Varicose veins of the lower limbs and venous capacitance in postmenopausal women: Relationship with obesity

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Objective: **The purpose of this study was to examine the association between body mass index (BMI), venous capacitance, and clinical evidence of varicose veins after adjustment for sex hormones in postmenopausal women.**
Methods: **This study group of the DIANA (DIet and ANdrogens) project (a randomized controlled trial on the effect of some dietary changes on sex hormone pattern in women with elevated androgenic hormone levels in Italy) was comprised of 104 healthy volunteer postmenopausal women, aged 48 to 65 years. The main outcome measures were physical examination to determine the presence and severity of varicose veins and plethysmographic measurement of lower limb venous capacitance and outflow.**
Results: **Women in the upper quartile of BMI (>30 kg/m^2) showed a positive association with clinical evidence of varicose veins (odds ration, 5.8; 95% CI, 1.2 to 28.2) after adjustment for age, estradiol, testosterone, and sex hormone binding globulin. No association was found between BMI and plethysmographic measurements of venous parameters.**
Conclusion: **Obesity is associated with clinical evidence of varicose veins independently from the influence of sex hormones in postmenopausal women and is not associated with venous capacitance. Increased body weight increases the risk of varicose veins. (J Vasc Surg 2002;36:965-8.)**

Venous disease of the lower limbs is a major problem affecting Western societies that results in considerable morbidity in the population and cost to the healthcare service.[1] Many epidemiologic studies on the prevalence of varicose veins have found an association between body mass index (BMI) and presence of varicose veins.[2-4] Other factors could play a role in the development of varicose veins, particularly sex hormone patterns.[5] To our knowledge, no study has investigated the association between BMI, varicose veins, and lower limb venous compliance, taking into account the concentration of sexual hormones of the individuals participating in the study.

One of the factors associated with primary venous dysfunction is an abnormal venous wall distensibility.[6] Estrogens promote the appearance of varicose veins because of an increased venous capacitance.[5] Strain-gauge plethysmography is one of the best available methods to study maximal venous capacitance.[7] In this study, we evaluated the relationships among BMI, clinical evidence of varicose veins, and plethysmographic measurement of venous capacitance, after controlling for age and sex hormone pattern (ie, serum estradiol, sex hormone binding globulin [SHBG], and testosterone), in a group of healthy postmenopausal women to clarify the role of obesity in the pathogenesis of venous dysfunction in the lower limbs.

PARTICIPANTS AND METHODS

Subjects. Progetto DIANA (DIet and ANdrogens) is a nutritional trial in the Milan area, Northern Italy, within the research activities of the Epidemiology Unit of the National Cancer Institute. The general objective of the project was to test the effect of a specific diet on the levels of serum testosterone together with other effects on sex and metabolic hormones in healthy female volunteers aged 48 to 65 years invited through newspapers and broadcasting advertisements.[8] Potential participants had to fulfill the following conditions: postmenopausal for at least 2 years, no history of ovariectomy, no hormonal replacement treatment for at least 6 months, no history of cancer or vascular disease (in particular no previous venous thromboembolism), no adherence to vegetarian or macrobiotic diet or to any other diet prescribed for medical reasons, no treatment for diabetes, and agreement of participation in the study with informed consent.

Three hundred and twelve women were recruited. However, because one of the main objectives of this project was to reduce testosterone levels through a nutritional approach, 104 were selected to participate in the trial on the basis of their serum testosterone levels (included in the upper tertile). An ancillary study of this nutritional project examined the relationship of varicose vein prevalence and

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lower limb venous function with BMI in this group of women before the trial started.

Written informed consent to participate in the study for research purposes was obtained from all women before enrollment. The Scientific and Ethical Committee of the National Cancer Institute, Milan, Italy, approved the research with human volunteers.

Design. Baseline observation of all the women recruited in the study included a physical examination for diagnosis and classification of varicose veins, a venous strain-gauge plethysmographic measurement of venous capacitance and outflow, standard anthropometric measurements, and blood sample collection.

