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Clinical Impact of Severe Obesity in Patients with Lymphoedema

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WHAT THIS PAPER ADDS

The epidemic proportions of weight gain have led to severe obesity associated lymphoedema with a shift in the demographics of the disease process. A two and a half fold increase in the incidence of cellulitis has been observed in these patients, raising both medical resource use and costs. These patients receive less specific therapy such as compression for lymphoedema, which has proven to reduce the incidence of cellulitis. It is important to increase awareness of the obesity correlation with lymphoedema, allowing prompt diagnosis and better care at an earlier stage.

Objective: With the rate of obesity increasing worldwide, patients with lymphoedema with and without a concomitant diagnosis of severe obesity (SO) were compared in regard to their baseline demographics, health related characteristics, treatment plans, and patient outcomes.

Methods: This was a retrospective observational cohort study The IBM MarketScan database was examined (2013 − 2019) for patients with a new diagnosis of lymphoedema. Of 60 284 patients with lymphoedema identified, 6 588 had SO defined by a body mass index $>$ 40 kg/m^2. The demographics and other characteristics of SO were compared with patients with lymphoedema without SO.

Results: SO and lymphoedema diagnosis increased two fold from 2013 to 2019. The lymphoedema SO+ group was younger (57.8 *vs.* 60.8 years, $p < .001$) and with a higher proportion of men (37.7% *vs.* 24.9%, $p < .001$) than the lymphoedema SO− group. More comorbidities were observed in the lymphoedema SO+ group than the lymphoedema SO− group: diabetes 46.0% *vs.* 24.9 % ($p < .001$), heart failure 18.3% *vs.* 7.4% ($p < .001$), hypertension 75.0% *vs.* 47.6% ($p < .001$), and renal disease 24.8% *vs.* 11.9% ($p < .001$). Use of diuretics in the lymphoedema SO+ group was greater: 57.6% *vs.* 38.0% ($p < .001$). Patients with lymphoedema SO+ had higher risk of cellulitis: 34.5% *vs.* 13.5% ($p < .001$). Specific lymphoedema treatment was given more often to lymphoedema SO−: 66.3% *vs.* 64.3% ($p = .003$). This was significant for manual lymphatic drainage (46.6% *vs.* 40.0%; $p < .001$) and physical therapy (55.4% *vs.* 51.6%; $p<.001$), but not for compression garments (18.2% *vs.* 17.7%; $p = .38$). However, more patients with lymphoedema SO+ received pneumatic compression device treatment: 20.9% *vs.* 13.7% ($p < .001$).

Conclusion: There was an increase in SO associated lymphoedema. Patients with lymphoedema SO+ have over a two and half fold increase in cellulitis incidence, with a significant increase in medical resource use and cost. Despite this, patients with lymphoedema and SO receive less specific therapy such as compression, which has proven to reduce cellulitis incidence.

Key words: Costs, Lymphoedema, Severe obesity, Treatment
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INTRODUCTION

Obesity is increasingly being recognised as a risk factor for lymphoedema.[1–4] Lymphoedema is characterised by a build up of fluid in the intercellular compartment, enriched with proteins including pro-inflammatory substances.[5,6] Among these, a significant increase in fibrosis and deposition of adipose tissue has been observed.[1,7,8]

Recent studies have found a close relationship between obesity and lymphoedema. Lymphatic trauma results in oedema, stimulating adipose tissue deposition, which causes further damage.[1] Adipose accumulation from lymphatic damage was shown by higher marker levels of adipocyte deposition such as CEBP-alpha, PPAR-gamma, and adiponectin.[1,8] Obesity has also been found to alter lymphatic functioning.[9–11] Obese mice had altered lymph node function and on lesioning tail lymphatics mounted an augmented

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inflammatory response with higher CD4+ levels, adipose accumulation, and fibrosis relative to lean mice.[11] A possible mechanism suggested for lymphatic alterations due to obesity has been the rise of inflammatory cells in the perilymph, including increases in T cell and nitric oxide synthase.[12]

Obesity in the United States is rising at epidemic proportions with a prevalence of 42.4% and annual healthcare cost of $147 billion.[13] While lymphoedema prevalence is limited to 0.13% of the population, it was found in 74% of morbidly obese patients in a sample taken from 17 US wound centres.[14] Integrating interventions for weight loss into lymphoedema treatment have already shown preliminary positive results.[15,16] There may be a potential body mass index (BMI) benchmark where lymphatic damage could be irreversible, increasing the need for early weight loss intervention.[17] Furthermore, obesity also increases the risk of cellulitis, which could cause secondary lymphatic dysfunction. Thus, in patients with obesity induced lymphoedema having a BMI $>$ 40 kg/m^2 weight loss should be a primary therapy.[18]

There is a growing impetus to understand the relationship between lymphoedema and obesity. The study aimed to accomplish this goal through analysing the demographic, treatment, and clinical profiles of patients with lymphoedema with and without severe obesity (SO).

MATERIALS AND METHODS

Study design and data source

A retrospective observational cohort design was employed to analyse data from an integrated US healthcare claims repository (IBM MarketScan Commercial Claims and Encounters [CCAE] and Medicare Supplemental and Coordination of Benefits [MDCR] databases). For this study, data spanned April 2012 to March 2020. Ethics committee approval and informed consent were not obtained as this study was done through a commercial claims database that does not have identifiable patient health information.

The CCAE database includes healthcare claims and enrolment information from employer sponsored plans throughout the United States that provide health benefits to working persons aged $<$ 65 years annually, including the employees, their spouses, and their dependents. The MDCR database includes healthcare claims and enrolment information for retirees who are Medicare eligible and have elected to enrol in employer sponsored Medicare supplementary plans (and for which both the Medicare paid amounts and employer paid amounts are available). Medicare is the federal health insurance program for all persons $>$ 65 years of age regardless of economic status.

Healthcare claims include medical and outpatient pharmacy claims. Data available for each facility and professional service claim include the dates and places of service, diagnoses, procedures performed or services rendered, and quantity of services (professional service claims). Data available for each outpatient pharmacy claim include the drug dispensed, dispensing date, dose, quantity dispensed, and number of therapy days supplied. Medical and pharmacy claims also include amounts paid by health plans and patients to healthcare providers for services rendered. Selected demographic and eligibility information also is available. Patient level data can be arrayed chronologically to provide a detailed longitudinal profile of all medical and pharmacy services used by each plan member.

Study population

Patients aged $\geq$ 18 years who, between 1 April 2013 and 31 March 2019, had evidence of primary or secondary lymphoedema based on $\geq$ 1 diagnosis code for lymphoedema (International Classification of Diseases [ICD]-9: 457.0, 457.1, 757.0; ICD-10: I97.2, I89.0, Q82.0) in the acute care hospital (inpatient) setting, or $\geq$ 2 diagnosis codes for lymphoedema—at least seven days apart—in the ambulatory (outpatient) setting were included. For all patients, the earliest date of lymphoedema diagnosis was designated the "index date".

Patients were excluded from the study population if they had $\geq$ 1 diagnosis code for lymphoedema at any time prior to their index dates; $<$ 12 months of healthcare coverage prior to their index dates; $<$ 365 day follow up; or $\geq$ 1 diagnosis of head or neck cancer before their index dates (presents with different symptoms of swallowing or phonation dysfunction rather than peripheral oedema). Patients with lymphoedema were categorised into two subgroups; those with *vs.* without SO, defined as having a BMI $>$ 40.0 kg/m^2. Among the various obesity categories, this study was focused on SO or class 3.[19] The ICD-9-CM 278.01 and ICD-10-CM E66.01 codes for SO were used.

Study measures

Lymphoedema treatment patterns were ascertained during follow up. The follow up duration was fixed to one year after the patient's respective index dates. Treatments included manual lymphatic drainage (MLD), physical therapy or occupational therapy (PT or OT), compression garments, simple pneumatic compression device, and advanced pneumatic compression device.

Each unique treatment course was identified, beginning with the first, and all qualifying encounters (i.e., with the same Current Procedural Terminology or Healthcare Common Procedure Coding System code) occurring within 30 days of each other was deemed to be part of the same treatment course. Patterns of treatment were characterised in terms of frequency of use, interval from index date to first evidence of treatment, intervals between treatments, and duration of treatment courses.

Use of selected procedures, drugs, and incidence of certain conditions were characterised, including diuretic therapy days, cellulitis (with and without antibiotics), and lymphangitis. Infection and lymphoedema related expenditures were also evaluated.

Baseline characteristics

Baseline characteristics of patients were ascertained during the 12 month period prior to their index dates, and included

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their demographic profile (age, sex, geographic region of residence, insurance type); clinical profile (lymphoedema related conditions, comorbidities); and treatment profile (diuretics, anti-inflammatory agents). Lymphoedema related conditions and comorbidities were identified based on $\geq$ 1 inpatient encounter or $\geq$ 2 outpatient encounters with a corresponding diagnosis code.

Data analysis

Baseline characteristics of patients stratified by presence (*vs.* absence) of SO, were described. Categorical variables were reported as counts and percentages; for continuous variables, means, 95% confidence intervals and standard deviations were reported. Use of alternative treatment modalities, treatment patterns, and clinical outcomes were similarly evaluated. Differences in baseline characteristics and study measures between patients with lymphoedema with and without SO were evaluated using an independent samples t test for continuous measures and chi square or Fisher's exact test for categorical measures. Due to the large sample size, the level of statistical significance was set to .005.

The IBM MarketScan Medicare supplementary database contains data from retirees with Medicare supplementary insurance paid by employers. The database includes the Medicare covered portion of payment, the employer paid portion, and out of pocket patient expenses. The MarketScan Medicare supplementary database provides detailed cost, use and outcomes data for healthcare services performed for inpatients and outpatients.

RESULTS

Baseline characteristics of patients with lymphoedema

The baseline demographics of 60 284 patients with lymphoedema were evaluated (Table 1). Among these, 10.9% of patients were designated to the SO+ cohort and the rest to the SO− cohort. The SO+ cohort was younger (57.8 *vs.* 60.8 years), with a higher proportion of male patients (37.7% *vs.* 24.9%) than the SO− cohort. The SO+ group also had a higher percentage of patients living in the south and Midwest regions (75.5%), and fewer in the northeast (15.5%) and west (8.6%) regions (Table 1). The percentage of patients diagnosed with lymphoedema from the SO+ cohort increased from 20.9% to 42.8% over the index date range (Table 2).

The SO+ group had higher proportions of comorbidities such as depression (31.8% *vs.* 27.7%), diabetes (46% *vs.* 24.9%), heart failure (18.3% *vs.* 7.4%), hypertension (75% *vs.* 47.6%), pulmonary hypertension (5.2% *vs.* 1.4%), and renal disease (24.8% *vs.* 11.9%) than the SO− group (Table 2). Specifically, more patients in the SO+ group were also diagnosed with cellulitis (34.5% *vs.* 13.5%), other infections, and deep vein thrombosis. Lastly, the SO+ group had a higher pre-index use of diuretics, ulcer dressings, and anti-inflammatory agents, but a lower use of lymphoscintigraphy compared with the SO− group (Table 2).

Treatment interventions in patients with lymphoedema

The treatment modalities chosen for the patients in the SO+ group significantly differed from those that were not (Table 3).

Table 1. Baseline demographics of patients with lymphoedema included in this retrospective cohort study based on healthcare claims, divided into severely obese and not severely obese patient cohorts

Characteristics	Lymphoedema patients by aetiology		*p*
	Not severely obese (n = 53 696)	Severely obese (n = 6 588)	
Age − y	60.8 ± 14.5	57.8 ± 11.8	<.001
Age groups − y			<.001
18–34	1 643 (3.1)	178 (2.7)	.11
35–44	4 624 (8.6)	677 (10.3)	<.001
45–54	11 514 (21.4)	1 591 (24.1)	<.001
55–64	17 788 (33.1)	2 589 (39.3)	<.001
65–74	7 731 (14.4)	965 (14.6)	.59
≥75	10 396 (19.4)	588 (8.9)	<.001
Sex			
Female	40 342 (75.1)	4 103 (62.3)	<.001
Male	13 354 (24.9)	2 485 (37.7)	<.001
Geographic region			<.001
Midwest	15 873 (29.6)	2 292 (34.8)	<.001
South	20 642 (38.4)	2 681 (40.7)	<.001
Northeast	10 334 (19.2)	1 022 (15.5)	<.001
West	6 448 (12.0)	566 (8.6)	<.001
Health plan			<.001
Health maintenance organisation	6 565 (12.2)	953 (14.5)	<.001
Preferred provider organisation/point of service	31 802 (59.2)	3 750 (56.9)	<.001
Indemnity	8 878 (16.5)	1 008 (15.3)	.011
Other	5 789 (10.8)	790 (12.0)	.003
Unknown	662 (1.2)	87 (1.3)	.54

Data are expressed as n (%) or as mean ± standard deviation.

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Table 2. Health related characteristics of patients with lymphoedema included in this retrospective cohort study based on healthcare claims, divided into severely obese and not severely obese patient cohorts

Characteristics	Lymphoedema patients by aetiology		*p*
	Not severely obese (*n* = 53 696)	Severely obese (*n* = 6 588)	
Lymphoedema associated conditions			
Iliac vein obstruction	210 (0.4)	33 (0.5)	.18
Cellulitis	7 274 (13.5)	2 272 (34.5)	<.001
Lymphangitis	71 (0.1)	35 (0.5)	<.001
Deep vein thrombosis	3 096 (5.8)	680 (10.3)	<.001
Other infections	22 887 (42.6)	4 316 (65.5)	<.001
Comorbidity profile			
Depression	14 883 (27.7)	2 092 (31.8)	<.001
Diabetes	13 350 (24.9)	3 028 (46.0)	<.001
Heart failure	3 975 (7.4)	1 207 (18.3)	<.001
With beta blocker therapy	2 580 (4.8)	780 (11.8)	<.001
Without beta blocker therapy	1 395 (2.6)	427 (6.5)	<.001
Hypertension	25 563 (47.6)	4 942 (75.0)	<.001
Obesity	6 815 (12.7)	6 588 (100.0)	<.001
Pulmonary hypertension	776 (1.4)	342 (5.2)	<.001
Renal disease	6 371 (11.9)	1 635 (24.8)	<.001
Use of selected drugs and procedures			
Diuretics	20 402 (38.0)	3 793 (57.6)	<.001
Dressings for venous leg ulcers	1 074 (2.0)	334 (5.1)	<.001
Anti-inflammatory agents	26 676 (49.7)	3 696 (56.1)	<.001
Lymphoscintigraphy	3 404 (6.3)	170 (2.6)	<.001
Year of index date			<.001
2013–2014	23 224 (43.3)	1 379 (20.9)	<.001
2015–2016	18 877 (35.2)	2 392 (36.3)	.065
2017–2019	11 595 (21.6)	2 817 (42.8)	<.001

Data are expressed as *n* (%).

A lower proportion of SO+ patients (64.3%, 95% CI 63.1 — 65.5) received lymphoedema targeted treatment than SO— patients (66.3%, 95% CI 65.9 — 66.8). Fewer SO+ patients received MLD and PT or OT than SO— patients ($p < .001$), but it was not significant for compression garments ($p = .38$). However, more SO+ patients received simple and advanced pneumatic compression device interventions ($p < .001$).

Outcomes in patients with lymphoedema

Patients in the SO+ group had poorer outcomes determined over one year of follow up with a higher healthcare burden (Table 4). The occurrence of cellulitis was higher for the SO+ cohort (40.8% 95% CI 39.6 — 42.0) compared with the SO— cohort (22.0%, 95% CI 21.7 — 22.4), with higher infection related ($6 826 *vs.* $2 266) and lymphoedema related expenditures ($3 957 *vs.* $3 470).

DISCUSSION

This study established an increase in SO associated lymphoedema. Patients with lymphoedema SO+ exhibited higher proportions of comorbidities. They also had over a two and half fold increase in cellulitis, raising their medical costs, but still received less specific therapy.

According to the recent literature, the expected interstitial fluid re-absorption via the venules simply does not occur and the return happens via the lymphatic system.[20,21] With the obesity epidemic there has been growing interest in understanding its contribution to lymphoedema. Patients with a higher BMI have increased intra-abdominal pressure.[22] The abnormal amount of adipose tissue and increased pressure could hinder venous return.[23] Obese patients have higher venous reflux, pressure, and femoral vein diameter.[23] They also have a higher incidence of chronic venous disease.[24] An increased deep vein thrombosis and iliac vein obstruction incidence can occur, as seen in the lymphoedema SO+ group. Ultimately, the enlarged venous volume would increase the filtration rate and could result in lymphoedema. In patients with leg lymphoedema, phlebolymphoedema was identified as the most common reason, and morbid obesity was common and significantly associated with the lymphoedema stage.[25] Given how lymphoedema can result from venous or lymphatic aetiologies, phlebolymphoedema is defined as dysfunction in both; lymphatic dysfunction co-exists with venous dysfunction at higher CEAP (Clinical, Etiological, Anatomical, Pathophysiological) levels C3 — C6, indicating that it takes longer for the lymphatic dysfunction to occur.[25,26] Although obesity related lymphoedema can be clinically improved, the lymphatic damage cannot be cured.[27] Lymphoedema that may be without clinical symptoms, but persistent underlying lymphatic dysfunction, is known as "systemic subclinical lymphoedema".[27] It was prevalent in ~16% of women with lipoedema and BMI < 30 kg/m^2 and increased

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Table 3. Comparison of different treatment options, including conservative care (manual lymphatic drainage, physical or occupational therapy, or compression garments) and simple or advanced pneumatic compression devices used in patients with lymphoedema included in this retrospective cohort study based on healthcare claims, divided into severely obese and not severely obese patient cohorts

Treatment options	Lymphoedema patients by aetiology		*p*
	Not severely obese (*n* = 53 696)	Severely obese (*n* = 6 588)	
Lymphoedema treatment			
CONS, SPCD, or APCD	66.3 (65.9–66.8)	64.3 (63.1–65.5)	.003
No CONS, SPCD, or APCD	33.7 (33.2–34.1)	35.7 (34.5–36.9)	
Conservative care			
Manual lymphatic drainage			
Treatment at any time during FU	46.6 (46.2–47.0)	40.0 (38.8–41.2)	<.001
Number of courses	1.5 (1.5–1.5)	1.4 (1.4–1.5)	<.001
Days from index date to first course	48.1 (47.1–49.1)	60.5 (57.1–63.9)	<.001
Days between courses	103.0 (101.3–104.6)	102.8 (97.8–108.6)	.96
Days from first to last to course	182.6 (180.5–184.8)	173.4 (167.0–179.9)	.007
Physical therapy/occupational therapy			
Treatment at any time during FU	55.4 (55.0–55.9)	51.6 (50.4–52.8)	<.001
Number of courses	1.6 (1.6–1.6)	1.6 (1.5–1.6)	.20
Days from index date to first course	47.4 (46.4–48.4)	60.5 (57.3–63.6)	<.001
Days between courses	117.9 (116.4–119.2)	115.1 (111.0–119.8)	.25
Days from first to last course	187.9 (186.1–189.9)	180.8(175.8–186.1)	.013
Compression garments			
Treatment at any time during FU	18.2 (17.8–18.5)	17.7 (16.9–18.6)	.38
Number of courses	1.4 (1.3–1.4)	1.4 (1.3–1.4)	.88
Days from index date to first course	73.1 (71.5–74.7)	91.5 (85.9–97.1)	<.001
Days between courses	136.9 (133.8–139.8)	125.9 (117.5–135.2)	.024
Days from first to last course	175.4 (171.6–179.0)	162.5 (152.2–172.4)	.020
Simple pneumatic compression device			
Treatment at any time during FU	5.0 (4.8–5.2)	7.2 (6.6–7.9)	<.001
Days from index date to first course	81.1 (77.5–84.8)	83.1 (75.7–90.2)	.68
Advanced pneumatic compression device			
Treatment at any time during FU	8.7 (8.5–8.9)	13.7 (12.9–14.5)	<.001
Days from index date to first course	89.0 (86.4–91.8)	85.6 (80.2–91.2)	.29

