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Wounds in chronic leg oedema

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Abstract

Wounds and chronic oedema are common disorders, but rarely studied together. The objective of this cross-sectional study was to investigate the point-prevalence and risk factors of wounds on the leg, in chronic leg oedema. Forty sites in nine countries were included. Of 7077 patients with chronic leg oedema, 12.70% had wounds. Independent risk factors were: peripheral arterial disease (odds ratio (OR) 4.87, 95% confidence intervals (CI) 3.63-6.52), cellulitis within the past 12 months (OR 2.69, 95% CI 2.25-3.21), secondary lymphoedema (OR 2.64, 95% CI 1.93-3.60), being male (OR 2.08, 95% CI 1.78-2.44), being over 85 years of age (OR 1.80, 95% CI 1.23-2.62), underweight (OR 1.79, 95% CI 1.14-2.79), bed bound (OR 1.79, 95% CI 1.01-3.16), chair bound (OR 1.52, 95% CI 1.18-1.97), diabetes (OR 1.47, 95% CI 1.23-1.77), and walking with aid (OR 1·41, 95% CI 1.17-1.69). 43.22% of those with wounds had clinically defined well-controlled oedema, associated with a significantly lower risk of wounds (OR 0.50, 95% CI 0.42-0.58, $P < .001$). Hard/fibrotic tissue (OR 1.71, 95% CI 1.19-2.48), and a positive Stemmers sign (OR 1.57, 95% CI 1.05-2.35) were associated with wounds. The study reinforces the importance of measures to control oedema, as controlled swelling was associated with a 50% lower risk of wounds.

KEYWORDS

chronic oedema, leg ulcers, LIMPRINT, lymphoedema, wounds and injuries

Key Messages

- chronic leg oedema (oedema >3 months) and wounds are frequent conditions, but have rarely been studied together. Little is known about mechanisms linking wounds and oedematous limbs

- the objective of this cross-sectional study was to investigate the point-prevalence and risk factors for wounds on the leg of diverse aetiologies, in chronic leg oedema. Forty sites in nine countries participated, including 7077 patients with chronic leg oedema
- the largest independent risk factor for wounds was peripheral arterial disease, followed by cellulitis within 12 months, secondary lymphoedema, male sex, being 85+ years, underweight, reduced mobility, and diabetes
- the study adds to the growing evidence, that treatment of swelling, for example, by compression, reduces the risk of wound development, OR 0.50, $P < .001$. A holistic approach for wound prevention is important, with a mandatory focus on control of oedema

1 | INTRODUCTION

Hippocrates recognised wounds on the legs were problematic 'In the case of an ulcer, it is not expedient to stand; more especially if the ulcer be situated in the leg'. He stated that treatment of the wound and swelling were both important.[1] Hippocrates's observations apply today; as the majority of problematic wounds occur on the legs,[2] but also due to the negative impact of oedema on wounds. The gold standard for the prevention and treatment of venous ulcers (VLU) is compression[3-6] with less attention on chronic oedema and mechanisms leading to wounds, outside the spectrum of venous oedema. Although factors affecting wound healing have been extensively reviewed,[7-9] there is little insight around oedema as a risk factor. None of these reviews stated oedema was associated with delayed wound healing.

The burden of chronic wounds cannot be overestimated, with a lifetime risk of 1% to 2%[10] and high expectation of recurrence. VLU are the commonest leg ulcer, with a recurrence rate of 55% within 12 months in community and hospitalised cases,[11] a significant reason being lack of compression causing uncontrolled oedema.[6] Whilst the impact on patients, families, and society is immeasurable[12,13] and treatment consumes 1% to 3% of the total health care budget in developed countries, the true burden of chronic oedema has yet to be evaluated. Chronic oedema, defined as oedema present longer than 3 months, is often multi-factorial, for example, due to primary and secondary lymphoedema; venous insufficiency, cancer, obesity, and immobility.[14] The estimated prevalence of chronic oedema is 57% in patients cared for by community nurses in the UK[15] and 38% in hospitals in Europe.[16] Complications associated with chronic oedema include cellulitis[17] and chronic wounds. Despite this, chronic oedema remains a neglected condition.

This international cross-sectional study aimed to examine the association of potential risk factors for patients with chronic leg oedema and a concurrent wound (acute or chronic). Identification of potential risk factors for such patients allows for targeted health interventions and assists in understanding the mechanisms of wound formation.

2 | MATERIALS AND METHODS

2.1 | Study design

An international, cross-sectional, multicentre study performed as a sub-study of the LIMPRINT*-project; a study designed to prospectively determine the scope and impact of chronic oedema within health services. Centres from nine countries participated between June 2014 and August 2017, including hospital (in/outpatients) and community cases.

2.2 | Ethical approval

Each country and centre acquired necessary approvals from the Ethical Review Committee and other committees.