Laboratory analyses. Blood samples were collected from the patients in the morning after an overnight fast. Serum for hormonal assays was stored at −30° C for a short time and then at −80° C. Circulating hormones were measured with commercial kits: RIA kits were purchased from ORION Diagnostic (Turku, Finland) for testosterone and estradiol (tailored for postmenopausal condition) and IRMA kits from Farmos (Oulunsalo, Finland) were purchased for SHBG.

Clinical examination of legs. Two medical research fellows trained in internal medicine with qualified experience in angiology together examined all the women. At the first inspection, with the patient erect, they judged the varicose veins as trunk varices (dilated trunks of the long or short saphenous veins or their principal branches), reticular varices (dilated or tortuous superficial veins that did not belong to the main trunk or its major branches), or hyphen-web varices (intradermal varices). During the clinical examination, the varicose veins were marked with the patient erect and then with the patient supine and the leg elevated. The fascial defects, which were often tender, were marked as possible perforating veins. Subsequently the saphenofemoral junction and the previously marked defects were controlled by the fingertips and the women were asked to stand. Control was tested with removal of the fingers in turn, examining for venous reflux at the fascial defects. This method of examination has been indicated to be more effective than the traditional Trendelenburg's test.[9] Subsequently, the CEAP classification[10] was used to discriminate the chronic venous diseases of the lower limbs on the basis of clinical signs, etiology, anatomic involvement of the superficial, perforating, or deep veins, and pathophysiology leading to evidence. Duplex scanning of the veins of the lower limbs was not performed to exclude deep venous thrombosis. However, all the participants in the study underwent a plethysmographic study, and all had normal values of maximum venous outflow, which is a sensitive marker of venous obstruction.

Plethysmography. On the same morning of the clinical examination, all the women underwent a plethysmographic examination of lower limb venous capacitance and outflow. The methodology has been described in detail in a previous paper.[5] However, a brief description of the principal points follows. With the patient on an examination bed with legs slightly elevated to facilitate venous drainage, two cuffs measuring 22 × 70 cm were wrapped around the thighs and two tension detectors (strain-gauge), with unstretched length about 90% of the circumference of the limb, were fixed around the calves at the point of maximum circumference. The cuffs began to inflate at 50 mm Hg, and the compression was kept until a relatively stable calf volume was achieved. The incremental volume represents a measure of the quantity of blood the examined district is able to receive because of its distension and is called venous capacitance or maximal incremental venous volume (MVIV). MVIV is expressed in mL/100 mL volume. Limbs with varicose veins have the largest venous capacitance.[7] After that, the cuffs were rapidly deflated. The downward slope is the function of emptying speed of the previous venous pooling of the leg and is measured as the maximum venous outflow and expressed in mL/100 mL/min.

Statistical analysis. Five women were not present at the venous vessel examination. For two patients, the results of the sex hormone determination were not available. Therefore, the final comparisons were based on 97 women. We tested the association between both the dichotomous variable varices (yes/no) and the MVIV (upper tertile versus others) with BMI. Adjustment for age, estradiol, testosterone, and SHBG values as covariates was performed in the model because of the relationship of estradiol with varices shown in this study in the logistic regression analysis (highest tertile versus others: OR, 3.0; 95% CI, 1.1 to 8.8) and the correlation of SHBG and testosterone with BMI shown in the Pearson correlation matrix (−0.40; $P < .01$; 0.21; $P < .05$, respectively). We computed odds ratios and 95% CIs with logistic regression analysis with SPSS Windows 98 release 10.0 (SPSS, Inc, Chicago, Ill).

RESULTS

Descriptive features of the women with trunk varices (cases) and control subjects are reported in Table I. Of 97 women, 31 (32%) had clinical varices ($C_2 + C_3$) and 66 (68%) had no visible or palpable signs of venous disease or only telangiectases or reticular veins ($C_0 + C_1$).

