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A Clinical Analysis of Phlebolymphedema and Its Relationship with Physical Activity and Disability

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: The clinical features and epidemiological data about patients with phebolymphedema or lymphedema related to Chronic Venous Disease in Mexico is limited and has been understudied; at the same time, the relationships between its clinical features, physical activity level and disability remained unknown.

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Methods: This is a longitudinal cohort study based on the analysis of clinical data of 90 patients gathered between 2021 and 2022. The statistical analysis was carried out using the software SPSS version 25 and GrandhPad Prism 8; a descriptive analysis was developed using measures of central tendency for the variables of a quantitative nature and frequency distribution for those categorical variables. The behavior of the variables was revealed through the Shapiro-Wilk statistic. The mean difference analysis was carried out with the Student's T for independent samples. To identify the effect of gender, age, and severity of the disease on the study variables, a three-way analysis of variance was obtained with a Sidak comparison analysis. For the associations between qualitative and dichotomous nature variables, the Chi-Square statistic was obtained along with the odds ratio to determine the intensity of the relationships found.
Results: A total of 90 patients were included in the analysis; 71% (64) were female and 29% (26) were male; with a mean age of 62.7 years old (± 30.5). A mean BMI of 33.2, 79.9% (77) of patients reached overweight and obesity ranges. 50% (45) of patients reported disability to perform one or more daily life activities related to the disease's condition (signs, symptoms, volume). Only 12% (10) of all patients performed at or above the minimum physical activity recommended for their population group, and 88% (80) of patients had no physical activity or performed under the proper population group's recommendation of minimal physical activity. It was found that the practice of physical activity, the number of compromised segments, the stage of the pathology, and the presence of cardiological and metabolic antecedents provide a statistically significant association with disability. Notable statistical difference among sex as a risk factor was not found. Regarding the BMI, the only differences were observed in the level of severity of the disease, regardless of the presence of any disability ($p=0.006$), evidencing that the greater the severity, the higher the BMI in both men and women. About physical activity, it is observed that inactivity or minimal practice of physical activity is a risk factor for referred disability ($p<0.05$), since it is prolonged that the non-practice of physical activity increases by 230% the chances of referring a disability associated to the disease compared to those people who referred to practice minimal or above minimal physical activity; the presence of a cardiological and/or metabolic history is related to an increase of about 150% to 180% of presenting disability compared to patients who do not have these pathologies.
Conclusion: This study shows clinical and epidemiological features of phlebolymphedema and their relationship with the level of physical activity and reported disability of 90 patients. Further studies are needed to improve and broaden the understanding of the clinical characteristics of phlebolymphedema and its correlations.

Keywords: Lymphedema; phlebolymphedema; chronic venous disease; disability; physical activity.

1. INTRODUCTION

Chronic venous disease (CVD) is a multifactorial, persistent, and progressive condition that includes a broad spectrum of venous abnormalities that compromise venous blood return [1] and may lead to clinical manifestations of chronic venous insufficiency as venous ulcers [2,3] and especially the under-considered phlebolymphedema [4,5], which not only requires extensive treatment and, in many cases, hospitalization, it also negatively impacts patient's quality of life; its complications represent substantial burdens on healthcare resources due to disability and its physical implications [6].

Lymphedema is a chronic-progressive disease that produces rich protein edema, caused by the obstruction of lymph vessels, lymph nodes, or by lymphatic function disorders [7]. It may occur due to congenital malformations of the lymphatic and venous system, or secondary to different events that damage lymphatic structures, when the pathophysiology of advanced CVD and Chronic Venous Insufficiency (CVI) leads to lymphatic failure and damage. This is known as phlebolymphedema or lymphedema related to CVD [8]. The diagnosis of phlebolymphedema is considered once CVD of one or both legs has reached at least the clinical stage C3 which is the clinical equivalent to Secondary Lymphedema clinical stage II; several characteristics are present as stages progress, such as: increase of volume of lower limb or limbs, stasis dermatitis, lipodermatosclerosis, Kaposi-Stemmer sign, dactylitis, papillomatosis lymphatica, ulcers, lymphorrhea, lymphedema rubra, frequent infections [8-11].

