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Impairment of Lymphatic Function in Women With Gynoid Adiposity and Swelling Syndrome

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The current study sought to investigate the factors, in particular anthropometric parameters, associated with an impairment of capillary permeability and lymphatic function in a large series of women complaining of a swelling syndrome. One hundred ninety-seven women with a swelling syndrome were investigated, 43 of whom were obese (body mass index [BMI] > 30 kg/m^2), 77 overweight (BMI = 25 to 30 kg/m^2). Thirty-five of the 197 women had abdominal adiposity (waist-to-hip ratio [WHR] > 0.85). Capillary filtration of albumin and lymphatic function were studied by means of an isotopic test using ^{99m}technetium-labeled albumin and venous compression. This test allowed measurement of interstitial albumin retention (AR) and the evaluation of lymphatic function by analyzing the radioactivity disappearance curve after removal of venous compression with the fast Fourier transform (low frequency/high frequency [LF/HF]). Body composition was studied by the bioelectrical impedance method. WHR correlated with fasting blood glucose (P = .03), serum triglyceride (P < .0001), and apoprotein B (P = .008) levels. AR was increased (≥8 %) in 117 women (59.4%) and LF/HF (≥1 %) in 149 cases (75.6%). Extracellular water (ECW) was increased (>107% of the theoretical value) in 144 cases (73.1%). LF/HF correlated negatively with age (P = .001), BMI (P = .006), WHR (P < .0001), and fat mass (P = .002). In the multivariate analysis taking age, BMI, and WHR as independent variables, LF/HF correlated significantly with WHR (P < .005). There was a trend to a higher prevalence of an increase in AR in the women with an increase in ECW (61.8 %) as compared with those without an increase in ECW (52.8%). We conclude that abdominal adiposity is associated with metabolic disorders secondary to insulin resistance as previously demonstrated, whereas lymphatic dysfunction is mainly associated with gynoid adiposity. Besides microcirculatory disorders, changes in the secretory regulation of hormones involved in salt and water retention are likely to play an important role in ECW excess.

OBESITY is sometimes complicated by lymphatic or venous disorders. Women who are or are not overweight often complain of swelling. We have recently demonstrated, using bioelectrical impedance analysis, that the swelling syndrome is indeed related to an increase in extracellular water (ECW).[1] The swelling sensation predominates in the lower limbs and is aggravated by orthostatism.[2] In overweight women a postural test consisting of walking around for 30 minutes induces a further increase in ECW.[1]

When venous insufficiency, or renal, hepatic, or cardiac disorders are not involved, we have previously shown by using an isotopic test with labeled albumin that the swelling syndrome appears to be related in most cases to an increase in capillary filtration of albumin and a defect in lymphatic pumps.[1,3-5]. Hormonal disorders are also likely to play an important role in the occurrence of edema. In particular, an enhancement of the renin-angiotensin-aldosterone system and an increase in the release of the antidiuretic hormone have been reported.[5-7] The regulation of antidiuretic hormone and atrial natriuretic peptide secretion is also impaired.[8]

The aim of the present study was to investigate the factors, in particular the anthropometric parameters and body composition, associated with an impairment of capillary permeability and lymphatic function in a large series of women complaining of a swelling syndrome, with or without obesity defined by body mass index (BMI) ≥ 30 kg/m^2.

SUBJECTS AND METHODS

Subjects

One hundred ninety-seven women with a swelling syndrome were investigated. All complained of swelling sensation predominating in

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Table 1. Clinical and Biological Parameters