After the CEAP classification, 55 women had C_0 (no visible or palpable signs of venous disease), 11 had C_1 (telangiectases or reticular veins), 29 had C_2 (varicose veins), and two had C_3 (edema). Other authors have shown that only trunk varices are associated in women with leg symptoms such as heaviness or tension, aching, and itching,[11] so we considered in our data analyses trunk varices (31 patients) as cases and we added in the control group the patients with only telangiectases or reticular veins (11 patients). No skin changes were ascribed to venous disease in the women participating the study. Ten of 31 women with varicose veins had telangiectases or reticular veins, too. All the women had primary varicose veins. Twenty-four of the women with trunk varices had venous disease only in the superficial veins, and seven had venous disease in the superficial and perforating veins. The clinical signs and symptoms of venous dysfunction in all the cases were the result of reflux.

Table I. Characteristics of study participants (97 women)

	Control subjects (n = 66)	*Cases (n = 31)*	P *value*
Age (y)	57.5 ± 0.5	56.8 ± 0.7	.43
BMI (kg/m^2)	26.4 ± 0.6	28.4 ± 0.9	.06
Waist circumference (cm)	82.8 ± 1.3	85.9 ± 2.2	.21
Hip circumference (cm)	101.6 ± 0.8	104.7 ± 1.4	.04
SBP (mm Hg)	137.6 ± 2.0	139.6 ± 2.7	.57
DBP (mm Hg)	80.8 ± 1.0	79.4 ± 1.5	.42
Estradiol (pg/mL)	9.6 ± 1.2	16.4 ± 4.7	.07
SHBG (nmol/L)	40.8 ± 2.1	43.7 ± 5.2	.54
Testosterone (ng/mL)	0.42 ± 0.01	0.46 ± 0.02	.56
Cholesterol (mg/dL)	244.0 ± 4.2	234.9 ± 8.8	.29
Tryglicerides (mg/dL)	112.1 ± 6.3	122.7 ± 13.9	.42
HDL cholesterol (mg/dL)	49.9 ± 0.9	51.1 ± 3.3	.64
MVO (mL/100 mL/min)	57.7 ± 1.5	76.2 ± 3.8	.001
MVIV (mL/100 mL)	1.9 ± 0.05	2.4 ± 0.1	.001

All values are mean ± standard error of mean.
SBP, Systolic blood pressure; *DBP,* diastolic blood pressure; *HDL,* high-density lipoprotein; *MVO,* maximum venous outflow.

The coefficients of intraassay and interassay variations of eight replicates for each hormone analyzed were: 4.2% and 12.5% for a testosterone value of 0.420 ng/mL; 5.2% and 11.1% for an estradiol value of 10 pg/mL; and 3.5% and 6.7% for an SHBG value of 34.0 nmol/L.[5] Quartiles of BMI were the following: first quartile, 20 to 23 kg/m^2; second quartile, 24 to 26 kg/m^2; third quartile, 27 to 29 kg/m^2; and fourth quartile, 30 to 42 kg/m^2. The women in the upper quartile of frequency distribution had more than 30 kg/m^2 and were classified as obese. Upper quartile versus others of BMI was used as independent variable, with varices and MVIV as dependent variables. The women with BMI in the upper quartile of the frequency distribution had a significant association with clinical evidence of varicose veins, after adjustment for age and serum concentration of estrogens, testosterone, and SHBG (Table II). Test for linear trend across quartiles was χ^2 of 4.4 ($P < .05$). Without the adjustment for testosterone, the results did not change. The highest quartile of BMI was associated with clinical evidence of varices with an odds ratio of 5.8 (95% CI, 1.2 to 27.8; $P < .05$). No association was found between BMI and MVIV; we tested that association with both linear regression (considering BMI and MVIV as continuous variables, $R^2 = .001$; $P = .7$) and logistic regression (considering MVIV a dichotomous variable and dividing BMI in quartiles; Table II).