The clinical and epidemiological data about patients with chronic venous disease and

phebolymphedema in Mexico is limited. A recent study reporting the clinical characteristics of 446 patients with lymphedema in Mexico found that 19.4% of them suffer phlebolymphedema or lymphedema related to CVD [12]. In the United States, it was reported a prevalence of 41% of phlebolymphedema among 440 patients with lymphedema, [13] which is a considerable amount and makes visible a problem to pay attention to.

Clinical guidelines of Mexican public health services barely suggest lymphedema management, it is only considered in the context of breast cancer processes [14], while CVD Mexican guidelines only contemplate lymphedema as a contraindication to surgery in CVI, without addressing any possible treatment or even mentioning any consideration about phlebolymphedema [15]. A similar absence of reports and awareness about lymphedema related to CVD or phlebolymphedema was identified in other recent studies in Mexico and Latin America; lymphedema related to CVD processes or phlebolymphedema remains neglected [14-16].

Thus, it was decided to explore the epidemiological and clinical features of this population.

The purpose of this study is to report on these features of patients with phlebolymphedema or CVD related lymphedema and its relationship with physical activity and disability.

2. MATERIALS AND METHODS

This study aims to obtain epidemiological and clinical information about Mexican lymphedema patients and its relationship with physical activity and referred disability, employing information collected via direct clinical interview and physical examinations, with previous written and verbal informed consent signed by patients or primary caregivers who agreed to share and grant the use of data in the study while keeping their privacy.

Between January 2021 and May 2022, 90 Mexican patients went to rehabilitation services due to phlebolymphedema. Each patient was assessed in the first instance by an angiologist that confirmed diagnosis of CVD clinically and with duplex ultrasound. The patients were clinically assessed and interviewed in Fi Fisioterapia Integral S.C., a private physiotherapy clinic that specializes in rehabilitation services for patients with lymphedema and vascular peripheral disorders.

The data was collected during clinical assessment appointments conducted by lymphedema specialized clinicians employing a datasheet file tool which included complete clinical history, physical characteristics, socio-demographic data, and physical functional status. A digital spreadsheet matrix was created employing all data and formatted to classify, and organize all the diverse items and information gathered, for a later statistical analysis.

For the selection of study participants, the inclusion criteria were that patients presented a confirmed diagnosis of CVD at any stage, with clinically stablished phlebolymphedema, patients with a previous diagnosis of non-cancer related lymphedema with confirmed late diagnosis of CVD, and patients with previous initial diagnosis of phlebolymphedema.

The exclusion criteria were those patients with any acute edema (less than 12 weeks) which its primary cause was cardiac, hepatic, nephrotic, pharmacological, orthostatic, and/or hormonal; lymphedema related to cancer treatment or tumor compression, primary lymphedema, syndromic lymphedema, complex vascular malformations or those with undetermined causes of lymphedema, and patients with any neurological and/or cognitive affectation that did not allow the gathering of information.

The following items were included in the clinical file datasheet and spreadsheet: sex, age, height, weight (measured at the clinic), body mass index, lymphedema clinical stage based on the American Venous Forum (C1-C6) [3,9], and International Society of Lymphology [7], affected segments, circumferential measures of segments, comorbidities history, surgery history, previous and ongoing treatments and their characteristics, pain (analogous visual scale employed), infection history, physical activity level based on total minutes per week and sessions per week classified according to the American College of Sport Medicine guidelines for each age group [17,18], self-reported disability for daily living activities caused by the clinical condition, occupation, and others for further studies. Specific questions for each item were made when the patient did not provide a clear answer.

2.1 Statistical Analysis

The statistical analysis was carried out using the SPSS version 25 software and GraphPad Prism 8; a descriptive analysis was completed using measures of central tendency for the variables of quantitative nature, and frequency distribution for the categorical variables.

The behavior of the variables was revealed through the Shapiro-Wilk statistic, which was used due to the statistical capability that this type of analysis has shown with large samples. Considering this, to determine the differences between the numerical variables and the categorical variables of study (referred disability), a mean difference analysis was carried out with a Student's T test for independent samples. Subsequently, to identify the effect of the gender, age, and severity of the disease on the study variable, a three-way analysis of variance was obtained with a Sidak comparison analysis.

Finally, to determine the association between the different study variables of a qualitative and dichotomous nature, the chi-square statistic was obtained along with the odds ratio to determine the intensity of the associations found. The statistical significance threshold for all statistical tests was set at $p < 0.05$. and a confidence of 95%.