2.3 | Study population

Adults 18 years and older, with clinically confirmed chronic leg oedema, irrespective of the cause (unilateral or bilateral), able to understand the study and give informed consent where required by local research and service development committees were included. Patients were excluded if they were unwilling to participate, receiving end-of-life care or if judged as not in the patient's best interest by the investigator.

2.4 | Outcomes

The presence of clinically assessed leg wounds (yes/no) in the sites affected by chronic leg oedema, and its relation to potential risk factors.

2.5 | Definitions

Chronic leg oedema: Defined as oedema, which has endured longer than 3 months.[14] The term lymphoedema has been used to describe oedema resulting from a failure of the lymphatics, due to lymphatic malformation, cancer, mechanical injury, filariasis, etc. However, newer research indicates the significant role of the lymphatic system in all chronic oedema, and thereby the introduction of this umbrella term was accepted. Chronic oedema is often multifactorial and includes different pathologies, for example, primary lymphoedema ('congenital') and secondary causes, that include venous insufficiency, cancer, heart failure, immobility, and obesity.[18] Oedema was confirmed in all cases by the 'Pitting Oedema Test[19,†] and/or the Stemmers[20] sign.[‡] The presence of either pitting or a positive Stemmers sign was confirmatory of chronic oedema (in longstanding and severe oedema, fibrotic tissue develops with no pitting). The duration was determined from the patient and clinician, and confirmed by review of medical records.

Wounds: An umbrella term that we broadly defined as 'loss of skin integrity', irrespective of the duration, wound characteristics, or aetiology (internal or external). It was clinically assessed by the investigator at the timepoint of examination, supported by information from medical records, imaging, and other investigations. The wound was classified as either foot/leg ulcer, pressure ulcer, surgical wound, or other. Only wounds on the legs were included in this analysis.

Sites with the expertise further classified foot/leg ulcers as venous, arterial, venous–arterial (mixed), diabetic (including neuropathic and neuro-ischemic), or other. The duration and size of the wounds were documented.

2.6 | Data collection and quality assessment

The validation of the methodology has previously been published.[21] A core tool developed by an international expert panel including a questionnaire and a clinical examination was used by all participants. Data were collected by trained health care professionals. Sites collecting additional wound data were assisted by wound care specialists. An additional tool was also used in centres able to undertake the staging procedure of the severity of oedema (ISL; International Society of Lymphology). Lymphoedema specialists assisted in the classification. All centres followed the study protocol and complied with standard operating procedures to ensure quality control. In lymphoedema specialist centres, data using the core tool were obtained from clinical records of all subjects currently attending nine specific specialist lymphoedema services.[22]

2.7 | Variables

Variables are listed in Table 1. Site of chronic oedema was recorded using a body map. The oedema was classified as primary/congenital or secondary/acquired lymphoedema,[§] and whether related to cancer due to treatment and/or metastasis. Oedema factors were venous disease, obesity, immobility, filariasis, and/or other (multiple options were possible). Duration of oedema and mobility status was collected. In selected centres, the severity of oedema was assessed, with the ISL-staging tool, by palpation and clinical evaluation,[23] initially developed for lymphoedema.[¶]

There are no internationally agreed definitions of control of swelling.[24] Here it was a subjective judgement by the investigator based on the clinical evaluation of the leg, clarified with the caregiver and if necessary the lead clinician, assessed as either present, absent or 'do not know', at the time of clinical assessment. The type (or absence) of treatment was noted, including the use of compression. Data were collected on demography and relevant comorbidities. Body mass index (BMI) was estimated according to WHO classifications as either underweight (BMI < 20), normal weight (BMI 20-30), obese (BMI 30-40), or morbidly obese (BMI > 40). Cellulitis defined as an acute onset of soft-tissue erythema, warmth, and tenderness that rapidly resolved with antibiotics within the last year was confirmed by a combination of physical examination, interview with the patient, and/or review of medical records.

2.8 | Statistical analysis

Statistics were prepared using Stata 12 (Statacorp, Texas). No formal sample size determination was performed. A cohort of over 5000 patients was expected to show the major factors associated with wounds. The principal analysis examined the binary outcome (wounds versus no wounds). Factors tested for an association with the outcome were broadly demographics, medical history and data about the limb. These variables were chosen as they were believed to be potentially associated with the

TABLE 1 Dependent and independent variables in the study

Dependent variable	Independent variable
Presence of wound(s) on the lower limb	Age
	Sex
	Body mass index
	Concomitant diseases
	Cellulitis within 12 months
	Classification of chronic oedema
	Aetiology of oedema
	ISL scale
	Duration of leg oedema
	Mobility
	Control of swelling
	Pitting oedema
	Tissue quality
	Stemmers sign

outcome and could be reliably collected in an international study. Logistic regression was the primary analysis. Univariate comparisons were followed by a multivariable model, using a stepwise elimination process until all factors remaining had an alpha <.05. Results were presented as OR and 95% confidence intervals. A further similar analysis examined the severity of chronic oedema in a subgroup of 738 patients. Missing data were not imputed and therefore remained missing.

