*) OR ("lipo-plast*") OR (lipoplast*) OR ("lipo-suction*") OR (liposuction*) OR (lipectom*) OR ("Lipectomy"[mhe]) OR ("fat* leg*") OR ("painful fat*") OR ("lipo-hyperplasia*") OR (lipohyperplasia*) OR ("lipo-lymphoedema*") OR (lipolymphoedema*) OR ("lipo-lymphedema*") OR (lipolymphedema*) OR (Lipoedema*) OR (Lipoedema*) OR ("Lipoedema"[mhe])
#28	"PAL* lipo*"
#27	"Smart-Lipo*"
#26	SmartLipo*
#25	Vibrasat*
#24	Liposat*
#23	((suction* OR aspiration*)) AND ("Adipose Tissue"[mhe])
#22	(suction* OR aspiration*)
#21	"Adipose Tissue"[mhe]
#20	(suction* OR aspiration*) NEAR (fat* OR lipolys* OR lipo-lys* OR adipos*)
#19	"lipo-sculture*"
#18	liposculture*
#17	"lipo-plast*"
#16	lipoplast*
#15	"lipo-suction*"
#14	liposuction*
#13	lipectom*
#12	"Lipectomy"[mhe]
#11	"fat* leg*"
#10	"painful fat*"
#9	"lipo-hyperplasia*"
#8	lipohyperplasia*
#7	"lipo-lymphoedema*"
#6	lipolymphoedema*
#5	"lipo-lymphedema*"
#4	lipolymphedema*
#3	Lipoedema*
#2	Lipoedema*
#1	"Lipoedema"[mhe]
Total hits: 9	

HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH