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Full Length Article

# Visceral obesity, but not metabolic syndrome, is associated with the presence of post-thrombotic syndrome

M. Rattazzi [a,b,*], E. Callegari [b], A. Sponchiado [b], S. Galliazzo [b], V. Pagliara [b], S. Villalta [b], P. Pauletto [a,b]

[a] Department of Medicine, University of Padova, Italy
[b] Medicina Interna I^, Ca' Foncello Hospital, Treviso, Italy

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ABSTRACT

*Introduction:* The relationship between metabolic syndrome (MetS), and the development of post-thrombotic syndrome (PTS) is currently unknown.
*Materials and Methods:* We enrolled 120 patients with a previous episode of deep venous thrombosis (DVT) diagnosed more than 2 years apart from the enrollment. Presence of MetS was identified according to NCEP ATP III criteria and Villalta Score (VS) was used to establish the presence of PTS (VS ≥ 5).
*Results:* We identified 49 (40.8%) subjects with clinical diagnosed of PTS. Patients with or without PTS showed comparable age and temporal distance from DVT event. We observed higher BMI ($p = 0.005$) and waist circumference ($p = 0.006$) among subjects with VS ≥ 5 as compared to patients without PTS. No differences between the two groups were found in terms of lipid profile, blood pressure, diabetes, hs-CRP level and ongoing medications. The prevalence of MetS was equally distributed among patients with or without PTS (20% vs 26% respectively, $p = 0.64$). Among the individual components of MetS only the prevalence of visceral adiposity was significantly increased in subjects affected by PTS (OR 2.81, $p = 0.008$). Moreover, a significant linear correlation was found between VS and waist circumference in the entire cohort ($r = 0{,}354$, $p < 0.0001$).
*Conclusion:* There is no evidence of association between MetS and PTS. However, the degree of visceral adiposity is strongly correlated with the presence and severity of post-thrombotic disease.


## Introduction

Post-thrombotic syndrome (PTS) is a common chronic complication observed in patients suffering from deep venous thrombosis (DVT). PTS can be considered as a form of secondary venous insufficiency that develops within few years in a limb previously affected by DVT [1,2]. This syndrome is characterized by a variety of symptoms (such as pain, heaviness, cramping) and signs (including edema, skin hyperpigmentation and leg ulceration). Development of PTS negatively affects the patient's quality of life and represents a considerable cost for the healthcare system, especially in case of leg ulceration. [3].

According to the different studies, PTS affects 20-50% of the patients with DVT and the presence of obesity represents a strong, independent predictor for its development [1,2,4,5]. Visceral adiposity (as assessed by measurement of waist circumference) is a major player in the onset of adverse cardiovascular consequences linked to obesity [6]. Abdominal fat accumulation has been associated with increased systemic inflammation, impaired insulin sensitivity and accelerated vascular damage [7]. Moreover, increased waist circumference is a major determinant of metabolic syndrome (MetS), a co-clustering of metabolic disorders that carries predictive value for future cardiovascular events [8]. In the last few years, a number of case-control studies indicated the existence of an association between MetS and history of venous thromboembolism (VTE)[9,10]. However, this correlation was not confirmed by prospective investigations, which instead identified visceral obesity as the only feature of MetS predictive of future VTE [11,12].

No specific investigation has been so far performed to study the link between MetS and the development of PTS. For this reason, we conducted a clinical research among patients with previous DVT to evaluate the association between the components of MetS and the presence of PTS.

## Material and Methods

### *Population*

We enrolled 120 patients who referred for clinical follow-up between April 2013 and February 2014 to the Thrombosis Unit of the Cà Foncello Hospital in Treviso and had had at least one objective diagnosed episode of DVT more than 2 years apart from the enrollment visit. At the onset of the VTE event, all the patients were treated with either intravenous adjusted-dose of unfractioned heparin or fixed dose

* Corresponding author at: Department of Medicine, University of Padova, Medicina Interna I^, Ospedale Ca' Foncello,Via Ospedale 1, 31100 Treviso, Italy. Tel.: +39 0498211867, +39 0422322207; fax: +39 0498754179.
*E-mail addresses:* marcello.rattazzi@unipd.it, mrattazzi@ulss.tv.it (M. Rattazzi).