3 | RESULTS

3.1 | Characteristics of countries, centres, and patients

Of 10 127 patients with chronic oedema in the LIMPRINT database, 1727 (17.05%) had a wound anywhere on the body. Seven thousand and seventy-seven (69.88%) patients had swelling of one or both legs; these were included in this analysis. Forty centres participated from Australia, Canada, Denmark, France, Ireland, Italy, Japan, Turkey, and United Kingdom, Table 2. These included specialist lymphoedema services (n = 14 centres), out-patient acute hospitals (10), hospitalised cases (seven), community nursing services (three), elderly care residential homes (one), nursing homes (one), and other (four). Six thousand one hundred and seventy-eight patients with leg oedema but no wound comprised the comparison group. Patient characteristics are presented in Table 3.

TABLE 2 Percentage of patients with leg oedema and a wound (n = 7077)

	Total patients	Leg wound	Percent
UK	4507	363	8.05
Denmark	818	278	33.99
Turkey	215	9	4.19
Japan	43	1	2.33
Canada	67	26	38.81
France	313	26	8.31
Australia	93	69	74.19
Italy	1002	120	11.98
Ireland	19	7	36.84
Total	**7077**	**899**	**12.70**

3.2 | Frequency of wounds in patients with chronic leg oedema

12.70% (n = 899) of the patients had a concurrent wound with a wide range of wound duration and size, classified as: 627 ft/leg ulcers (aetiology not defined), 103 VLU, 100 pressure ulcers, the rest being arterial, mixed ulcers, diabetic foot ulcers (DFU), traumatic or surgical wounds. Some had multiple aetiologies. 2315 (49.49%) of those with secondary lymphoedema were reported to have venous insufficiency, which could indicate that many of the wounds identified as foot/leg ulcers on more detailed classification would have been VLU. The frequency of chronic wounds by country ranged between 2.33% in Japan and 74.19% in Australia. In those assessed for the severity of the chronic oedema (n = 738) wounds affected 27.33% with ISL stage I, 38.67% in stage II, and 34.00% in stage III. Only 43.22% of the patient cohort with wounds had well-controlled chronic leg oedema.

3.3 | Risk factors by univariate analysis

Statistically significant associations were found between wounds and being male (OR 2.29), diabetes (OR 2.14), heart failure/ischemic heart disease (OR 1.89), and neurological disease (OR 1.33). Increasing age was significantly associated, with the highest odd ratios in those over 85 years (OR 3.87). Although nutritional status was associated, only underweight yielded statistically significant results (OR 2.70). Morbid obesity was not statistically significant (OR 1.19). Levels of mobility were significantly associated: walking with aid (OR 2.19), chair bound (OR 2.39), and bedbound patients (OR 3.63) Table 4.

TABLE 3 Demographics of patients with chronic leg oedema (n = 7077)

Characteristic(s)	Number of patients (%)
Age, mean	64.91 (SD = 16.38)
Missing	2
Female	5007 (70.75)
Missing	0
Body weight	
Underweight	143 (2.03)
Normal weight	2922 (41.39)
Obesity	2505 (35.48)
Morbidly obesity	1490 (21.10)
Missing	17
Concomitant disease	
Diabetes	1304 (18.43)
Missing	0
Heart failure/ ischemic heart disease	1111 (15.70)
Missing	0
Peripheral arterial disease	246 (3.48)
Missing	0
Neurological disease	614 (8.70)
Missing	19
Facility	
Hospital-based cases	6643 (93.87)
Community cases	110 (1.55)
Other	324 (4.58)
Missing	0
Wound type (n = 899)	
Foot/leg ulcer (unspecified)	627 (70.06)
Diabetic	37 (4.13)
Pressure ulcer	100 (11.17)
Venous	103 (11.51)
Arterial	13 (1.45)
Mixed	23 (2.57)
Traumatic	9 (1.01)
Surgical	16 (1.79)
Other	1
Missing	4
Wound duration (n = 179)	
<1 wk	23 (13.29)
1–2 wk	27 (15.61)
2–4 wk	23 (13.29)
4–6 wk	35 (20.23)
6 wk to <3 mo	41 (23.70)
>3 mo	24 (13.87)
Missing	6

(Continues)

TABLE 3 (Continued)

Characteristic(s)	Number of patients (%)
Wound area (n = 179)	
Small; <10 cm^2	115 (64.61)
Medium; >10 cm^2 - < 25 cm^2	42 (23.60)
Large; > 25 cm^2	21 (11.80)
Missing	1
Classification of chronic oedema	
Primary lymphoedema	1376 (19.61)
Secondary lymphoedema	5642 (80.39)
Missing	59
Related to cancer or its treatment	934 (16.62)
Non-cancer	4686 (83.38)
Missing	22
Venous disease	2315 (49.49)
Immobility	1708 (36.51)
Obesity	1416 (30.27)
Filariasis	10 (0.21)
Missing	8
Unilateral leg oedema	1728 (24.42)
Bilateral leg oedema	5349 (75.58)
Missing	0
ISL scale[a] (n = 738)	
I	184 (24.97)
II	397 (53.87)
III	156 (21.17)
Missing	1
Duration of leg oedema	
3 mo to <1 y	742 (10.51)
1–2 y	706 (10.00)
2–5 y	1469 (20.80)
>5–10 y	1598 (22.62)
>10 y	2548 (36.08)
Missing	14
Mobility	
Normal	4011 (56.75)
Walking aid	2325 (32.89)
Chair bound	639 (9.04)
Bedbound	93 (1.32)
Missing	9
Treatment with compression therapy (n = 7077)	
Compression garment	4892 (69.37)
Multilayer bandage	1744 (24.73)
Compression wrap	631 (8.95)
At least one of the above	5553 (78.74)

TABLE 3 (Continued)

Characteristic(s)	Number of patients (%)
No compression	1499 (21.26)
Missing	25
Good control of swelling	4135 (62.71)
Missing[b]	483
Antibiotics	413 (5.86)
Missing	25

[a]The ISL scale has the following: stage I: early onset of the condition, with a collection of tissue oedema that decreases with limb elevation. The oedema may be pitting; stage II: limb elevation alone rarely reduces swelling and pitting is manifested; stage III: the tissue is fibrotic (hard) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop.
[b]Includes cases were the control of swelling was judged as 'uncertain' by the investigator.

Peripheral arterial disease (PAD) (OR 7.40), cellulitis the last year (OR 3.02), and secondary lymphoedema were significantly associated with wounds compared with primary lymphoedema (OR 4.48). A non-cancer cause of the oedema was of significant risk (OR 7.35), but specifically oedema classified as due to venous disease (OR 2.40), as opposed to oedema caused by obesity and immobility.** Swelling duration >1 year had a lower risk, with ratios varying between OR 0.62 and 0.73 compared with <1 year. Subjects with control of swelling had a significantly lower risk of wounds (OR 0.40) Table 4.

3.4 | Independent risk factors

Factors remaining after multivariable analysis were PAD (OR 4.87), cellulitis (OR 2.69), secondary lymphoedema (OR 2.64), being male (OR 2.08), being 85+ years (OR 1.80), underweight (OR 1.79), being bed bound (OR 1.79), chair bound (OR 1.52), diabetes (OR 1.47), and walking with aid (OR 1.41). Patients with controlled swelling had a markedly lower risk of wounds, OR 0.50 (95% CI 0.42-0.58, $P < .001$), Table 5.

3.5 | Severity of oedema, a sub-group analysis

The risk of a wound was significantly increased in cases with hard/fibrotic tissue (OR 1.71) and positive Stemmers sign (OR 1.57), in patients assessed for the severity of oedema (n = 738, Table 6). The relationship regarding the ISL-scale was complex. On univariate analysis, a lower risk of wounds was seen in stage II (OR 0.60) but increased in stage III (OR 1.69). However, after adjustment for sex, age, mobility, diabetes, PAD, control of oedema, cellulitis, and secondary lymphoedema, none remained statistically significant, albeit with a tendency of an increased risk in stage III (OR 1.75, 95% CI 0.95-3.24).

4 | DISCUSSION

In this study, the frequency of leg wounds of diverse aetiology in chronic leg oedema was common, with a point-prevalence of 12.70%. Independent risk factors for wounds included PAD, diabetes, being male, cellulitis, secondary lymphoedema, being over 85 years old, underweight and reduced mobility. Our findings add to the growing evidence that well-controlled oedema is crucial; associated with a 50% lower risk of wounds ($P < .001$). This should not be surprising, as compression is gold standard with a high level of evidence for treatment and prevention of VLU.[3-6] Yet, only 43% of the patients with wounds had well-controlled oedema. Assessment of risk factors has been a topic of research, mostly for VLU,[25-30] DFU[31-33] and pressure ulcers,[34] but this is the first international study in chronic oedema. Inclusion of diverse types of leg wounds sheds new light on the topic. The large cohort, and the clinical confirmation of both chronic oedema and wounds, strengthens the validity of our data.