With upper quartiles versus others of waist, hip, and thigh circumferences as independent variables and presence of varicose veins as a dependent variable, without adjustments, a significant association was found for hip circumferences (odds ratio, 3.8; 95% CI, 1.1 to 13.5) and for thigh circumferences (odds ratio, 3.6; 95% CI, 1.0 to 12.9). No association was detected between waist circumference and varicose veins (odds ratio, 1.5; 95% CI, 0.4 to 4.9).

Table II. Odds ratios (95% CI) of varices and MVIV in relation to BMI

	BMI >30 kg/m^2	
	Odds ratio	
	Crude	*Adjusted**
Varices (y/n)	3.8 (1.1-13.2)	5.8 (1.2-28.2)
MVIV >2.2 (mL/100 mL)	1.2 (0.4-4.1)	2.0 (0.4-9.1)

*Adjusted for age, estradiol, sex hormone binding globulin, and testosterone.

DISCUSSION

To our best knowledge, this is the first article that examines the association between BMI and varicose veins in a setting that allows the availability of serum concentration of sex hormones and plethysmographic measurements of venous capacitance in postmenopausal women. The prevalence of varicose veins varies among different populations. Its prevalence is low in African or Australian aborigine populations (0 to 5%)[12,13] and is high in Western countries (25% to 75%).[14-17] Different epidemiologic terminology, population sampling, and varicose vein definitions account for much of the variation in the literature. In this study, we used the CEAP classification of varicose veins of the lower limbs to permit a comparison of this survey with other studies.

In an Italian observation, the prevalence of varicose veins in the elderly population of the Campania region (1319 subjects; mean age, 74 years) was 35.2% in women,[18] and in agreement with these data, our study reports a prevalence of varicose veins in 32% of postmenopausal women. In our data, although women were selected for high testosterone levels, they had the classical characteristics of a large number of postmenopausal women, such as a high prevalence of obesity and lower limb varicosity.

We found that obesity (BMI >30 kg/m^2) in postmenopausal women was associated with a higher prevalence of varicose veins, whereas no association was found with the plethysmographic measures of venous capacitance. A possible explanation of this finding is that obesity could hamper the normal blood flow exchange between superficial and deep veins of the lower limbs because of augmented adipose and fibrous tissue surrounding veins. The increase of adipose tissue disturbs the cutaneous venous circulation and damages the drainage veins, provoking stasis and subsequently the appearance of varicose veins.[19] According to our results, there is a linear trend of augmented prevalence of varicose veins at increasing levels of BMI, and for values exceeding 30 kg/m^2, there is a significant excess risk of venous disease in menopause. The association between higher BMI and varicosity still remains after adjustment for age, estradiol, testosterone, and SHBG concentrations.

Epidemiologic studies have observed that other factors could play a role in the development of venous varicosity of the lower limbs, such as pregnancy, long-standing sedentary activities, and positive family history.[20-22] Most of these studies have documented an influence of obesity on the development of varices, at least in the female gender.

This study confirms these previous observations, clarifies that the association between BMI and varicose veins is independent of sex hormone levels, and suggests that other physiopathologic mechanisms, different from augmented venous distensibility, play a role in determining the clinical evidence of varicose veins in obesity. In women, the regional distribution of fat in obesity is particularly abundant in the lower abdomen, gluteal region, and thighs, so it is not surprising that we have found an association between varicose veins and higher hip and thigh circumferences and no association with waist circumferences.

Our results suggest that increased body weight plays a specific and independent role in the development of varicose veins of the lower limbs in selected groups of postmenopausal women with high testosterone levels and give more support to the concept that obesity is not a simple risk factor but a specific distinct disease with cardiovascular implications. This finding is of clinical interest and provides another reason to treat overweight patients before a shift to frank obesity. In most instances, increased body weight is associated with varicose veins of the lower limbs.

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