	All Patients	WHR ≤ 0.85	WHR > 0.85
No. of subjects	197	162	35
Age (yr)	41.2 ± 0.9	39.6 ± 0.9	51.6 ± 1.7†
Body weight (kg)	71.1 ± 0.9	70.0 ± 1.0	82.5 ± 3.0†
BMI (kg/m^2)	22.3 ± 0.3	21.3 ± 0.8	26.8 ± 1.9*
WHR	0.77 ± 0.05	0.74 ± 0.01	0.91 ± 0.01
ECW (L)	15.2 ± 0.2	15.2 ± 0.2	16.9 ± 0.7†
FFM (kg)	49.7 ± 0.5	49.5 ± 0.6	53.9 ± 1.7
Fat mass (kg)	21.4 ± 0.5	20.5 ± 0.5	28.6 ± 1.4
Fasting blood glucose (mmol/L)	5.17 ± 0.14	5.11 ± 0.16	5.66 ± 0.27
Total cholesterol (mmol/L)	5.45 ± 0.08	5.44 ± 0.08	6.01 ± 0.18*
Triglycerides (mmol/L)	1.18 ± 0.04	0.95 ± 0.03	1.46 ± 0.11†
Apoprotein A_1 (g/L)	1.46 ± 0.03	1.46 ± 0.03	1.45 ± 0.07
Apoprotein B (g/L)	1.03 ± 0.02	1.00 ± 0.02	1.17 ± 0.04*
Proteins (g/L)	70.4 ± 0.3	70.4 ± 0.4	70.4 ± 0.9

P value: *< .01, †< .001 *v* patients with WHR ≤ 0.85.

the lower limbs with aggravation by orthostatism and warm temperature, pins and needles, and frequent increase in body weight by more than 2 kg from day to day and even from morning to evening. Edema was visible on the legs and ankles at the investigation time. They were aged 41.2 ± 0.9 (SEM) years. Forty-three of the women were obese (BMI > 30 kg/m^2) and 77 were overweight (BMI = 25 to 30 kg/m^2). Thirty-five of the 197 women had abdominal adiposity defined by a waist-to-hip ratio (WHR) greater than 0.85; the others with WHR ≤ 0.85 had gynoid adiposity. All were normotensive and none had clinical evidence of venous or lymphatic dysfunction. Electrocardiogram, blood cell counts, plasma proteins, creatinine, bilirubin, alkaline phosphatases and transaminases, and serum thyroid-stimulating hormone (TSH) were normal. None had proteinuria and none was diabetic according to the 1997 American Diabetes Association criteria (fasting blood glucose < 1.26 g/L).[9] All medications modifying diuresis and blood pressure and all vasodilative drugs or venous tropic agents were stopped at least 1 month before the study period. Diets included 100 mEq sodium per day for at least 1 month. The main clinical and metabolic parameters are shown in Table 1.

Methods

Isotopic test of capillary filtration of albumin and lymphatic function. The isotopic test was performed as previously described.[3,4,8,10] Briefly, it was performed on a woman at rest and seated with her arms maintained horizontally. It consisted of injecting 1 mL of human serum albumin labeled with 99m technetium (100 MBq/mL) into an antecubital vein and measuring the radioactivity externally at the forearm with a gammacamera. Ten minutes after the injection, venous compression (80 mm Hg) was exerted on one arm, inducing vascular stasis and therefore an increase in the radioactivity curve. Twelve minutes later, venous compression was removed, inducing a decrease in the radioactivity curve, which reached the basal level in 1 to 3 minutes in normal subjects. The initial decrease, during the first minute, was due to a rapid venous washout of labeled albumin associated with a rapid return of venous compliance to the basal state. The later decrease was mainly due to lymphatic uptake of interstitial albumin.[11]

Albumin retention (AR) was evaluated 10 minutes after the removal of venous compression by calculating the percentage: [(residual radioactivity at 10 min − basal radioactivity)/(maximal radioactivity − basal radioactivity)] × 100. Thus, AR is linked to capillary filtration of albumin and lymphatic function. The last part of the radioactivity disappearance curve recorded after removal of venous compression was also analyzed by the fast Fourier transform.[3,9,11] Four peaks of different frequencies, with amplitudes higher than the other harmonics, were identified. The ratio of the amplitude of low (LF: 2 and 3.2 mHz) and high (HF: 209 and 630 mHz) frequency peaks was calculated.

In a large series of control women with normal body weight and without swelling syndrome, we had found that AR was 0% in most cases and was always less than 8% and that the LF/HF ratio was never above 1%.[4] During the present study we investigated 16 healthy women; the mean ± SEM AR value was 0.5% ± 0.4% and LF/HF was 0.08% ± 0.21%. Therefore, AR was considered to be increased when it was ≥ 8%, and a LF/HF value ≥1% was considered abnormal.