We confirm the anecdotal observation that secondary lymphoedema has a higher association with wounds than primary lymphoedema. This may indicate that other factors contribute to the wound, or that the oedema has different biological properties or localization in the tissue. Oedema seems primarily confined to the subepidermis in lipodermatosclerosis (venous insufficiency), lower in the dermis in lymphoedema, and involves the deep dermis/subcutis in heart failure. This might explain some of the different clinical manifestations; in lipodermatosclerosis brownish fibrotic tissue with ulcers is often seen, as opposed to epidermal hyperproliferation, warty skin, and fewer wounds in lymphoedema. Heart failure rarely

TABLE 4 Univariate analysis on leg wounds and chronic oedema (n = 7077)

	No wound		Wound			
	N	%	N	%	OR 95% CI	*P*-value
Sex						
Female	4519	73.15	488	54.28	1.00	
Male	1659	26.85	411	45.72	2.29 (1.99-2.65)	<.001
Age						
<45 y	846	13.70	55	6.12	1.00	
45 to 64 y	1978	32.02	239	26.61	1.86 (1.37-2.52)	<.001
65 to 74 y	1455	23.56	212	23.61	2.24 (1.65-3.05)	
75 to 84 y	1310	21.21	244	27.17	2.87 (2.11-3.89)	
85+ y	588	9.52	148	16.48	3.87 (2.79-5.37)	
Body weight						
Normal weight	2566	41.64	356	39.64	1.00	
Under weight	104	1.69	39	4.34	2.70 (1.84-3.97)	<.001
Obese	2213	35.91	292	32.52	0.95 (0.81-1.12)	
Morbidly obese	1279	20.76	211	23.50	1.19 (0.99-1.43)	
Leg mobility						
Walks unaided	3660	59.31	351	39.13	1.00	
Walks with aid	1922	31.15	403	44.93	2.19 (1.88-2.55)	<.001
Chair bound	520	8.43	119	13.27	2.39 (1.90-3.00)	
Bedbound	69	1.12	24	2.68	3.63 (2.25-5.85)	
Diabetes						
Absent	5144	83.26	629	69.97	1.00	
Present	1034	16.74	270	30.03	2.14 (1.82-2.50)	<.001
Heart failure/ischemic heart disease						
Absent	5285	85.55	681	75.75	1.00	
Present	893	14.45	218	24.25	1.89 (1.60-2.24)	<.001
Neurological disease						
Absent	5649	91.62	795	89.13	1.00	
Present	517	8.38	97	10.87	1.33 (1.06-1.68)	.014
Peripheral arterial disease						
Absent	6052	97.96	779	86.65	1.00	
Present	126	2.04	120	13.35	7.40 (5.70-9.60)	<.001
Cellulitis within 12 mo (n = 7064)						
Absent	5337	86.56	611	68.04	1.00	
Present	829	13.44	287	31.96	3.02 (2.58-3.54)	<.001
Control of swelling (n = 6594)						
Absent	1973	34.38	486	56.78	1.00	
Present	3765	65.62	370	43.22	0.40 (0.34-0.46)	<.001
Swelling duration (n = 7063)						
<1 y	614	9.96	128	14.24	1·00	
1 to 2 y	613	9.94	93	10.34	0.73 (0.54-0.97)	.002
2 to 5 y	1281	20.78	188	20.91	0.70 (0.55-0.90)	
5 to 10 y	1401	22.73	197	21.91	0.67 (0.53-0.86)	
>10 y	2255	36.58	293	32.59	0.62 (0.50-0.78)	

TABLE 4 (Continued)

	No wound		Wound			
	N	%	N	%	OR 95% CI	*P*-value
Classification (n = 7018)						
Primary lymphoedema	1324	21.63	52	5.80	1.00	<.001
Secondary lymphoedema	4798	78.37	844	94.20	4.48 (3.36-5.97)	
Secondary cause (n = 5620)						
Cancer	908	19.00	26	3.09	1.00	<.001
Non-cancer	3871	81.00	815	96.91	7.35 (4.94-10.94)	
Related to cancer or its treatment (n = 930)						
Cancer treatment						
Absent	125	13.83	6	23.08	1.00	
Present	779	86.17	20	76.92	0.53 (0.21-1.36)	.18
Cancer metastatic						
Absent	801	88.61	21	80.77	1.00	
Present	103	11.39	5	19.23	1.85 (0.68-5.02)	.22
Non-cancer (n = 4678)						
Venous						
Absent	2095	54.19	268	33.00	1.00	
Present	1771	45.81	544	67.00	2.40 (2.05-2.82)	<.001
Immobility						
Absent	2442	63.17	528	65.02	1.00	
Present	1424	36.83	284	34.98	0.92 (0.79-1.08)	.32
Obesity						
Absent	2708	70.05	554	68.23	1.00	
Present	1158	29.95	258	31.77	1.09 (0.93-1.28)	.31
Lymphatic filariasis						
Absent	3858	99.79	810	99.75		
Present	8	0.21	2	0.25		.69

causes major skin changes,[35] except from soft pitting oedema. It is suggested that the oedema in fibrotic lipodermatoslerosis causes a localised increased skin tension leading to ulceration, opposed to the more freely distributed fluid in lymphoedema and heart failure.[35,36] Hard/fibrotic tissue, as manifested in advanced stages of chronic oedema, was a risk factor in our study, supported by others reporting lipodermatosclerosis associated with VLU recurrence.[30] Interventions to prevent progression into severe stages of chronic oedema should be mandatory. Whether increased levels of cytokines, growth factors, or lipids in lymphatic fluid in lymphoedema (possibly driving adipogenesis)[37] have a protective role for wounds is yet to be determined.