Data are expressed as % (95% confidence interval) or mean (95% confidence interval)
CONS = conservative care; SPCD = simple pneumatic compression device; APCD = advanced pneumatic compression device; FU = follow up.

Table 4. Other health related and economic outcomes in patients with lymphoedema included in this retrospective cohort study based on healthcare claims, divided into severely obese and not severely obese patient cohorts

Clinical and economic outcomes	Lymphoedema patients by aetiology		*p*
	Not severely obese (*n* = 53 696)	Severely obese (*n* = 6 588)	
Diuretic therapy days	267 (264.1–269.3)	283 (276.6–289.4)	<.001
Cellulitis	22.0 (21.7–22.4)	40.8 (39.6–42.0)	<.001
With antibiotics	15.9 (15.6–16.2)	31.4 (30.3–32.5)	<.001
Without antibiotics	6.1 (5.9–6.3)	9.4 (8.7–10.1)	<.001
Lymphangitis	0.54 (0.48–0.60)	0.88 (0.65–1.11)	.009
Infection related expenditure − $	2 266 (2 149–2 393)	6 826 (6 154–7 524)	<.001
Lymphoedema related expenditures − $	3 470 (3 415–3 536)	3 957 (3 770–4 163)	<.001

Data is expressed as % (95% confidence interval) or mean (95% confidence interval).

with higher BMI, illustrating the exacerbating role obesity plays.[28] However, as such, subclinical lymphoedema is being under recognised and undertreated. In operations on lymphoedema afflicted regions, not only fluid accumulation but also fat deposits are prominent.[21] Liposuction has been successful to treat lymphoedema by decreasing the volume of the limb, improving psychological well being, and future disease management.[29,30]

First, it was found that patients with lymphoedema SO+ had more comorbidities. They had higher occurrences of diabetes, hypertension, and heart failure. Obese patients are generally known to suffer from several such comorbidities and have a higher mortality rate.[31] Several factors contribute to this, including lack of physical activity.[32] A US healthcare database study found that patients with higher BMI had higher rates of hypertension, type 2 diabetes, and

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cardiovascular issues.[31] There is additionally a complex interplay between the lymphatic system, obesity, and comorbidities such as diabetes or heart disease.

The lymphatic system has been implicated in inflammatory processes and the development of chronic degenerative diseases.[33] The lymphatic system is closely linked to lipid levels by clearing cholesterol in interstitial fluid and absorption from food via lacteals.[34] A mutualistic relationship was found where pathology in the lymphatic system can predispose to obesity, and obesity can conversely further its dysfunction.[1,34] The lymphatic system also influences development of atherosclerosis.[35] Lymphatic impairment in diabetes has been linked to higher lymphangiogenesis, lesser lymph node uptake, and increased thoracic duct flow.[34] Given the lymphatic involvement, it is not surprising that patients with lymphoedema often had diabetes, heart failure, and hypertension. This was especially true in SO patients whose risk of these comorbidities was compounded. SO patients with lymphoedema have more complex pathologies and higher comorbidity risks, necessitating specialised care and attention. It should be emphasised that weight reduction, an often ignored approach is essential not only to treat lymphoedema,[36] but all other associated comorbidities as well.

Cellulitis was more common in the patients with lymphoedema SO+. Since lymphatics are significantly involved in the adaptive immune system, their dysfunction could explain an increased risk of cellulitis.[21] A French case control study showed that this risk was 71 fold (95% CI 5.6 — 908), but unlike this study where controls included patients with lymphoedema who were not obese, their controls had conditions such as trauma, infection, abdominal surgery, and others without lymphoedema.[37] Similar trends have been shown in Canada where patients with lymphoedema with an occurrence of cellulitis had higher BMI, with a third of the obese cohort having suffered from it.[38] A study in Poland on patients with cellulitis or erysipelas found the recurrent condition to be correlated with obesity and lymphoedema.[39] While lymphoedema could be the trigger for cellulitis, lymphoedema could also be augmented from cellulitis causing lymphatic dysfunction.[40] Understanding this association may be instrumental because, as suggested in the study, therapies such as antibiotic prophylaxis could be proposed for obese patients with lymphoedema.[39]

