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C Subclinical systemic lymphedema caused by increased BMI in patients with lower limb lymphedema

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Abstract

Lymphedema is a clinical condition that results from the buildup of macromolecules in the interstitial space leading to an accumulation of fluids. The objective of the present study is to correlate intracellular and extracellular fluid variations by comparing patients with lymphedema and different body mass indexes (BMIs): between 25 and 30, between 31 and 37 and greater than 37. Sixty consecutive medical records of patients with stage III lymphedema (elephantiasis) of the legs treated were evaluated in a cross-sectional study. The only inclusion criteria were clinical stage III lymphedema of the lower limbs and BMI greater than 25. Patients were evaluated by bioimpedance (InBody S10) to measure the intracellular and extracellular fluid content. Patients were divided into three groups depending on their BMI (25-30, 31-37 and >37). Fisher's exact test was used for statistical analysis with an alpha error of 5% (p-value < 0.05) being considered statistically significant. Significant abnormal increases (the difference between the actual and expected values) were found for both extracellular and intracellular fluids dependent on the increase of BMI. Obesity and its progression are associated with greater retention of intracellular and extracellular fluid, confirming the changes to the lymphatic system observed in animal studies. This aspect produces a specific type of subclinical systemic lymphedema involving body edema.

Keywords: Lymphedema, body mass index, bioimpedance, intracellular fluid, extracellular fluid

Introduction

Lymphedema is a clinical condition that results from the buildup of macromolecules in the interstitial space leading to an accumulation of fluids. It is associated with primary and secondary alterations of the lymphatic system. In primary lymphedema, the patient is born with some alteration of the lymphatic system and in secondary lymphedema, the patient acquires alterations during their lifetime. [1,2]

Diagnosis is based on the clinical history and physical examination however when there is diagnostic uncertainty, complementary exams should be requested. Of the available exams, lymphoscintigraphy provides a functional and anatomical evaluation of the lymphatic system, but evaluations, such as water volumetry, limb circumference measurements and bioelectrical impedance analysis, are necessary to confirm the condition of clinical lymphedema.[2,3]

In recent years, an important link has been identified between obesity, changes in the lymphatic system and inflammatory processes. Moreover, changes in immune response associated with obesity have been reported in animal studies. [4-10] Obesity results in perilymphatic inducible nitric oxide synthase (iNOS) expression and accumulations of T cells and macrophages and it inhibits cutaneous lymphatic collecting vessel pumping.[4] One study showed a perilymphatic inflammatory process, fluid accumulation between lymphatic endothelial cells and negative modulation of Vascular endothelial growth factor receptor-3 (VEGFR-3). [5]

In an animal study, aerobic exercise was correlated to decreased pericapillary inflammation and improvement of existing lymphatic insufficiency. [6]

Study demonstrated that the use of iNOS resulted in the inhibition of T cell differentiation, increased lymphatic vessel density and decreased iNOS expression with increased lymphatic pumping that restored flow. [7]

Obesity reduces the migration of dendritic cells to lymph nodes as well as significantly decreasing T cells and increasing B cells in lymph nodes. [8]

By assessing the number of vessel contractions after mechanical stimulation in patients who had gained weight on a high fat diet, Blum et al. reported a decrease in lymphatic function. [9]

Diets with fatty acids cause hyperpermeability of lymphatic capillaries and blood vessels and hypertrophy of adipocytes.[10]

A combination of therapeutic techniques is recommended for the treatment of lymphedema, as the result is quicker. However, isolated therapies can be indicated depending on the needs of each patient. An intensive outpatient regimen has been described that can reduce the edema volume by around 50% within five days.[2] Of particular note are therapies that include manual and mechanical lymph drainage, compression mechanisms, and myolymphokinetic exercises and activities.[11-13]

Bioelectrical impedance analysis is a exam used to evaluate body composition and nutritional status by assessing the impedance, reactance and phase angle.[14-16]

On evaluating patients with lymphedema using bioimpedance, some subjects presented increases in intracellular and extracellular fluids compared to the normal pattern. Further investigations by the authors found that morbidly obese patients had greater changes in body fluids. The objective of the present study is to correlate intracellular and extracellular fluid variations by comparing patients with lymphedema and different body mass indexes (BMIs): between 25 and 30, between 31 and 37 and greater than 37.

Methods

Patients

Sixty consecutive medical records of patients with stage III lymphedema (elephantiasis) of the legs treated at the Clinica Godoy in São Jose do Rio Preto in 2015 and 2016 were evaluated in a cross-sectional study. The only inclusion criteria were clinical stage III lymphedema of the lower limbs independent of the cause (primary or secondary) and BMI greater than 25. Patients with associated morbidities such as cardiac and renal disease, and hypoproteinemia, all of which might be the cause of lymphedema were excluded.