PAD was the strongest risk factor for wounds, underlining the importance of vascular evaluation. As oxygen is critical for wound healing,[38] it is logical that hypoxia caused by PAD is harmful. High oxygen consumption by metabolically active cells such as inflammatory cells depletes the wound from oxygen.[7,38] Due to pain, patients with severe limb ischemia often sleep with dependent legs, aggravating oedema. Cyclic intervals of ischemia and reperfusion induce a proinflammatory state, by increasing neutrophil flood into the tissue, causing cell damage. Repeated ischemia–reperfusion cycles seem to be worse for wound healing than prolonged phases of single ischemia.[38]

The mechanisms causing oedema in diabetes are complex. The risk of wounds is correlated to the duration of diabetes and complications such as neuropathy and PAD,[32] with a risk of complex wounds and secondary infection. Up to 38% of the patients with DFU have

TABLE 5 Logistic regression analysis: independent factors associated with leg wounds and oedema (n = 6503)

	Odds ratio	OR 95% CI	*P*-value
Sex			
Male	2.08	1.78 to 2.44	<.001
Age			
45 to 64 y	1.13	0.81 to 1.57	
65 to 74 y	1.13	0.80 to 1.59	.003
75 to 84 y	1.40	0.99 to 1.97	
85+ y	1.80	1.23 to 2.62	
Mobility			
Walks with aid	1.41	1.17 to 1.69	
Chair bound	1.52	1.18 to 1.97	.003
Bed bound	1.79	1.01 to 3.16	
Body weight			
Underweight	1.79	1.14 to 2.79	
Obese	0.84	0.70 to 1.02	.007
Morbidly obese	1.03	0.83 to 1.28	
Diabetes			
Present	1.47	1.23 to 1.77	<.001
Peripheral arterial disease			
Present	4.87	3.63 to 6.52	<.001
Control of swelling			
Present	0.50	0.42 to 0.58	<.001
Cellulitis within 12 mo			
Present	2.69	2.25 to 3.21	<.001
Secondary lymphoedema			
Present	2.64	1.93 to 3.60	<.001

oedema, being more frequent in those who require amputation.[39] Renal disease and congestive heart failure in diabetes, antidiabetic drugs,[40] and autonomic dysfunction may predispose oedema formation. Whilst off-loading is mandatory for foot ulcers,[41] compression therapy in PAD and diabetes is a subject of intense debate because of the fear of compromising the circulation, and causing pressure wounds in neuropathy.[42,43] However, intact and even improved microperfusion locally and distally by compression has been measured.[44-46] The safety in moderate PAD is supported by a prospective study (n = 94)[45] and a RCT (n = 80) in diabetics and PAD.[40]

We found that being male had a greater association with wounds than diabetes. Male predominance has been reported in chronic wounds,[47] VLU,[26,27] and DFU.[31,32] Yet, contradictory results for VLU have been reported[28,48] and sex was not a risk factor in pressure ulcers.[34] Male predominance may be due to biological[49,50] and behavioural factors.

The negative impact of being aged and inactive was significant; the older and less mobile being at greatest risk. Similar results on immobility have been reported for VLU[48] and chronic wounds.[47] This is complex and can reflect poor general health, worsened oedema, or increased tendency of pressure ulcers. Regular walking (≥5 d/wk) has been found to be an independent protective factor from VLU (OR 0.26, 95% CI 0.08-0.90).[25] Being underweight was also associated with wounds.[47] Studies have contradictory findings regarding obesity, perhaps due to the wound type[32,48] and we did not find an independent association. The growing evidence of the connection between obesity and lymphoedema[37] is worthy of further investigations.