3. RESULTS

A total of 90 out of 112 patients were included in the analysis, who fully met the inclusion criteria; 71% (64) were female and 29% (26) were male; with a mean age of 62.7 years old (± 30.5). According to the age distribution, 56% (50) of patients were elderly adults, while 44% (40) were under 65 years old.

As for their occupations, there is the following information: 46% (42) of patients only performed home chores, 12% (11) did office work, 6% (5) are health professionals, 12% (11) are retired, 11% (10) merchants, 10% (9) performed tasks that require physical effort and 2% (2) did not answer, 21% (19) reported a family background of CVD in first degree relatives, 18% (16) were active alcohol consumers and 15% (13) were active smokers.

The anatomical distribution was 32% (29) for a unilateral presentation of CVD, among these patients 51% (15) for the left leg and 49% (14) for the right leg. 68% (61) presented a bilateral pathology, although this was asymmetrical, with a mild tendency for the left leg 52% (32) to be in a more advanced stage than the right leg.

Anthropomorphic data showed a mean height of 162 cm and 88.5 kg weight. A mean BMI of 33.2 was found, having a distribution of 79.9% (77) of patients who ranged in overweight and obesity. The following distribution of BMI was found: 1.1% (1) in <18.5 BMI or low weight; 21.1% (10) 18.5–24.9 BMI in normal weight range; 26.6% (24) 25-29.9 in overweight range; 53.3% (48) >30 BMI in obesity range; 7.7% (7) were unable to evaluate due to clinical difficulties during assessments such as extreme mobility limitation to measure weight and/or height Table 1.

The general distribution of phlebolymphedema clinical staging is as follows: 8% (7) of patients in stage I, 79% (1) in stage II, 13% (12) in stage III; while CVD staging is as follows: for C1 was 1% (1), C2 1% (1), C3 70% (63), C4 9% (8), C5 7% (6), C6 12% (11).

Table 1. BMI and comorbidities report

BMI	**% Patients**
Low weight (-18.5)	1.1% (1)
Normal (18.5-24.9)	21.1% (10)
Overweight (25-29.9)	26.6% (24)
Obesity (30)	48% (48)
Not Reported	7.7% (7)
Number of comorbidities	**% Patients**
Without comorbidities	27% (25)
Between 1 and 2 comorbidities	38% (34)
Between 3 and 4 comorbidities	28% (25)
More than 4 comorbidities	7% (6)

27% (25) of the patients did not present comorbidities and 38% (34) presented between one and two comorbidities; 35% (31) of patients had at least three or more comorbidities Table 1.

Comorbidities distribution is as follows: 66% (60) cardiac disease, 13% (12) nephrotic disease, 9% (8) hepatic disease, 9% (8) autoimmune disease, 11% gastric disease, 7% (6) neurologic disease, 11% (10) psychiatric disease, 13% (12) lung disease, 3% (3) hematological disease, 24% (22) diabetes, 47% (42) arterial hypertension. 19% (17) of patients had an active ulcer or an antecedent in the affected limb.

Previous events of regional or local infection such a bacterial cellulitis, lymphangitis and/or dermatolymphangioadenitis in the affected limb was reported by 30% (27) of patients. A 29% (26) of patients had a record of previous thrombotic events in any of the affected limbs. 30% (27) suffered a history of trauma in the limb such as: traumatological injury, vascular surgery, or trauma surgery. Among the participants, 50% (45) reported pain experience in the affected limbs, all patients referred that the pain was causally related to the evolution of their leg's clinical condition.

50% (45) of patients reported disability to perform one or more daily life activities related to the disease's condition (signs, symptoms, volume); difficulties to perform daily tasks and chores were referred, some of them like moving the limb, wearing clothes, independent personal care, walking, using stairs, working, getting up from a chair or a bed, changing position, participating in social and family activities, lifting objects, exercising.

Concerning physical activity, patients' activity level and exercise habits were classified into 3 groups, these are: below minimum, minimum, and above the minimum physical activity recommended for their age group.

The recommendations were taken from American College of Sports Medicine (ACSM), 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity activity, or an equivalent combination, and muscle-strengthening activities at least 2 days/week for each major muscle group [17,18].