Reproducibility of both AR and LF/HF indexes using labeled albumin was tested by performing 2 measurements on 10 healthy women with an interval of not more than 2 months between measurements. Both AR and LF/HF for the 2 tests correlated well ($P < .001$). Reproducibility was also checked with a 1-month interval in diabetic patients.[12] We also confirmed the reproducibility by performing the same procedure 1 hour after labeled-albumin injection and inducing a second venous compression for 12 minutes.

The LF/HF ratio is an index of lymphatic uptake of interstitial albumin and is not believed to reflect a phenomenon occurring in blood circulation. Indeed the same test performed with both indium 111–labeled albumin and technetium 99m–labeled erythrocytes has shown that LF/HF is always normal with erythrocytes, even when LF/HF is ≥1% with albumin.[3] In addition, we have recently investigated 10 women with an upper limb lymphostasis secondary to mastectomy and axillary lymph nodes curage for breast carcinoma, and 10 control women matched for age and body weight. The isotopic test with ^{99m}Tc-labeled albumin and a lymphoscintigraphy with colloid particles labeled with technetium 99m were performed on the same limb at a 3-day interval. In the patients with lymphostasis, LF/HF was markedly higher than in the control women (9.4% ± 2.3 % *v* 0.05% ± 0.01%), as well as the half-time of labeled colloid disappearance from the injection site (131 ± 18 minutes *v* 85 ± 5 minutes). In these patients, there was a perfect rank correlation (Spearman test: $r = 1.000$) between both parameters.

Assessment of body composition. Body composition was estimated by bioelectrical impedance analysis (BIA) using a double-frequency device, respectively 5 kHz and 1 MHz, and 4 subcutaneous electrodes (IMP-B01, Eugedia, Chambly, France). Electrodes were implanted on the dorsal side of hands and feet, allowing measurement of whole-body impedance. It has been shown that HF and LF currents predict total body water and ECW, respectively.[13-16] Measurements were determined after 30 minutes in a recumbent position, 2 to 3 hours after breakfast, after emptying the bladder. Reproducibility of ECW measured with this device was evaluated in 36 women by performing a second measurement after 30 additional minutes in the recumbent position. The coefficient of variation was 2.65% ± 0.09% (mean ± SEM).

Fat free mass (FFM) was derived from total-body water by assuming that FFM has a hydration constant of 0.73 (FFM = total body water/0.73). Fat mass was obtained by the difference between body weight and FFM.

Statistical analyses. Data are shown as mean ± SEM values. Comparisons were performed by Student's *t* tests. Linear correlations were calculated between 2 sets of quantitative data, and chi-square tests were used in comparisons between qualitative parameters. Multivariate analyses were performed. Statistical analyses were performed with the SPSS package (SPSS Inc, Chicago, IL) on a Hewlett-Packard computer (Palo Alto, CA).

RESULTS

Anthropometric Parameters

WHR correlated with age ($r = 0.407$, $P < .0001$), body weight ($r = 0.382$, $P < .0001$), BMI ($r = 0.454$, $P < .0001$),

Table 2. Anthropometric Parameters, Body Composition, and Biological Parameters in Patients With an Abnormal (≥ 1%) or a Normal (< 1%) LF/HF Index

	LH/HF	
	<1%	≥1%
No. of subjects	48	149
Age (yr)	43.7 ± 1.7	40.3 ± 1.0‡
Body weight (kg)	73.6 ± 1.9	70.2 ± 1.1
BMI (kg/m^2)	27.9 ± 0.7	26.2 ± 0.4*
WHR	0.80 ± 0.01	0.76 ± 0.01‡
Thigh circumferences (cm)		
10 cm above the patella	47.1 ± 0.8§	46.5 ± 0.5¶
20 cm above the patella	55.7 ± 0.9§	55.2 ± 0.6¶
ECW (L)	15.2 ± 0.3	15.2 ± 0.2
ECW (% of theoretical value)	113.2 ± 2.0	115.6 ± 1.3
FFM (kg)	50.1 ± 1.0	49.5 ± 0.6
Fat mass (kg)	23.5 ± 1.1	20.7 ± 0.6†
Fasting blood glucose (mmol/L)	5.29 ± 0.16	5.15 ± 0.18
Total cholesterol (mmol/L)	5.41 ± 0.13	5.47 ± 0.10
Triglycerides (mmol/L)	1.19 ± 0.07	1.17 ± 0.04
Apoprotein A_1 (g/L)	1.45 ± 0.53	1.47 ± 0.03
Apoprotein B (g/L)	1.02 ± 0.04	1.03 ± 0.03
Proteins (g/L)	69.7 ± 0.8	70.7 ± 0.4