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low molecular weight heparin (LMWH) and then shifted to vitamin K antagonists (VKA) for at least three months. VKA treatment was then prolonged on the individual basis according to the risk of recurrent VTE. Information about VTE characteristics were obtained from the medical record of the patients. In particular, we collected data about the type of VTE (unprovoked or provoked) the site of DVT (proximal or distal), presence of pulmonary embolism (PE), history of recurrence, and presence of thrombophilia. The screening for thrombophilic conditions was available for 87 patients and included: anti-thrombin III, factor V Leiden mutation, prothrombin G20210A mutation, protein C and protein S deficiency, lupus anticoagulant. We considered as "provoked VTE" the events linked to surgery, trauma, bone fracture, immobilization, acute medical disease, oral contraceptives, hormonal replacement therapy or pregnancy. Patients with history of cancer were excluded from the study. All the VTE events without triggering condition were identified as "unprovoked". We also collected information about the use of elastic compression stockings (ECS).

The study has been carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association and was approved by the local Ethics Committee. All the subjects enrolled gave written informed consent.

### *Data Collection and Biochemical Analysis*

For each patient we collected the following informations: age, sex, height, weight, waist circumference, body mass index (BMI, calculated as body weight (Kg) divided by the square of the height (m)), history of atherosclerotic cerebro-cardiovascular events (ischemic stroke, transient ischemic stroke, acute coronary syndrome), smoking status, known arterial hypertension, known diabetes, current use of antihypertensive drugs, oral anticoagulants, antiplatelet drugs and lipid lowering treatment. Waist circumference was measured by using a measuring tape as previously described.[13] Blood pressure was measured in sitting position considering the mean of three measures one minute apart. Diabetes was defined as self-reported, use of diabetes medication or fasting blood glucose ≥ 126 mg/dl. All patients underwent fasting blood sampling to measure: total cholesterol (TC), HDL-C, triglycerides, glycemia, creatinine. LDL-cholesterol (LDL-C) levels were determined by using the Friedwald formula. Estimated glomerular filtration rate (eGFR) was calculated through the MDRD equation. High-sensitivity CRP levels (hs-CRP) were determined by using a chemiluminescent immunometric assay (IMMULITE, Siemens), following manufacturer's instruction.

### *Definition of Metabolic Syndrome*

Presence of MetS was diagnosed following the NCEP ATP III criteria. In particular MetS was identified with the presence of three or more of the following characteristics: i) SBP ≥ 130 mmHg or DBP ≥ 85 or ongoing antiihypertensive therapy ii) fasting blood glucose ≥ 100 mg/dL or ongoing hypoglycemic therapy, iii) waist circumference ≥ 102 cm in men and ≥ 88 cm in women, iv) triglycerides ≥ 150 mg/dL or ongoing treatment for hypertriglyceridemia, v) HDL-C ≤ 40 mg/dL in men, ≤ 50 mg/dL in women.

### *Clinical Assessment of PTS*

The presence/absence of PTS was identified in each patient by using the Villalta scale [1]. This score is based on the evaluation of the following parameters in the DVT-affected leg: i) venous symptoms: pain, cramps, heaviness, paresthesia, and pruritus, ii) venous signs: pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression, iii) presence/absence of ulcer. Each symptom and sign received one of the following score: none = 0, mild = 1, moderate = 2, severe = 3. A total Villalta score (VS) ≥ 5 (or the presence of ulcer) is indicative of PTS.

### *Statistical Analysis*

Subject's characteristics are presented as mean ± standard deviation (SD) or median ± interquartile range (IQR) depending on parameter distribution. Comparison between groups for continuous variables was performed by using Student's *t*-test for normally distributed parameters and Mann-Whitney *U* test for variables without normal distribution. Chi-square test was used for comparison of categorical variables. Linear relationship between variables was investigated by using Pearson's correlation coefficient. All statistical analyses were performed using SPSS statistics 21.0 (IBM, USA).

## Results

### *Population Characteristics*

General characteristics of the population under investigation are summarized in Table 1. We identified 49 (40.8%) patients with a total VS ≥ 5, which is indicative of PTS. Patients with or without PTS showed comparable age ($p = 0.71$) and temporal distance from DVT event ($p = 0.47$). We observed a slightly higher prevalence of female gender in the PTS group (0.052).