Lymphedema was diagnosed considering the patient's clinical history and by a physical examination. Patients were evaluated by bioimpedance (InBody S10) to measure the intracellular and extracellular fluid content. This device apart from measuring the actual fluid levels provides the expected levels of both intracellular and extracellular fluid for each patient. Patients were divided into three groups depending on their BMI (25-30, 31-37 and >37).

This study was approved by the Research Ethics Committee of the Medical School in Sao Jose do Rio Preto (FAMERP).

Statistical analysis

Fisher's exact test was used for statistical analysis with an alpha error of 5% (p-value < 0.05) being considered statistically significant.

Results

Sixty (45 female and 15 male) patients with ages ranging from 21 to 72 years (mean age: 48.2 years) were analyzed. Of these 15 patients had BMIs between 25 and 30, 25 patients had BMIs from 31 to 37 and 20 patients had BMIs above 37 (Tables 1, 2 and 3).

Table 4 shows the statistical analysis using Fisher's exact test. Significant abnormal increases (the difference between the actual and expected values) were found for both extracellular and intracellular fluids dependent on the increase of BMI. In particular, intracellular fluid levels were higher in patients with BMIs above 37 than in subjects with BMIs between 31 and 37.

Table 1 - Age, body weight, and extracellular and intracellular fluids of patients with BMIs from 25 to 30

			Extracellular fluid		Intracellular fluid	
Age	**Weight**	**BMI**	**Actual**	**Expected**	**Actual**	**Expected**
27	74.2	28.6	12.8	13.2	21.8	21.6
56	76.6	27.2	13.1	14.0	21.1	22.9
64	68.5	27.1	11.9	12.9	18.5	21.0
37	82.5	27.2	17.4	17.4	28.4	28.4
63	70.5	26.9	13.3	13.3	20.2	21.8
71	67.4	28.4	13.4	12.1	17.8	19.7
42	66.0	27.1	14.5	12.4	20.3	20.2
23	80.9	26.7	17.2	17.4	25.1	28.4
35	72.4	28.1	14.4	13.1	20.4	21.3
67	71.2	30.0	11.6	12.1	16.7	19.7
38	83.2	26.3	20.4	15.8	28.6	25.9
40	68.1	27.6	13.2	12.5	19.1	20.5
69	79.4	30.0	14.1	13	20.6	21.2
49	78.3	27.7	12.8	14.4	19.9	23.4
25	88.5	29.1	16.8	17.5	26.3	28.5

Table 2 - Age, body weight, and extracellular and intracellular fluids of patients with BMIs from 31 to 37

			Extracellular fluid		Intracellular fluid	
Age	**Weight**	**BMI**	**Actual**	**Expected**	**Actual**	**Expected**
36	84.2	34.2	12.2	12.5	20.2	20.5
43	118.9	35.9	26.9	19.0	37.3	31.0
37	117.7	36.7	20.0	16.3	30.4	26.6
66	87.2	31.6	16.0	15.8	25.5	25.9
46	108.4	33.1	22.8	18.8	33.6	30.7
31	83.7	31.9	15.7	13.3	22.1	21.8
65	80.9	34.6	12.0	11.9	17.2	19.5
46	80.8	32.4	15.2	12.6	21.1	20.7
69	79.4	31.0	14.1	12.5	20.6	21.8
65	130.5	36.1	27.1	20.8	39.7	33.9
78	76.3	34.8	10.7	11.1	15.6	18.1

59	88.8	33.8	14.1	13.3	22.3	21.8
73	86.4	36.4	14.3	12.1	19.4	19.7
82	95.5	34.7	16.2	15.8	23.4	25.9
61	84.3	35.3	15.0	12.1	20.3	19.8
30	165.0	37.4	32.9	25.3	54.6	41.4
76	92.5	35.2	15.2	13.3	21.7	21.8
26	79.1	30.5	13.6	13.2	20.8	21.6
58	79.5	30.9	13.2	13.1	20.4	21.3
55	133.9	40.0	25.1	17.0	41.1	27.8
31	99.0	36.8	16.2	13.6	24.3	22.3
60	103.5	37.1	14.9	14.2	21.8	23.1
76	107.5	38.3	18.0	14.3	24.2	23.3
53	106.7	39.7	15.1	13.6	23.4	22.3
35	101.1	39.5	15.2	13.0	22.3	21.2

Table 3 - Age, body weight, and extracellular and intracellular fluids of patients with BMIs >37