P value : *< .02, †< .01, ‡< .001 *v* patients with LF/HF < 1%. §,¶data for §37 and ¶112 patients, respectively.

fat mass ($r = 0.489$, $P < .0001$), and FFM ($r = 0.204$, $P = .004$). Regarding biochemical parameters, WHR correlated with fasting blood glucose ($r = 0.157$, $P = .03$), serum triglycerides ($r = 0.400$, $P < .0001$), and apoprotein B ($r = 0.196$, $P = .008$) (Table 1).

Isotopic Test

The AR index was abnormal (≥8%) in 117 women (59.4%). The LF/HF index was abnormal (≥1%) in 149 cases (75.6%). The biochemical parameters did not differ significantly in the patients with normal or abnormal AR or LF/HF indexes (Table 2).

Extracellular Water

Compared with the theoretical value given for height, body weight, and age, ECW was considered to be increased when it was higher than 107% of the theoretical value. Such was the case in 144 cases (73.1%), and the highest value of the measured ECW/theoretical ECW ratio was 156%. ECW correlated with age ($r = 0.152$, $P = .035$) and BMI ($r = 0.228$, $P = .002$). Controlling for age, ECW correlated significantly with BMI ($r = 0.202$, $P = 0.005$).

Correlation Between the Isotopic Parameters and Anthropometric Parameters and Body Composition

There was no significant correlation between AR and any of the anthropometric parameters. The prevalence of an AR increase did not differ significantly in the obese women (51.2%) and the non-obese women (61.3%), or in those with WHR greater than 0.85 (62.8%) or ≤0.85 (58.6%) (Table 3). There was a trend to a higher prevalence of an increase in AR in the women with an increase in ECW (61.8%) as compared with those without an increase in ECW (52.8%) (Table 3).

LF/HF correlated negatively with age ($r = -0.221$, $P = .001$), BMI ($r = -0.182$, $P = .006$), WHR ($r = -0.311$, $P < .0001$) (Fig 1), and fat mass ($r = -0.222$, $P = .002$) (Fig 2). WHR was significantly lower in the women with LF/HF ≥ 1% than in those with LF/HF less than 1% (Table 2). Thigh circumferences 10 and 20 cm above the upper rim of patella were measured on the dominant side and were similar in the women with LF/HF less than 1% or ≥1% (Table 2). There was a trend to a lower prevalence of an increase in LF/HF index in the obese group (65.1%) than in the non-obese group (78.6%) ($P = .06$) and in the women with WHR greater than 0.85 (65.7%) than in those with WHR ≤ 0.85 (77.8%) ($P = .10$) (Table 3). LF/HF was significantly higher in the women with WHR ≤ 0.85 than in those with WHR greater than 0.85: 10.1% ± 0.8% versus 4.8% ± 0.9%, $P < .005$ (Table 1). The proportion of women with an increase in ECW (>107% of the theoretical value) was similar in the patients with an increase in LF/HF and in those with a normal LF/HF level (Table 3).

In the multivariate analysis, with the LF/HF index as a dependent variable and age, BMI, and WHR as independent variables, LF/HF correlated significantly and independently with WHR ($P < .005$). Controlling for age, BMI, and fat mass, LF/HF correlated significantly with WHR ($r = -0.199$, $P = .003$).

