ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 09, pp.23041-23044, September, 2018

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

SUBCLINICAL SYSTEMIC LYMPHEDEMA MANIFESTING EARLY IN PATIENTS WITH CLINICAL LYMPHEDEMA

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ARTICLE INFO

Article History:
Received 20th June, 2018
Received in revised form
21st July, 2018
Accepted 06th August, 2018
Published online 30th September, 2018

Key Words:
Lymphedema,
Body mass index,
Bioimpedance.

ABSTRACT

Objective: The objective of the present study is to compare intracellular and extracellular fluid variations in patients with lymphedema and body mass indexes between 25 and 37 with a control group. **Subjects:** A cross-sectional study was carried out of 30 consecutive patients with grade III (elephantiasis) leg lymphedema and BMI between 25 and 37 treated at the Clinica Godoy in São Jose do Rio Preto-Brazil. Variations in intracellular and extracellular fluid were evaluated by bioelectrical impedance analysis. Diagnosis of lymphedema was made by the clinical history, physical examination, and measurement of intracellular and extracellular fluid levels. The unpaired t-test and Fisher's exact test were used for statistical analysis with an alpha error greater than 5% (p-value <0.05) being considered significant. **Results:** Obese patients with lymphedema have more intracellular and extracellular fluid compared to obese patients without lymphedema. **Conclusion:** Subclinical systemic lymphedema caused by obesity manifests earlier in patients with lymphedema and worsens with the progression of obesity.

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Citation: José Maria Pereira de Godoy and Henrique Jose Pereira de Godoy and Maria de Fatima Guerreiro Godoy, O.T. 2018. "Subclinical systemic lymphedema manifesting early in patients with clinical lymphedema", *International Journal of Development Research*, 8, (09), 23041-23044.

INTRODUCTION

Lymphedema is a clinical condition caused by failure of the lymphatic system. This leads to an accumulation of macromolecules in the interstitial space with consequential fluid retention. Lymphedema can be primary, where the patient is born with some alteration of the lymphatic system or secondary, when the patient acquires lesions during their lifetime (Lee, 2014 and Pereira De Godoy, 2012). The clinical history and physical examination may define the diagnosis, but when there is doubt, complementary tests should be performed. These tests include lymphoscintigraphy which gives a functional and anatomical evaluation of the lymphatic system, and volumetric evaluations, such as volumetry, limb circumference measurements and bioelectrical impedance analysis, which are necessary to confirm the condition of clinical lymphedema (Pereira De Godoy, 2012 and Pereira De Godoy, 2013). Obese patients have an increase in the number and size of fat tissue cells. Body mass index (BMI) is the parameter most often used to diagnose obesity in adults. It is calculated by dividing the weight of the individual by their height squared. This is the gold standard used by the World Health Organization (WHO) with normal weight being defined as a BMI between 18.5 and 24.9 (Nuttall, 2015). By evaluating impedance, reactance and phase angle, bioelectrical impedance analysis is a method of evaluating body composition and nutritional status (Gupta, 2004). Animal studies have shown that obesity is associated with changes in the pumping of the lymphatic system, inflammatory processes, changes in immune response and altered capillary permeability (Nitti, 2016; Torrisi, 2016 and Weitman, 2003). Studies have identified that

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increased obesity is associated with worsening edema in patients with Grade III leg lymphedema. Study characterize obesity as a novel cause of lower extremity lymphedema and body mass index (BMI) predicted the lymphoscintigram result, which was abnormal if the body mass index was greater than 60 kg/m and normal if it was less than 50 kg/m (Weitman, 2013; Greene, 2015 and Greene, 2016). A case report shows bilateral lymphoscintigraphic changes of lower limbs in an obese patient with a BMI above 80 and that did not normalize with weight loss and another report of upper limb (Greene, 2015 and Greene, 2013). Therefore, an evaluation of obesity in respect to lymphedema parameters is important to define whether obesity is a cause or an aggravating factor of lymphedema. The objective of the present study is to compare intracellular and extracellular fluid variations between patients with lymphedema and BMIs between 25 and 37 with a control group.