Despite the higher comorbidities and infection rates, patients with lymphoedema SO+ still received less targeted medical intervention. The primary treatment for lymphoedema is complex decongestive treatment (CDT), including compression, exercise, and MLD.[33] Interestingly, these interventions have been shown to reduce the incidence of cellulitis in patients with oedema.[41,42] Although the percent difference of targeted medical intervention was small, yet statistically significant, one would expect people with more severe disease to receive a lot more treatment and as early as possible. In this study, the severely obese cohort received less MLD and PT or OT. They also received less compression, albeit not statistically significant. One potential reason could be more misdiagnoses in obese patients from lymphoedema complicated differential diagnosis. The manifestation of lymphoedema can be similar to other oedematous conditions such as venous issues, drug related oedema, lipoedema, endocrine pathology, trauma, infection, and obesity.[43,44] Specifically in obese patients, on conducting a physical examination it is hard to distinguish externally whether an obese leg is affected by lymphoedema.[17] Furthermore, a diagnostic technique for lymphoedema such as a Stemmer sign can be false positive in those with obesity due to the higher adipose accumulation.[17] Obesity related lymphoedema can also be misdiagnosed as lipoedema.[17] Lipoedema is an adipose pathology prevalent in women that is distinct from obesity and presents as painful fat accumulation, primarily in the legs, and cannot be treated through diet or exercise interventions.[17,45] Further differentiating it from lymphoedema, it presents with a negative Kaposi—Stemmer sign, excludes the feet and has a normal lymphoscintigraphy, but it can progress to lipolymphoedema.[17,46] Increasing awareness of the obesity correlation with lymphoedema and considering it in diagnostic protocols could allow for more efficient treatment. Apart from CDT, more well rounded treatment approaches should also be taken regarding epigenetic influences such as nutrition and lifestyle.[33,36] Another reason for reduced intervention could be that obese patients pursue medical help later than others due to the stigma and poor treatment they receive by the healthcare community leading to a vicious circle.[47]

Obesity has also huge financial implications. Those with SO had twice the probability of having medical costs than the normal weight group.[48] It could be attributed to higher drug related costs, in or outpatient care, and explained by the occurrence of more comorbidities with obesity like heart disease.[14,48] In this study, the lymphoedema SO+ group had higher infection related and lymphoedema related costs than the lymphoedema SO— group. Recognising obesity as a risk factor and addressing it could help reduce the healthcare burden for patients with lymphoedema.

The demographics of patients with lymphoedema with SO were found to be altered when compared with those without. The lymphoedema SO+ patients were younger, with male preponderance and most living in the south and Midwest, than the lymphoedema SO— group.

Study limitations

This study has several limitations. Administrative claims are observational without the usual statistical rigour of a randomised controlled trial. Propensity score matching can be used to account for the observational nature of the data but does not substitute for a fully randomised data set. The identification of lymphoedema and associated comorbidities within the administrative claims relies on the proper use of diagnosis coding for claims algorithms. Lymphoedema, other comorbidities, and procedures can only be identified if they are coded correctly. The IBM MarketScan database provides basic characteristics of the population,

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which include gender, age, and geographic location of the subscriber in the United States, but in this database race, ethnicity, and income status are not provided. The IBM MarketScan database contains commercially insured patients and does not include the original (parts A and B) fee for service Medicare patients. As a result, the data set may under represent Medicare and Medicaid populations. The IBM MarketScan Medicare supplementary database, however, contains data from retirees with Medicare supplementary insurance paid by employers. This database includes the Medicare covered portion of payment (represented as Coordination of Benefits Amount or COB), the employer paid portion, and out of pocket patient expenses. The MarketScan Medicare Supplementary Database provides detailed cost, use, and outcomes data for healthcare services performed in both inpatient and outpatient settings. Furthermore, claims data do not indicate the severity or initial lymphoedema onset, therefore the study cannot examine trends in more severe patients or compare treatment timing relative to diagnosis (if outside the span of provided data). Finally, this study set the threshold to class 3 obesity, but many people fall below this and the previous categories of obesity deserve to be studied further as well.

Conclusion

Given the obesity epidemic, this study focused on understanding its contribution to lymphoedema. It was found that severely obese patients with lymphoedema were younger, with more men, and faced higher rates of comorbidities. They were also two and half fold more likely to suffer from cellulitis. However, they still received less targeted lymphoedema treatments such as PT, OT or MLD and had a higher healthcare expenditure making the disease both a health and economic burden.