The two groups showed similar lipid profile, blood pressure levels, glomerular filtration rate, blood glucose and levels of hs-CRP (Table 1). Subjects with PTS had significantly higher BMI ($p = 0.005$) and waist circumference ($p = 0.006$). Frequency of diabetes, and previous atherosclerosis-related events were low and similar between the two groups. No significant differences were seen also for the use of statins, antihypertensive therapy, antiaggregants and VKA. As for VTE characteristics, the two groups showed similar prevalence of unprovoked ($p = 0.13$) and proximal ($p = 0.44$) DVT (Table 2). Also the presence of thrombophilic defects ($p = 0.30$) and the use of ECS for at least six months ($p = 0.24$) were equally distributed among the two populations. The only difference was seen in the prevalence of PE that was slightly increased in patients affected by PTS ($p = 0.028$) (Table 2).

**Table 1**
Population characteristics.

| | no PTS (VS <5) | PTS (VS ≥ 5) | *p* |
|---|---|---|---|
| *N* | 71 | 49 | |
| Mean age, years (SD) | 58.6 (14.6) | 59.5 (12.9) | ns (0.71) |
| Female sex, n (%) | 25 (35.2) | 26 (53.0) | ns (0.052) |
| Mean Villalta score (SD) | 2.3 (1.1) | 7.5 (2.7) | <**0.0001** |
| Mean distance from DVT, months (SD) | 68.4 (38.6) | 74.3 (51.1) | ns (0.47) |
| Smokers, n (%) | 23 (32.3) | 23 (46.9) | ns (0.11) |
| History of atherosclerotic events, n (%) | 9 (12.6) | 4 (8.1) | ns (0.55) |
| BMI (SD) | 26.2 (3.6) | 28.6 (5.5) | **0.005** |
| Waist circumference, cm (SD) | 95.4 (11.7) | 101.8 (13.2) | **0.006** |
| Mean SBP, mmHg (SD) | 133.3 (20.7) | 133.8 (17.7) | ns (0.89) |
| Mean DBP, mmHg (SD) | 85.6 (12) | 87.3 (10.1) | ns (0.44) |
| Mean eGFR male, (SD) | 77.6 (21.6) | 84.4 (28.3) | ns (0.28) |
| Mean eGFR female, (SD) | 82.8 (15.3) | 78.2 (26.6) | ns (0.46) |
| Mean Total cholesterol, mg/dl (SD) | 199.5 (35.1) | 206.9 (32.3) | ns (0.24) |
| Mean HDL-C, mg/dl (SD) | 55.9 (15.6) | 58.6 (14.3) | ns (0.34) |
| Mean LDL-C, mg/dl (SD) | 120.2 (29.2) | 125.5 (30.8) | ns (0.34) |
| Median triglycerides, mg/dl (SD) | 104 (79.5-144) | 95.5(74-123.5) | ns (0.93) |
| Median glycemia, mg/dl (IQR) | 95 (89.5-102) | 94 (86-105.5) | ns (0.58) |
| Antihypertensive therapy, n (%) | 28 (39,4) | 25 (51) | ns (0.23) |
| Diabetes, n (%) | 7 (9.8) | 5 (10.2) | ns (0.97) |
| Statin therapy, n (%) | 12 (16.9) | 7 (14.2) | ns (0.67) |
| Antiplatelet therapy, n (%) | 3 (4.2) | 5 (10.2) | ns (0.20) |
| Ongoing oral anticoagulation, n (%) | 48 (67.6) | 26 (53.0) | ns (0.086) |
| Median hs-CRP, mg/dl (SD) | 0.34 (0.14-0.87) | 0.14 (0.05-0.42) | ns (0.056) |

SD: standard deviation, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, hs-CRP: high sensitivity C-reactive protein, eGFR: estimated glomerular filtration rate, IQR: inter-quartile range.