			Extracellular fluid		**Intracellular fluid**	
Age	**Weight**	**BMI**	**Actual**	**Expected**	**Actual**	**Expected**
47	117.0	45.1	17.0	13.2	25.7	21.6
41	131.1	45.4	31.4	16.6	21.7	27.1
58	105.0	36.8	15.8	14.5	24.6	23.6
36	156.0	58.4	25.1	13.6	35.0	22.2
50	120.4	45.3	17.4	15.3	25.8	24.9
47	133.0	43.2	28.8	17.7	39.5	28.8
41	138.9	51.0	17.4	13.9	27.0	22.5
41	131.3	43.2	23.6	18.4	34.7	30.0
32	103.5	40.4	18.6	14.7	28.5	24.0
43	130.3	49.6	16.9	13.3	25.8	21.8
39	99.8	41.0	14.2	12.4	20.7	20.2
60	129.2	53.1	18.5	12.4	25.5	20.2
44	153.0	62.5	19.4	12.4	31.1	20.4
67	106.1	49.1	17.9	11.0	23.3	17.9
76	119.5	52.4	15.3	11.6	22.6	18.9
46	108.8	40.5	18.3	13.6	25.7	22.3
55	93.2	40.3	14.4	11.8	21.6	19.1
59	97.3	41.6	13.7	11.9	20.6	19.5
63	152.0	48.5	24.1	18.0	37.1	29.4
75	95.5	45.7	14.1	10.7	19.2	17.4

Table 4 - Comparisons of abnormalities of intracellular and extracellular fluid between different BMIs

Fluid location	**BMI Range**		**p-value***
extracellular	25-30	31-37	0.0007
extracellular	25-30	>37	0.0001
extracellular	31-37	>37	0.3
intracellular	25-30	31-37	0.054
intracellular	25-30	>37	0.0001
intracellular	31-37	>37	0.001

* Fisher exact test

Discussion

The present study shows correlations of intracellular and extracellular fluid accumulation in patients with clinical stage III leg lymphedema and obesity. Patients with BMIs greater than 30 present above normal intracellular and extracellular fluid levels. The higher the BMI, the greater the water retention with this leading to a clinical picture of subclinical systemic lymphedema.

In the literature, animal studies show that lymphatic and inflammatory involvement is correlated to obesity.[4-10] In these studies, obesity was associated with important changes that aggravate lymphedema such as changes in cell permeability, an inflammatory process, changes in the contractile mechanisms of lymphangions and immunological involvement.

On analyzing studies with animals, mechanical changes were observed in relation to the lymphatic pumping of lymphangions. The lymphangions function as micro-hearts and impairment of their functioning alone without any other lesions can cause lymphedema. Changes in permeability constitute another aggravating factor for lymphedema that further affects the volumes of interstitial fluid and lymph to be drained.

Changes in the immune response interfere with one of the main functions of the lymphatic system, making the patient susceptible to a greater number of infections including erysipelas that can further damage lymphatic vessels. [17]

The present study demonstrates that with an increase in the BMI there are increases in the accumulation of both intracellular and extracellular body fluid. Knowledge gained from animal studies with lymphatic system disorders may explain the therapeutic difficulties seen specifically in obese patients. These cases not only have lymphatic lesions of the limb related to the lymphedema, but they have general changes of intracellular and extracellular fluid drainage caused by obesity. These patients have a subclinical systemic lymphedema characterized by a systemic increase in body fluids as well as the clinical leg lymphedema; this combination may aggravate the lymphedema even further.

The pathophysiological explanation of this type of subclinical systemic lymphedema is alterations in lymphangion function, that is, changes in lymph pumping. This is combined with changes in capillary permeability that may be due to inflammatory processes. Studies in animals show that improvements in inflammation are associated with improvements of the lymphatic system suggesting that inflammatory processes interfere in capillary permeability.

The effect of the inflammatory process with alterations in capillary permeability causes greater fluid leakage into the interstitial space that in turn means a greater volume of fluid to be drained by lymphatic capillaries. This situation may cause dynamic insufficiency of the lymphatic system. This condition associated with impairment of lymphangion pumping exacerbates lymphatic insufficiency not only of the lymphedematous limb but also of the body as a whole, thereby increasing the difficulty to treat obese patients. Thus, this disorder combines a mechanical deficiency (contractions of lymphangions) and dynamics due to the increase in extracellular fluid and lymph flow in lymphatic vessels.

One aspect to be considered is that these cases have edema of the entire body and not just of the leg. This study demonstrates that what changed in these patients is the obesity, as the BMI increases, the body fluid overload increases.

Animal studies show that active exercises are associated with improvements of the lymphatic system, even if the animals do not lose weight. Thus, an important aspect regarding the treatment of lymphedema may involve physical activity such as exercising or even day-to-day occupational physical activities.

The main pathophysiological mechanism involved in lymphedema is the accumulation of macromolecules in the interstitial space which leads to the retention of fluids that also accumulate in the interstitial space. However, these findings show that intracellular fluids also increase leading to an accumulation.

In summary, this study shows that intracellular and extracellular fluid overload is associated with obesity. Animal studies suggest that the involvement of the lymphatic system is related to reduced drainage of extracellular and intracellular fluids due to impaired lymphangion pumping mechanisms, alterations in capillary permeability and immunological aspects.

Conclusion

Obesity and its progression are associated with greater retention of intracellular and extracellular fluid, confirming the changes to the lymphatic system observed in animal studies. This aspect produces a specific type of subclinical systemic lymphedema involving body edema.

Disclosure Statement

The authors certify that no have financial support and conflict interest. The authors confirmed participated in all phases of the study.

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