Our results regarding ISL staging and the relationship to wounds are difficult to interpret, but suggest that advanced stages of chronic oedema with fibrotic tissue (ISL stage III) may be associated with wounds. Whilst the ISL scale might be useful, we acknowledge that the

TABLE 6 Wounds and leg swelling: lymphoedema factors (n = 738)

	No wound		Wound			
	N	%	N	%	OR 95% CI	*P*-value
Pitting						
Non pitting	196	33.33	39	26.00	1.00	
Pitting	392	66.67	111	74.0	1.42 (0.95-2.13)	.085
Tissue quality						
Soft	410	69.73	86	57.33	1.00	
Hard	178	30.27	64	42.67	1.71 (1.19-2.48)	.004
Stemmers sign						
Negative	231	39.97	41	29.71	1.00	
Positive	347	60.03	97	70.29	1.57 (1.05-2.35)	.026
ISL scale[a]						
Stage I	143	24.36	41	27.33	1.00	
Stage II	339	57.75	58	38.67	0.60 (0.38-0.93)	<.001
Stage III	105	17.89	51	34.00	1.69 (1.05-2.74)	
ISL scale after adjustment for sex, age, mobility, diabetes, peripheral arterial disease, control of swelling, cellulitis, secondary lymphoedema						
Stage I					1.00	
Stage II					0.73 (0.43-1.23)	.087
Stage III					1.75 (0.95-3.24)	

[a]The ISL scale has the following: stage I: early onset of the condition, with a collection of tissue oedema that decreases with limb elevation. The oedema may be pitting; stage II: limb elevation alone rarely reduces swelling and pitting is manifested; stage III: the tissue is fibrotic (hard) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop.

classification can be difficult in people with ISL stage II as they may have pitting and fibrosis on different anatomical parts of the limb at the same time point. The complex relationship with wounds in the ISL scoring may reflect the influence of important confounders (as indicated by the multivariable analysis).

Why is chronic oedema associated with wounds? Many controversies surround our understanding of the mechanisms of wounds in chronic oedema, with most research focusing on venous ulceration. In VLU, venous hypertension injures endothelial cells, causing release of inflammatory molecules, prothrombotic precursors, and leakage of fluid into the interstitial space, presenting as oedema. Migration of inflammatory cells into the tissue is seen, setting up an inflammatory cascade with production of cytokines and matrix metalloproteinases (MMPs), leading to degradation of extracellular matrix, ulceration,[51] and fibrosis. Difficult-to-eradicate bacterial biofilms, inevitable in chronic wounds, attract leucocytes, maintaining the inflammation.[38] Others hypothesise that oedema primarily interferes with oxygen and nutrient exchange in the skin.[35] A decrease in the number of capillaries and a decline in the skin oxygen content ($tcPO_2$) is correlated with the severity of venous insufficiency, possibly leading to ulceration.[52] Compression seems to improve both inflammation and microvascularity, lowering venous hypertension, decreasing capillary filtration, and increasing lymphatic drainage.[53] Decreased expression of pro-inflammatory cytokines has been measured in lymphoedema and in VLU, respectively,[54-56] with a reduction of MMPs,[57] and increased capillary density and $tcPO_2$.[52] Venous eczema, and sometimes fibrosis, can be reversed.[6,53] The risk of cellulitis (strongly associated with wounds in this study) can also be prevented by compression.[17] The proposed mechanisms and its relation to our findings can be seen in Figure 1.

Limitations to our study must be noted. Despite training using agreed wound classification and access to specialist teams, variation in correctly defining the wound type in a large international study may have occurred. Secondly, wounds of diverse aetiology were included, introducing complex interactions. Thirdly, the assessment of 'well-controlled' oedema was a matter of a subjective assessment. Fourthly, it is acknowledged that many other clinical, psychological, and social factors may influence why wounds occur in this population which lie outside the scope of this study. Fifthly, a generalisation of our results should be made cautiously as the majority