Only 12% (10) of all patients performed at or above the minimum physical activity recommended for their population group, 88% (80) of patients had no physical activity or performed under the proper population group's recommendation. The rest were unable to be classified or did not answer. The distribution of activity level by stage is shown in Table 2.

Table 3 shows the behavior of different analysis variables with the disability reported by the participants of the study. Regarding sex, even though 55.6% of the people who reported having a disability are women, this variable does not present any type of relationship or risk factor for the study. It was found that the practice of physical activity, and the amount of compromised segments obtained contrasted statistics for Chi square, *p value <0,05; while the stage of the pathology, the presence of cardiological and metabolic antecedents present a statistically significant association with disability.

Regarding physical activity, it is observed that inactivity or minimal practice of physical activity is a risk factor with the referred disability ($p<0.05$), since it is prolonged that the non-practice of physical activity has a probability of 2.3 times more risk of presenting disability compared to people who refer doing physical activity. The presence of a cardiological and metabolic history is related to an approximate increased risk of 1.5 and 1.8 times respectively of presenting disability compared with patients who do not have these comorbidities.

Table 2. Activity level distribution by clinical stage

Clinical Stage	Above recommended	Recommended	Below recommended or no physical activity
C1			
C2		100% (1)	
C3	3.1% (2)	9.5% (6)	85.7% (54)
C4		12.5% (1)	84.5% (7)
C5			100% (6)
C6			100% (1)

Table 3. Association with referred disability

		Referred disability		
		Yes	No	P (OR)
		%	%	
Sex	Male	38,5	61,5	0,142
	Female	55,6	44,4	
Physical activity	Inactive	57,1	42,9	0,000*
	Active	0	100	(2,33)
Afected segment	Bilateral	86,4	52,2	0,000*
	Unilateral	13,6	47,8	(5,80)
Clinical Stage	Stage I	42,9	57,1	0,029*
	Stage II	44,9	55,1	(16,0)
	Stage III	84,6	15,4	
Cardiac disease	Yes	66,7	33,3	0,045*
	No	43,5	56,5	(1,53)
Diabetes	Yes	72,7	27,3	0,017*
	No	43,3	56,7	(1,68)

Table 4. Student's T independent samples

	Referred disability		P value
	Yes	No	
	Mean (SD)	Mean (SD)	
Age (years)	66,8 (15,3)	58,6 (18,5)	0,047*
Height (cm)	161,7 (9,5)	162,5 (10,08)	0,584
Weight (kg)	89,69 (31,02)	87,5 (23,3)	0,925
BMI	33,6 (10,04)	32,85 (8,25)	0,845

cm: centimeters, kg: kilograms, BMI: body mass index; SD: standard deviation

Table 4 shows the behavior of age, height, weight, and BMI between patients with and without disabilities; it is possible to notice that there is a high prevalence of obesity in the entire participating population evaluated from the BMI, however, the BMI, weight and height did not show differences between subjects with and without disabilities. In contrast with the above, the only variable that presents statistically significant evidence is age (p=0.047), highlighting that people who report disability are older on average compared to those who do not report it.

While performing the analysis of proportions, it was found that there is a significant statistical difference related to the amount of physical activity. The performance of physical activity translates into a lower score in CEAP.

Considering the previous analysis and with the aim of identifying whether age, sex, and the presence or absence of disability influenced the severity of the disease (CEAP), a three-way analysis of variance was performed, which is shown in Fig. 1.