DISCUSSION

Obesity is associated with expanded circulatory volume and an increased extracellular to intracellular fluid ratio.[17] An enhanced body sodium content has been reported in obese subjects.[18] Bioelectrical impedance was used in the present study to measure ECW in overweight or lean women with a swelling syndrome. This method has been validated after comparing it with deuterium and bromide-dilution techniques.[19] Under standardized conditions, the within-subject reproducibility of ECW measurement is good, as previously reported by other investigators.[14,17,20] ECW was found here to be increased in more than 70% of the women with a swelling syndrome, a proportion similar to the one we have recently reported.[1] Moreover, orthostasis may increase ECW and account for the aggravation of

Table 3. Percentages of Patients With an Increase in AR (≥ 8%) and LF/HF (≥ 1%) Indexes According to BMI, WHR, and ECW

	BMI		WHR		ECW	
	≤ 30 kg/m^2	>30 kg/m^2	≤0.85	>0.85	≤107%	>107%
No. of subjects	154	43	162	35	53	144
AR ≥ 8%	95 (61.3%)	22 (51.2%)	95 (58.6%)	22 (62.8%)	28 (52.8%)	89 (61.8%)
LF/HF ≥ 1%	121 (78.6%)	28 (65.1%)	126 (77.8%)	23 (65.7%)	38 (71.7%)	111 (77.1%)

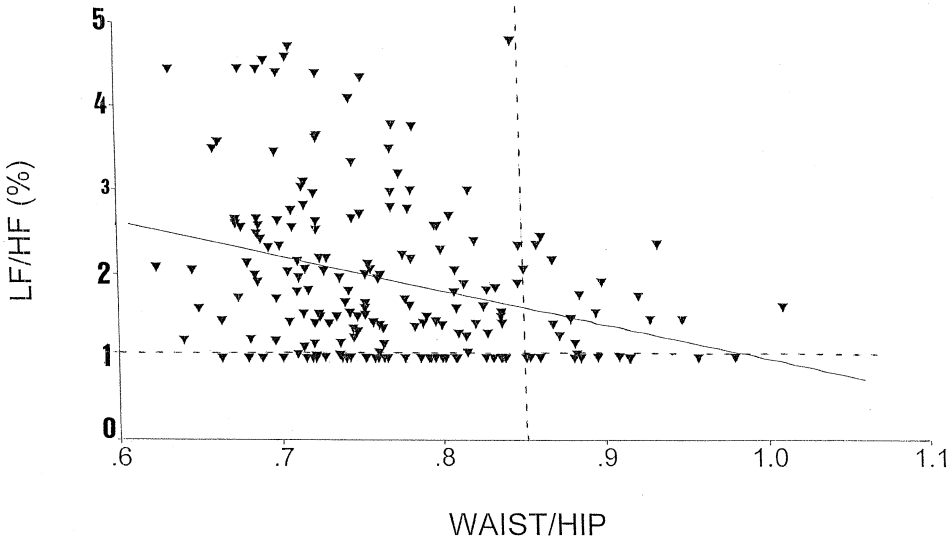

Fig 1. Correlation between lymphatic dysfunction evaluated by the LF/HF index and WHR.

the swelling sensation in the upright position as previously shown.[1]

Mechanisms of ECW Increase

The increase in ECW is very likely to be a consequence of an increase in capillary filtration of albumin and a defect in lymphatic function. However, the weak correlation between ECW and the microcirculatory disorders evaluated by the isotopic test with labeled albumin suggests that ECW might be a poor indicator of the lower limb water excess. The thigh circumferences were similar in the patients with LF/HF less than 1% or $\geq$ 1%, despite significantly lower BMI in those with LF/HF $\geq$ 1%. This is consistent with higher lower limb water in the latter. Methods based on the determination of local impedance might be useful in identifying the excess in lower limb water. However, various hormonal disorders may play an important role in the increase in ECW both in the recumbent and the upright position,[5-8] including an enhancement of the renin-angiotensin-aldosterone system, an increase in antidiuretic hormone release, and a decrease in atrial natriuretic peptide secretion or activity.[5-8] At least these disorders need to be present with microcirculatory disorders to make the swelling syndrome and the increase in ECW manifest.

Mechanisms of Lymphatic Dysfunction: Role of Gynoid Adiposity

In this series of women complaining of a swelling syndrome, the isotopic test using labeled albumin provided evidence of an increase in interstitial albumin retention in 59.4% of the cases. The rate of a clear-cut increase in the LF/HF ratio, which accounts for a decrease in lymphatic uptake of interstitial albumin, was higher (75.6%). Therefore, lymphatic dysfunction is likely to result from an increase in albumin and water transcapillary leakage and a saturation of lymphatic pumps.