MATERIALS AND METHODS

Patients: Thirty patients with lower limb lymphedema treated at the Clinica Godoy in São Jose do Rio Preto in 2015 and 2016 were consecutively evaluated. Fifteen patients had BMIs between 25 and 29.9 and 15 had BMIs between 30 and 37. Two control groups were formed of patients without lymphedema: 15 people had BMIs between 25 and 29.9 and 15 subjects with BMIs between 30 and 37. Patients with grade III lower limb lymphedema and BMI between 25 and 37 were included in this study. Patients and controls with a BMI below 25 or BMI above 37 and subjects with associated morbidities such as cardiac and renal disease, and hypoproteinemia that may be the cause of lymphedema were excluded. The diagnosis of lymphedema was made by clinical history and physical examination. Intracellular and extracellular fluid levels were assessed by bioimpedance (InBody S10). The placement occurs at each right and left extremities, being upper limbs thumb and middle finger, lower limbs malleolus, in the dorsal decubitus position, rest 10 minutes before starting the evaluation, according to the parameters of the device. This device also calculates the normal (according to body weight, height, age) values of extracellular and intracellular fluid for each patient. The study was approved by the Research Ethics Committee of the Medical School in Sao Jose do Rio Preto (FAMERP), number 016433/2017.

Statistical analysis

Fisher's exact test and paired t-test was used for statistical analysis with alpha errors of 5% (p-value < 0.05) being considered statistically significant.

RESULTS

Tables 1, 2, 3 and 4 show the age, weight, intracellular and extracellular fluid levels and expected fluid levels for the Control Group with BMIs from 25-29.9, Control Group with BMIs from 31-37, Patient Group with BMIs from 25-29.9 and Patient Group with BMIs from 31-37, respectively. It was found that 13 of the 15 patients with lymphedema and only 1 of 15 of the Control Group had extracellular fluid above expected levels (Fisher's exact test: p-value = 0.0001). Furthermore, 6 of the 15 patients and only 1 of 15 of the control group had intracellular fluid levels higher than expected (Fisher's exact test: p-value = 0.004) (Table 5). Comparing intracellular fluid in subjects with and without lymphedema found higher intracellular fluid levels in the patients with lymphedema (paired t-test; p-value < 0.005).

Table 1. Age, weight, intracellular and extracellular fluid levels and normal fluid levels of the Control Group with BMIs from 25-29.9

		Intracellular Fluid		Extracellular Fluid	
Weight	BMI	Actual	Expected	Actual	Expected
70	26.3	20.6	22.0	12.1	13.5
61.7	27.4	15.2	18.7	10.3	11.4
68.5	29.6	17.2	19.1	10.5	11.8
66	28.9	16.6	18.9	10.9	11.6
62.1	25.5	20.2	20.2	12.4	12.4
58.5	27.1	16.4	17.9	10.2	11.0
64	26.6	16.5	19.9	10.1	12.2
68.3	27.0	20.6	21.0	12.2	12.9
76.9	26.1	20.6	24.4	12.9	15.0
76.4	27.4	21.3	26.2	12.9	16.1
70	26.7	28.6	21.8	15.5	13.3
51.5	25.5	15.2	16.7	9.2	10.2
62.9	26.2	17.3	19.9	10.9	12.2
59.5	27.9	16.5	17.7	10.1	10.9
70.7	28.7	18.7	20.5	11.6	12.5

Table 2. Age, weight, intracellular and extracellular fluid levels and normal fluid levels of the Control Group with BMIs from 31-37

			Intracellular Fluid		Extracellular Fluid	
Age	Weight	BMI	Actual	Expected	Actual	Expected
61	64.5	30.3	15.7	17.7	9.7	10.9
55	87.3	36.3	19.4	19.9	11.9	12.2
46	75.5	30.2	20.2	20.5	12.3	12.5
64	75.0	30.2	19.2	20.6	12.5	12.6
47	80.4	31.0	21.8	21.6	13.2	13.2
68	75.0	32.5	16.7	19.1	10.0	11.8
73	71.0	31.6	16.0	18.7	10.3	11.4
73	75.5	32.7	18.5	19.1	11.3	11.8
65	89.0	35.7	19.9	20.7	12.7	12.6
56	92.4	36.1	20.4	21.2	12.9	13.0
71	75.4	30.2	18.6	20.7	12.0	12.6
74	71.0	30.7	16.2	19.1	10.7	11.8
67	75.4	33.3	16.1	18.8	10.2	11.6
62	70.1	32.9	15.4	17.7	9.7	10.9
57	78.5	32.1	19.9	20.4	12.1	12.4

Table 3. Age, weight, intracellular and extracellular fluid levels and normal fluid levels of the Patient Group with BMIs from 25-29.9

			Intracellular Fluid		Extracellular 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	13.0	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

Moreover, higher extracellular fluid levels were found in patients (paired t-test; p-value < 0.005) (Table 6). There was no significant difference between the BMIs (paired t-test; p-value = 0.4) nor the ages (paired t-test; p-value = 0.1) comparing subjects with and without lymphedema. Patients

with lymphedema were heavier than those in the control group (paired t-test; p-value = 0.007).