CONFLICT OF INTEREST

Derek Weycker received consultative reimbursement from Tactile for his independent performance of the health economic analysis. Antonios Gasparis is a consultant to Tactile Medical. Thomas O'Donnell Jr is a consultant to Tactile Medical

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REFERENCES

1 Mehrara BJ, Greene AK. Lymphedema and obesity: is there a link? *Plast Reconstr Surg* 2014;**134**:154e–60e.
2 Helyer LK, Varnic M, Le LW, Leong W, McCready D. Obesity is a risk factor for developing postoperative lymphedema in breast cancer patients. *Breast J* 2010;**16**:48–54.
3 Rebegea LF, Stoleriu G, Manolache N, Serban C, Craescu M, Lupu MN, et al. Associated risk factors of lower limb lymphedema after treatment of cervical and endometrial cancer. *Exp Ther Med* 2020;**20**:181.
4 Leray H, Malloizel-Delaunay J, Lusque A, Chantalat E, Bouglon L, Chollet C, et al. Body mass index as a major risk factor for severe breast cancer-related lymphedema. *Lymphat Res Biol* 2020;**18**:510–6.
5 Keast DH, Despatis M, Allen JO, Brassard A. Chronic oedema/lymphoedema: under-recognised and under-treated. *Int Wound J* 2015;**12**:328–33.
6 Rockson SG. Advances in lymphedema. *Circ Res* 2021;**128**:2003–16.
7 Tashiro K, Feng J, Wu SH, Mashiko T, Kanayama K, Narushima M, et al. Pathological changes of adipose tissue in secondary lymphoedema. *Br J Dermatol* 2017;**177**:158–67.
8 Aschen S, Zampell JC, Elhadad S, Weitman E, De Brot Andrade M, Mehrara BJ. Regulation of adipogenesis by lymphatic fluid stasis: part II. Expression of adipose differentiation genes. *Plast Reconstr Surg* 2012;**129**:838–47.
9 García Nores GD, Cuzzone DA, Albano NJ, Hespe GE, Kataru RP, Torrisi JS, et al. Obesity but not high-fat diet impairs lymphatic function. *Int J Obes (Lond)* 2016;**40**:1582–90.
10 Weitman ES, Aschen SZ, Farias-Eisner G, Albano N, Cuzzone DA, Ghanta S, et al. Obesity impairs lymphatic fluid transport and dendritic cell migration to lymph nodes. *PLoS One* 2013;**8**:e70703.
11 Savetsky IL, Torrisi JS, Cuzzone DA, Ghanta S, Albano NJ, Gardenier JC, et al. Obesity increases inflammation and impairs lymphatic function in a mouse model of lymphedema. *Am J Physiol Heart Circ Physiol* 2014;**307**:H165–72.
12 Torrisi JS, Hespe GE, Cuzzone DA, Savetsky IL, Nitti MD, Gardenier JC, et al. Inhibition of inflammation and iNOS improves lymphatic function in obesity. *Sci Rep* 2016;**6**:19817.
13 CDC. Overweight & Obesity. Available at: https://www.cdc.gov/obesity/data/adult.html. Accessed 31 January 2022.
14 Fife CE, Carter MJ. Lymphedema in the morbidly obese patient: unique challenges in a unique population. *Ostomy Wound Manage* 2008;**54**:44–56.
15 Keith L, Rowsemitt C, Richards LG. Lifestyle Modification group for lymphedema and obesity results in significant health outcomes. *Am J Lifestyle Med* 2017;**14**:420–8.
16 Shaw C, Mortimer P, Judd PA. A randomized controlled trial of weight reduction as a treatment for breast cancer-related lymphedema. *Cancer* 2007;**110**:1868–74.
17 Greene AK. Diagnosis and Management of Obesity-Induced Lymphedema. *Plast Reconstr Surg* 2016;**138**:111e–8e.
18 Sudduth CL, Greene AK. Current overview of obesity-induced lymphedema. *Adv Wound Care (New Rochelle)* 2022;**11**:392–8.
19 CDC. Defining Adult Overweight & Obesity: Available at: https://www.cdc.gov/obesity/basics/adult-defining.html#:~:text=Class%201%3A%20BMI%20of%2030,categorized%20as%20%E2%80%9Csevere%E2%80%9D%20obesity. [Accessed 4 July 2022].
20 Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovasc Res* 2010;**87**:198–210.
21 Mortimer PS, Rockson SG. New developments in clinical aspects of lymphatic disease. *J Clin Invest* 2014;**124**:915–21.
22 Noblett KL, Jensen JK, Ostergard DR. The relationship of body mass index to intra-abdominal pressure as measured by multichannel cystometry. *Int Urogynecol J Pelvic Floor Dysfunct* 1997;**8**:323–6.
23 van Rij AM, De Alwis CS, Jiang P, Christie RA, Hill GB, Dutton SJ, et al. Obesity and impaired venous function. *Eur J Vasc Endovasc Surg* 2008;**35**:739–44.
24 Davies HO, Popplewell M, Singhal R, Smith N, Bradbury AW. Obesity and lower limb venous disease – the epidemic of phlebesity. *Phlebology* 2017;**32**:227–33.
25 Dean SM, Valenti E, Hock K, Leffler J, Compston A, Abraham WT. The clinical characteristics of lower extremity lymphedema in 440 patients. *J Vasc Surg Venous Lymphat Disord* 2020;**8**:851–9.
26 Partsch H, Lee B. Phlebology and lymphology – a family affair. *Phlebology* 2014;**29**:645–7.
27 de Godoy JMP. Systemic subclinical lymphedema due to obesity as the cause of clinical lymphedema: a new concept. *Med Hypotheses* 2019;**131**:109312.
28 Pereira de Godoy LM, Pereira de Godoy HJ, Pereira de Godoy Capeletto P, Guerreiro Godoy MF, Pereira de Godoy JM. Lipedema and the evolution to lymphedema with the progression of obesity. *Cureus* 2020;**12**:e11854.