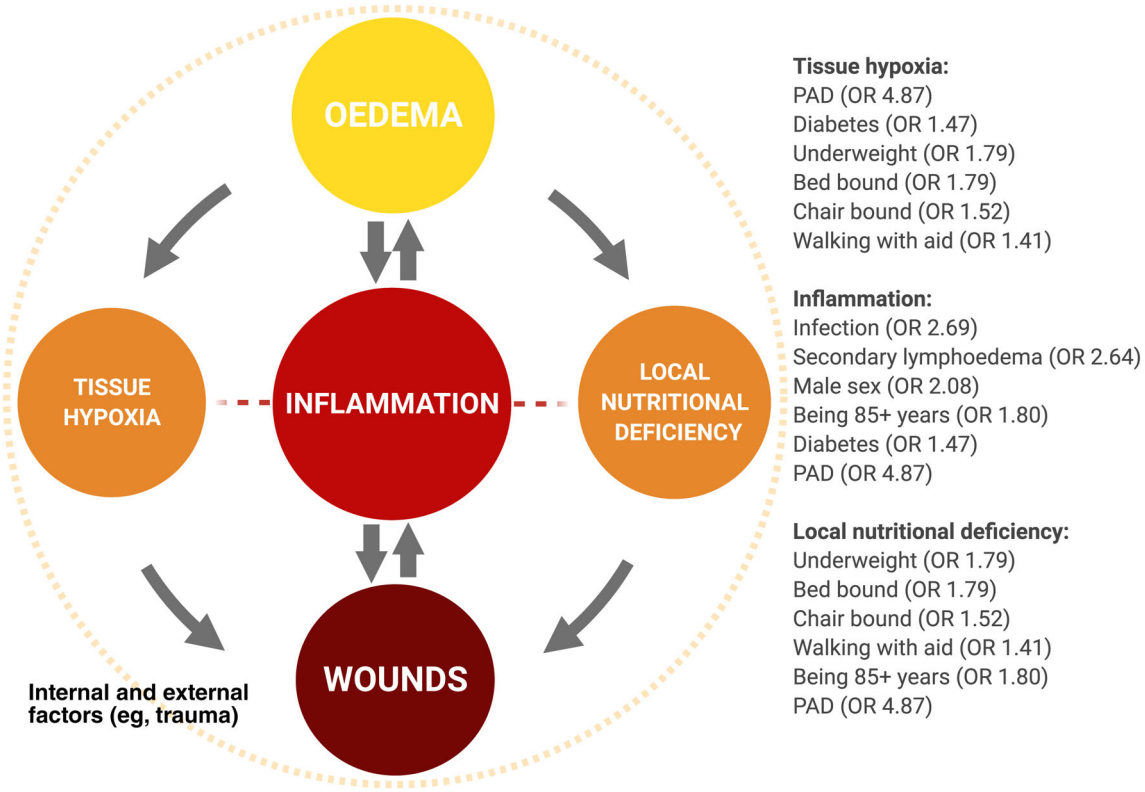

FIGURE 1 Simplified hypothesis linking chronic oedema with wounds. Wounds and oedema are known to go hand in hand; wounds can cause oedema by inflammation, but oedema can also predispose to wounds, through several possible mechanisms. Other internal and external factors, for example, trauma, also influence the development of a wound. Figure created with BioRender.com

of cases were included from hospitals skewing data towards more severe cases, with selection bias. The wide range of wound prevalence in different countries is probably explained by the different types of services patients were recruited from (eg, wound centre vs lymphoedema clinic). Lastly, a cross-sectional design does not allow for firm views on causation to be formed.

In conclusion, our study highlights the global challenge of chronic leg oedema and wounds. The development of leg wounds in chronic leg oedema is frequent and multifactorial. Although multiple guidelines support the usage of compression therapy to prevent and treat wounds, only 43% had well-controlled oedema. For some, it may be tempting only to apply a dressing on the wound, rather than treating the underlying cause. In this study, those with well-controlled oedema reduced their risk of a concurrent wound by half. The important association between different wound types, chronic oedema, and compression is worthy of further studies.

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CONFLICT OF INTEREST

No support was received from any organisation for the submitted work during the conduct of the study, except for PJF from ILF. Reponex Pharmaceuticals and Coloplast sponsors EAB in her PhD, who has also been an investigator for clinical research for Genentech, Reapplix, Ilkos therapeutic, and SoftOx Solutions, through payments to the department, outside the submitted work. CJM is sponsored by Thuasne and Essity Healthcare for consulting in compression therapy, and by ILF for work on different research, outside the submitted work. SN is sponsored by ILF for work on projects outside the submitted work. KKM receives personal fees from SoftOx Solutions as medical advisor and minor shareholder, outside the submitted work

and holds a patent, acetic acid against biofilm infections, issued to SoftOx Solutions. RK has no conflicts related to this work. TK is sponsored by Coloplast regarding stomas and wound healing as part of an advisory board membership, has been an investigator for clinical research for Genentech, and is a medical advisor for Reponex Pharmaceuticals, outside the submitted work. PJF has received grants from Tactile Medical, outside the submitted work. IQ has received honoraria for consulting and as a speaker from Thuasne in the last 3 years and was an investigator for clinical research for Thuasne and Medi, fees were paid to the hospital. No other relationships or activities that could appear to have influenced the submitted work.

ENDNOTES

* Lymphoedema Impact and Prevalence – International Lymphoedema Framework.

† Carried out by pressing the thumb into the site of swelling for 10 s. If a pit remained after removal of the finger, oedema was judged as present.

‡ A positive Stemmer's sign: A skin fold cannot be pinched at the base of the second toe and is diagnostic of lymphoedema.

§ The term secondary lymphoedema in the manuscript includes all other causes for oedema than primary lymphoedema, for example, oedema due to venous insufficiency, cancer, filariasis, heart failure, immobility, and obesity.

¶ The ISL stage tool has the following: stage I: early onset of the condition, with a collection of tissue oedema that decreases with limb elevation. The oedema may be pitting; stage II: limb elevation alone rarely reduces swelling and pitting is manifested; stage III: the tissue is fibrotic (hard) and pitting is absent. Skin changes such as thickening, hyperpigmentation, increased skin folds, fat deposits, and warty overgrowths develop.

** The number of cases with filariasis was too small to assess an association.

DATA AVAILABILITY STATEMENT

Author elects to not share data.

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