Table 4. Age, weight, intracellular and extracellular fluid levels and normal fluid levels of the Patient Group with BMIs from 31-37

			Intracellular Fluid		Extracellular 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
76	92.5	35.2	15.2	13.3	21.7	21.8
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
58	79.5	30.9	13.2	13.1	20.4	21.3
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
58	79.5	30.9	13.2	13.1	20.4	21.3
82	95.5	34.7	16.2	15.8	23.4	25.9
26	79.1	30.5	13.6	13.2	20.8	21.6

Table 5. Patients with expected and abnormal intracellular and extracellular fluid levels in each of the BMI ranges

Group	Extracellular		Intracellular	
	Abnormal	Normal	Abnormal	Normal
Control - 25-29.9	1	14	1	14
Control - 31-36	1	14	1	14
Lymphedema -25-29.9	6	9	3	12
Lymphedema - 31-36	13	2	6	9

Table 6. Comparisons of intracellular and extracellular fluid levels between the different groups

Extracellular fluid		p-value*
25-29.9 - Control	31-37 - Control	0.99
25-29.9 - Control	25-29.9 - Lymphedema	0.04
25-29.9 - Control	31-37 - Lymphedema	0.0001
31-37 - Control	25-29.9 - Lymphedema	0.04
31-37 - Control	31-37 - Lymphedema	0.0001
25-29.9 - Lymphedema	31-37 - Lymphedema	0.01
Intracellular fluid		
25-29.9 - Control	31-37 - Control	0.99
25-29.9 - Control	25-29.9 - Lymphedema	0.3
25-29.9 - Control	31-37 - Lymphedema	0.04
31-37 - Control	25-29.9 - Lymphedema	0.3
31-37 - Control	31-37 - Lymphedema	0.04
25-29.9 - Lymphedema	31-37 - Lymphedema	0.2

*Fisher's exact test

DISCUSSION

The present study shows that patients with lymphedema and BMIs from 29.9-30 and from 29.9-37 have more intracellular and extracellular fluid than a control group of subjects without lymphedema. In the literature, no studies compare intracellular and extracellular fluid levels in respect to lymphedema. This study confirms findings from a previous study by the authors (in the publication phase) that shows that as the BMI increases there is an increase in intracellular and extracellular fluid in patients with lower limb lymphedema suggesting a subclinical systemic lymphedema. The doubt of this previous study was whether obesity was a cause of lymphedema or an aggravating factor in patients with elephantiasis regardless of the type (primary or secondary). The evaluation of this control group shows that obesity in isolation is not a cause of increases in intracellular and extracellular fluid levels in patients with BMIs between 25 and 37. In the early stages of obesity, that is, in patients with BMIs between 25 and 30, lymphedema is correlated with the development of a systemic subclinical lymphedema. This condition worsens with the progression of obesity. Not only the lower limb is affected, the body fluid content as a whole increases significantly with the progression of obesity. Thus, the presence of clinical lymphedema appears to contribute to the development of subclinical systemic lymphedema in obese patients. Studies show that obesity is associated with the development of lymphedema. The present study provides some possible explanations regarding the effect of obesity on lymphedema. The authors' observations suggest that obesity is a cause of subclinical systemic lymphedema because it causes generalized edema in the chest and extremities as it progresses. However, when there is an injury to the lymphatic system, the onset of subclinical systemic lymphedema is earlier. Another detail is the effect of gravitational pressure that leads to the appearance of clinical lymphedema of the lower limbs with the progression of the patient's age and obesity. Study shows that obesity can lead to changes in lymphoscintigraphy and that there is no regression with weight loss (Greene, 2015). In summary, the effect of obesity of patients with lymphedema leads to the earlier onset of subclinical systemic lymphedema. This new concept of lymphedema is, in principle, of a secondary cause but we need to evaluate the genetic factors that might contribute to this association. In this case, obesity aggravates lesions of the lymphatic system and may affect the therapeutic approach to clinical lymphedema.

Conclusion

The subclinical systemic lymphedema caused by obesity manifests earlier in patients with lymphedema and this condition worsens as the obesity progresses.

Conflict Interest

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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