**Table 2**
DVT characteristics and PTS.

| | no PTS (VS <5) | PTS (VS ≥ 5) | *p* |
|---|---|---|---|
| *N* | 71 | 49 | |
| Type of VTE, unprovoked (%) | 38 (53.5) | 33 (67.3) | ns (0.13) |
| DVT site, proximal (%) | 46 (64.8) | 35 (71.4) | ns (0.44) |
| Thrombophilic defect, yes (%)* | 23 (43.4) | 11 (23.4) | ns (0.30) |
| Pulmonary embolism, yes (%) | 10 (14.1) | 15 (30.6) | **0.028** |
| History of recurrence, yes (%) | 13 (18.3) | 9 (18.4) | ns (0.99) |
| Pregnancy/estroprogestin, yes (%) | 7 (9.9) | 5 (10.2) | ns (0.95) |
| Stockings for at least 6 ms, yes (%) | 39 (54.9) | 33 (67.3) | ns (0.24) |

* data available for 87 patients (53 with VS <5 and 34 with VS ≥5).

*Metabolic Syndrome and PTS Risk*

The prevalence of MetS was equally distributed among patients with or without PTS (OR 1.19 (0.56- 2.51), p = 0.64) (Table 3). When we looked at the interaction between each component of the MetS and the presence of PTS the only significant association was found for elevated waist circumference (OR 2.81 (1.31 -6.03), p = 0.008), a finding that remained significant even after adjustment for age and gender (OR 2.51 (1.12 - 5.61), p = 0.025) (Table 3). No association was observed between presence of PTS and the level of blood pressure, HDL-C and triglycerides. Of interest, a correlation analysis performed on the whole population demonstrated a positive, significant correlation between VS and waist circumference, (r = 0,354, p < 0.0001) (Fig. 1), a finding that remained significant even after adjustment for age and gender (p < 0,0001).

## Discussion

A number of clinical studies investigating PTS pathogenesis identified obesity, older age, previous ipsilateral venous thrombosis and common femoral or iliac vein DVT as major risk factors for PTS [1,2,4,14]. In the present study, we sought to evaluate whether MetS, as a whole, can be associated with the risk of PTS. However, data collected in our population of patients with previous DVT indicate that MetS is not significantly correlated with the presence of PTS. In addition, separate analyses of individual component of MetS suggest that the atherogenic lipid profile (low HDL-C and high triglycerides) could play a minor role in PTS development.

In agreement with previous studies we observed a strong, significant correlation between PTS and the presence of obesity [4,5]. We deepened earlier data by showing that the increase in waist circumference is the only determinant of MetS showing significant correlation with PTS. This observation is coherent with data from perspective studies showing that visceral adiposity is the only component of MetS harboring independent predictive value of future VTE risk [11,12]. Of note, when we performed a correlation analysis on the whole population we found a significant association between the measure of waist circumference and the VS value. This observation suggests the existence of direct relationship between the degree of visceral adiposity and the severity of PTS.

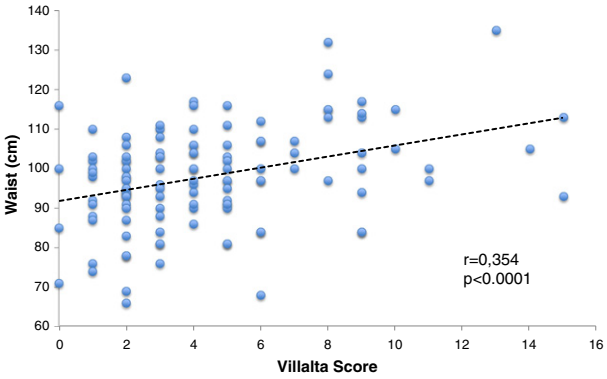


**Fig. 1.** Correlation between waist circumference and Villalta score. A correlation analysis between the Villalta Score and the value of waist circumference was performed on the entire population under investigation (n = 120). As can be seen in the figure a significant, direct correlation was found between Villalta Score and waist (r = 0,354, p < 0.0001).