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29 Boyages J, Kastanias K, Koelmeyer LA, Winch CJ, Lam TC, Sherman KA, et al. Liposuction for advanced lymphedema: a multidisciplinary approach for complete reduction of arm and leg swelling. *Ann Surg Oncol* 2015;**22**:S1263–70.
30 Hoffner M, Bagheri S, Hansson E, Manjer J, Troëng T, Brorson H. SF-36 shows increased quality of life following complete reduction of postmastectomy lymphedema with liposuction. *Lymphat Res Biol* 2017;**15**:87–98.
31 Pantalone KM, Hobbs TM, Chagin KM, Kong SX, Wells BJ, Kattan MW, et al. Prevalence and recognition of obesity and its associated comorbidities: cross-sectional analysis of electronic health record data from a large US integrated health system. *BMJ open* 2017;**7**:e017583.
32 Booth FW, Roberts CK, Thyfault JP, Ruegsegger GN, Toedebusch RG. Role of inactivity in chronic diseases: evolutionary insight and pathophysiological mechanisms. *Physiol Rev* 2017;**97**:1351–402.
33 Cavezzi A, Colucci R, Paccasassi S, Piergentili M. Lymphology and translational medicine. *Int Angiol* 2020;**39**:422–32.
34 Jiang X, Tian W, Nicolls MR, Rockson SG. The lymphatic system in obesity, insulin resistance, and cardiovascular diseases. *Front Physiol* 2019;**10**:1402.
35 Vuorio T, Nurmi H, Moulton K, Kurkipuro J, Robciuc MR, Ohman M, et al. Lymphatic vessel insufficiency in hypercholesterolemic mice alters lipoprotein levels and promotes atherogenesis. *Arterioscler Thromb Vasc Biol* 2014;**34**:1162–70.
36 Cavezzi A. Medicine and phlebolymphology: time to change? *J Clin Med* 2020;**9**:4091.
37 Dupuy A, Benchikhi H, Roujeau JC, Bernard P, Vaillant L, Chosidow O, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. *BMJ* 1999;**318**:1591–4.
38 Shallwani SM, Hodgson P, Towers A. Examining obesity in lymphedema: a retrospective study of 178 new patients with suspected lymphedema at a Canadian hospital-based clinic. *Physiother Can* 2020;**72**:18–25.
39 Sapuła M, Krankowska D, Wiercińska-Drapało A. In search of risk factors for recurrent erysipelas and cellulitis of the lower limb: a cross-sectional study of epidemiological characteristics of patients hospitalized due to skin and soft-tissue infections. *Interdiscip Perspect Infect Dis* 2020;**2020**:1307232.
40 Al-Niaimi F, Cox N. Cellulitis and lymphoedema: a vicious cycle. *J Lymphoedema* 2009;**4**:38–42.
41 Webb E, Neeman T, Bowden FJ, Gaida J, Mumford V, Bissett B. Compression therapy to prevent recurrent cellulitis of the leg. *N Engl J Med* 2020;**383**:630–9.
42 Karaca-Mandic P, Hirsch AT, Rockson SG, Ridner SH. The cutaneous, net clinical, and health economic benefits of advanced pneumatic compression devices in patients with lymphedema. *JAMA Dermatol* 2015;**151**:1187–93.
43 Grada AA, Phillips TJ. Lymphedema: pathophysiology and clinical manifestations. *J Am Acad Dermatol* 2017;**77**:1009–20.
44 Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 consensus document of the International Society of Lymphology. *Lymphology* 2020;**53**:3–19.
45 Buck 2nd DW, Herbst KL. Lipedema: a relatively common disease with extremely common misconceptions. *Plast Reconstr Surg Glob Open* 2016;**4**:e1043.
46 Buck 2nd DW. Obesity-Induced Lymphedema: Clinical and Lymphoscintigraphic Features. *Plast Reconstr Surg* 2016;**137**:646e–7e.
47 Kirk SFL, Penney TL. Managing obesity in healthcare settings: stigma or support? *Obesity and Weight Management* 2010;**6**:21–4.
48 Arterburn DE, Maciejewski ML, Tsevat J. Impact of morbid obesity on medical expenditures in adults. *Int J Obes (Lond)* 2005;**29**:334–9.

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