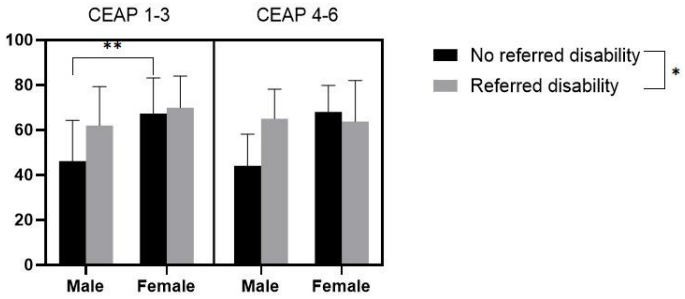

Fig. 1. Three-way analysis of variance, vertical axis being age

Table 5. Odds ratio for referred disability in relation to risk factors

		Referred disability			
		Yes	No	P value	Odds Ratio (CI 95%)
		%	%		
Sex	Male	38,5	61,5	0,142	0,68 (0,275 – 1,72)
	Female	55,6	44,4		
Physical activity	Inactive	57,1	42,9	0,000* (2,33)	2,33 (1,22 – 4,64)
	Active	0	100		
Afected segment	Bilateral	86,4	52,2	0,000* (5,80)	5,80 (2,05 – 16,38)
	Unilateral	13,6	47,8		
Clinical Stage	Stage I	42,9	57,1	0,029* (16,0)	16,0 (1,97 – 129,90)
	Stage II	44,9	55,1		
	Stage III	84,6	15,4		
Cardiac disease	Si	66,7	33,3	0,045* (1,53)	1,53 (0,95 – 3,01)
	No	43,5	56,5		
Diabetes	Si	72,7	27,3	0,017* (1,68)	1,68 (1,15 – 2,44)
	No	43,3	56,7		

In general, a higher proportion of older women is observed, compared to men in the two categories of analysis (CEAP 1 - 3 and CEAP 4 - 6), these differences being statistically significant (p=0.02); equally, an older age is correlated to disability regardless of the CEAP stage in people with disabilities compared to those who do not report a disability.

Regarding the BMI, the only differences were observed in the level of severity of the disease, regardless of the presence of disability (p=0.006); evidencing that the greater the severity, the higher the BMI in both men and women.

A set of 5 relevant risk factors was identified (p <0,05), with 95% odds ratio among all the items in relation to referred disability, in which being inactive shows 233% more risk to develop disability in this patient's population; 580% for those who present bilateral phlebolymphedema; 160% of those with lymphedema (ISL classification system) in the late-stage, 153% for those with cardiac disease, and 168% for those with a diagnostic of diabetes. A significant statistical difference among sex as a risk factor was not found.

4. DISCUSSION

This data allows a preliminary better understanding of CVD and phlebolymphedema's clinical features and its relations with disability and physical activity level, in a context of absence of this type of studies within the literature; it is to be noted that during the research we were unable to find information related to broad clinical analysis of phlebolymphedema and its relation to variables analyzed in this study. This information may guide not only a better integral understanding of the disease, but also extract key elements to aim for better treatments, improve clinical approaches or the development of clinical guidelines.

Due to the fact that CVD, and its presentation as phlebolymphedema, is a highly prevalent disease, greater samples are possible to be analyzed. Unfortunately, it becomes challenging to do it when it comes to identify and diagnose phlebolymphedema as a concrete clinical entity due to its under-recognisement.

The female-male distribution (71%-29%) is something to pay attention to, as well as to the fact that around 90% live a life of low physical demand; this pathology affects and causes disability to adults who are still in a productive stage of their life (almost a half of the patients), but in conditions that might make us wonder the quality of life they have considering that the mean BMI was in the range of established obesity, and that more than 50% had two or more comorbidities, have a sedentary lifestyle and half of them referred disability to perform daily life activities. Therefore, sociodemographical factors must be deeply investigated, especially those that influence the lifestyle of this population and that seem to determine the risk and prognosis of the disease, as well as the associated quality of life once the pathology is established. Simultaneously, to develop integral healthcare practices, it should

be considered to assess the socioeconomic level that could be conditioning these variables [19-22].

This study brings out relevant information about phlebolymphedema and critical points to be taken in count when it comes to develop possible treatment strategies that require not only treatment of the disease locally but integrally in its complexity; especially considering the axis of correlations among BMI, physical activity level, disability, number of comorbidities, and clinical stage; where could be found and intimate correlation to worsening the pathology through solid statistical analysis.

A set of questions arise. What in this axis came first? What is conditioning each other? What is the priority to address with to succeed in the management of this disease? We hypothesize that factors like physical activity level, disability and BMI are both risk factors that detonate the worsening or development of phlebolymphedema, it may also be a consequence of CVD given the two-way relationship among this axis.

5. CONCLUSION

This study reports clinical features of phlebolymphedema and its relationship with physical activity and disability of 90 Mexican patients. Further studies are needed to increase and broaden the awareness of the clinical characteristics of phlebolymphedema and its correlations, to improve understanding of the disease and its possible treatment.

DATA ACCESS

Data is available under reasonable request.

CONSENT

As per international standards or university standards, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards, written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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