Previous investigation showed that adiposity is associated with venous hypertension and impaired systemic fibrinolysis [15]. Moreover, visceral adipose tissue (VAT) is now considered an important source of inflammatory molecules that can be implicated in the progression of vascular damage [15,16]. All these factors might represent a possible explanation for the association between abdominal obesity and the development of PTS. In fact, accumulation of visceral fat can be accompanied by increase in intra-abdominal pressure [17]. The latter can be transmitted to the veins of the extremities and contribute to the onset of venous hypertension, the major pathogenic determinant of PTS. In agreement with this possibility previous studies showed that obese subjects have increase iliofemoral veins pressure,[17] increased femoral vein diameter and higher outflow resistance as compared to non-obese individuals [18]. On the whole, these hemodynamic changes can lead to venous stasis, venous valve dysfunction and increased vein wall damage. In our population only a limited number of patients were obese (31 patients had BMI ≥ 30) and the correlation between waist circumference and VS was observed in the whole population under investigation (Fig. 1). These findings suggest that even moderate increase in visceral adiposity can lead to impairment of lower limb venous outflow and contribute to PTS.

Whether the VAT can play an active role in promoting the inflammatory damage of the venous system is currently unknown. In our cohort, circulating levels of hs-CRP were similar in the two groups of patients. This finding, which is in line with recent studies [19], may indicate a lack of sustained inflammatory response in patients with PTS. If this was the case, the role of systemic inflammation in the amplification of venous damage could be of low relevance. Additional investigations are needed to clarify this aspect.

In agreement with previous investigations we observed that the characteristics of the DVT event, including the presence of thrombophilic defects, play a minor role in predicting the development of PTS [1,4]. A modest, but significant increase in the number of PE events was found among subjects with PTS. We speculate that this association could be explained by the extent of the initial proximal DVT event. In fact, even if the prevalence of proximal DVT was identical in the two groups, patients

**Table 3**
Association of metabolic syndrome and its individual components with the risk of PTS.

| | PTS (n = 49) | No PTS (n = 71) | OR (95% CI) | *p* | Adjusted OR (95%CI)* | *p* |
|---|---|---|---|---|---|---|
| MetS, n (%) | 20 (36.6) | 26 (40.8) | 1.19 (0.56- 2.51) | ns (0.64) | 0.91 (0.41 – 2.03) | ns (0.82) |
| SBP ≥ 130 mmHg or DBP ≥ 85 mmHg, n (%) | 40 (81.6) | 51 (71.8) | 1.74 (0.71 – 4.24) | ns (0.22) | 2.89 (0.94 – 8.85) | ns (0.062) |
| HDL-C ≤40 mg/dl male or ≤50 mg/dl, female, n (%) | 12 (24.5) | 25 (35.2) | 0.59 (0.26 -1.34) | ns (0.21) | 0.49 (0.20 - 1.15) | ns (0.10) |
| TG ≥ 150 mg/dl, n (%) | 11 (22.4) | 8 (11.3) | 2.28 (0.84 – 6.17) | ns (0.10) | 2.46 (0.89 –6.83) | ns (0.082) |
| Glycemia ≥100 mg/dl, n (%) | 15 (30.6) | 28 (39.4) | 0.67 (0.31 – 1.46) | ns (0.32) | 0.73 (0.32 – 1.67) | ns (0.45) |
| Waist circumferences ≥102 cm male or ≥88 cm female, n (%) | 33 (67.3) | 30 (42.3) | 2.81 (1.31 -6.03) | **0.008** | 2.51 (1.12 - 5.61) | **0.025** |

* adjusted for age, gender.

with PTS could be more affected by DVT involving the common femoral or the iliac vein, which is known to be a strong predictor for both PE and PTS development [20,21].

Major limitations of our study are the retrospective design, the heterogeneous distance of the DVT events from PTS assessment and the lack of information about the existence of MetS and previous primary venous insufficiency at DVT occurrence. Previous and ongoing pharmacological treatments can also represent a confounding factor for the interpretation of the findings. However, in our cohort, only 12 subjects were diabetics (10%), 19 were taking statins (15%) and the antihypertensive treatment was equally distributed between the two groups (see Table 1). Nevertheless, despite these limitations, data collected so far suggest that the implementation of weight lose strategies among patients with DVT might help to reduce the risk of PTS.

In conclusion, in the present study we observed a lack of association between presence of MetS as a whole and the development of PTS. Nevertheless a strong, significant correlation was found between the degree of visceral adiposity and PTS severity, which warrants further investigation.

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## Conflict of Interest Statement

There are no conflicts of interest.

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