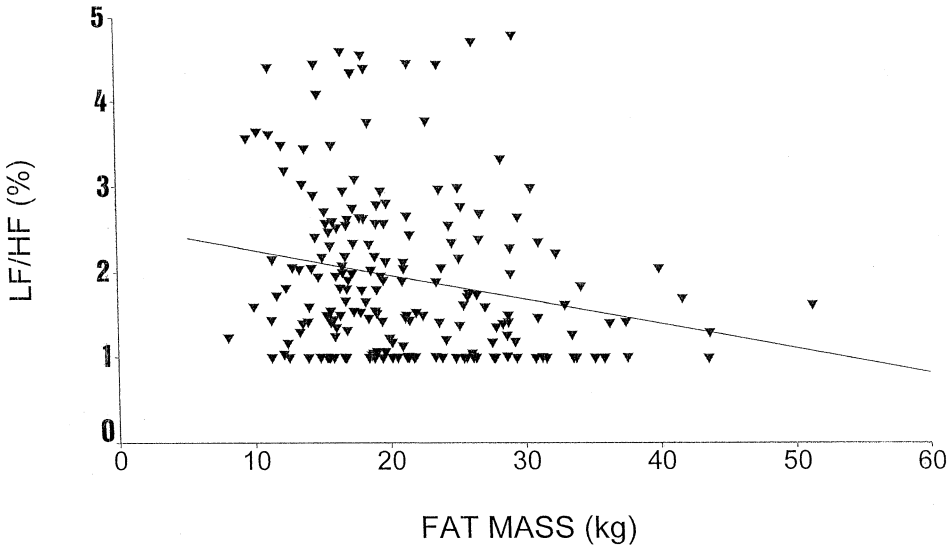

Fig 2. Correlation between lymphatic dysfunction evaluated by the LF/HF index and fat mass (impedancemetry).

Interstitial AR occurs presumably as a consequence of lymphatic dysfunction. The mechanisms leading to an increase in albumin and water transcapillary leakage may result from an increase in capillary flow and capillary pressure. We have previously shown that peripheral vasoconstriction induced by maneuvers that activate the sympathetic nervous system is reduced in obese subjects.[21] This disorder may be involved in the increase of capillary blood flow and may thus be a contributive factor to the increase in capillary permeability.

Lymphatic dysfunction seems to be reduced with increasing age, BMI, and fat mass. On the contrary, it is more severe in the women with lower levels of WHR. Moreover, in the multivariate analysis the significant negative correlation between LF/HF and WHR indicates that lymphatic dysfunction is mainly influenced by the gynoid type of adiposity, independently of age, BMI, and fat mass. This association suggests that lymphatic dysfunction may be a consequence of an excess in crural adiposity, leading to an increase in venous and capillary pressure and capillary filtration and a reduction in lymph return. But the association between lymphatic dysfunction and crural adiposity is also consistent with the deleterious effect of a defect in lymph circulation on triglyceride return to blood flow, inducing an accumulation of triglycerides in crural adipocytes.

However, the android type of adiposity characterized by higher WHR levels correlated with higher values of fasting blood glucose and triglycerides, probably as a consequence of insulin resistance. Thus the present data confirm what many other previous reports have shown: the association between abdominal obesity and metabolic disorders.[22,23]

In conclusion, the present study confirms that the subjective swelling sensation in both overweight and lean women is related to an increase in ECW. While the metabolic disorders associated with insulin resistance are well-demonstrated complications of android adiposity, the present data show clearly that the gynoid type of adiposity is associated with a more severe lymphatic dysfunction which may lead to a swelling sensation and even clinically evident lymphoedema in some patients. In such cases, vasculotropic agents,[12] metformin,[4] and lymph drainage may alleviate the symptoms and improve both capillary filtration and lymph function. However, secretory changes in the hormones involved in salt and water retention seem to be necessary to account for an increase in ECW. Therefore, anti-aldosterone or angiotensin-converting enzyme inhibitors may be helpful for a short time during outbreaks of the symptoms.

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