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Metabolic syndrome and risk of venous thromboembolism: Longitudinal Investigation of Thromboembolism Etiology (LITE)

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Abstract

Background: In a recent case-control study, the odds of metabolic syndrome (MetSyn) among deep vein thrombosis cases was almost twice the odds as among controls. We tested the hypothesis that the incidence of non-cancer-related venous thromboembolism (VTE) is higher among adults with MetSyn and further, that associations are stronger for idiopathic than secondary VTE.

Methods: 20,374 middle-aged and elderly adults were followed for over 12 years for incident VTE in the Longitudinal Study of Thromboembolism Etiology (LITE). All hospitalizations were identified and VTEs validated by chart review. Baseline MetSyn was defined usingATP III guidelines including ≥3 of abdominal obesity, elevated blood pressure, low HDL-cholesterol, high triglycerides, and high glucose. Because sex modified the relation between MetSyn and VTE ($p_{interaction}$=0.001), proportional hazards regression analyses were stratified by sex to assess the associations of MetSyn and its components with risk of incident non-cancer related VTE, adjusting for potential confounders.

Results: Incident VTE (n=358) included 196 idiopathic events. Baseline MetSyn was associated with risk of total VTE (Hazard Ratio (HR) 1.84; 95%CI 1.30, 2.59) and idiopathic VTE (HR 1.59, 95% CI 1.02, 2.47) among men, but not women. The association was largely attributable to abdominal obesity (HR of VTE = 2.10, 95% CI 1.51, 2.93 in men and 1.70, 95% CI 1.24, 2.34 in women), with no additional contribution by the other MetSyn components.

Conclusion: Although abdominal obesity was associated with increased risk of VTE in both men and women, MetSyn and its other components do not seem important in VTE etiology.

INTRODUCTION

Several studies suggest a link between venous thromboembolism (VTE) and atherosclerosis via common risk factors, including central adiposity (1,2), obesity (3,4), smoking (1,3), hypertension (3), low HDL-cholesterol (5), high LDL-cholesterol (5), high levels of lipoprotein (a) (6), and diabetes (4). However, results have been inconsistent (1,3-7). In the Longitudinal

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Investigation of Thromboembolism Etiology (LITE), obesity and type 2 diabetes were associated with VTE, but not other traditional atherosclerosis risk factors (4). Several of these risk factors are components of the metabolic syndrome (MetSyn), known to be associated with atherosclerotic disease risk (8).

According to national surveys (9), about 23% of the US adult population has the MetSyn (defined as 3 or more of the following risk factors: central adiposity, elevated systolic blood pressure, elevated triglycerides, elevated glucose or diagnosed with diabetes, low HDL-cholesterol). In a recent case-control study, over 50% of idiopathic deep vein thrombosis (DVT) cases had the MetSyn compared to 35% of controls. After adjusting for age, sex, body mass index, and smoking, the prevalence of the MetSyn was almost twice as likely in idiopathic DVT cases as controls (OR 1.93; 95% CI: 1.05, 3.56) (10). Results from another case-control study showed 35% of recurrent VTE patients had the MetSyn compared to 20% of controls (OR = 2.2; 95% CI: 1.1, 4.3) (11). The mechanism by which the MetSyn could be associated with VTE may be through endothelial dysfunction and a procoagulant state, reflected by elevated factors such as factors VII and VIII, and vonWillebrand factor (12-15).

To date, there are no published prospective studies investigating the relation between MetSyn and risk of incident VTE in middle-aged and elderly men and women. We tested the hypothesis in the LITE study of VTE in the Atherosclerosis Risk in Communities (ARIC) study and the Cardiovascular Health Study (CHS), that incidence of non-cancer related VTE is higher among adults with the MetSyn compared to those without, independent of age, sex, race, and factor VIIIc. In addition, we hypothesized that associations would be stronger for idiopathic than secondary VTE.

METHODS

Study design and population

The Longitudinal Investigation of Thromboembolism Etiology (LITE) is a prospective study of VTE occurrence in two population-based cohorts: the Atherosclerosis Risk in Communities (ARIC) study (16) and the Cardiovascular Health Study (CHS) (17,18). ARIC examined 15,792 45- to 64-year old African American and white female and male residents recruited in 1987-89 from the city of Jackson, MS; selected suburbs of Minneapolis, MN; Forsyth County, NC; and Washington County, MD. CHS examined 5,888 65+ year-old primarily white and African American female and male residents recruited in 1989-90 or 1992-93 from the city of Pittsburgh, PA; Forsyth County, NC; Sacramento County, CA; and Washington County, MD and who were randomly selected from the Health Care Financing Administration (or Medicare) eligibility lists.

Data Collection

The Institutional Review Boards of all participating centers approved this study. Study participants underwent a comprehensive baseline examination for cardiovascular disease (CVD) risk factors. In both studies, seated blood pressure was measured using a random-zero sphygmomanometer. BMI was calculated as weight in kilograms divided by the square of standing height in meters. Waist circumference was measured at the umbilicus. Fasting blood specimens were collected, centrifuged at 4° C., and plasma and serum frozen at −70° C. until analysis in central laboratories. Lipids, glucose, fibrinogen, and factors VIIc and VIIIc were measured at baseline (19). Diabetes status (yes or no) was defined at baseline as fasting glucose ≥ 126 mg/dL, nonfasting glucose ≥ 200 mg/dL, or a history of or treatment for diabetes. Smoking status, hormone replacement use in women, and medication use were also obtained at baseline.

MetSyn was defined according to ATP III recommendations as 3 or more risk factors (20), including:

- Abdominal obesity: waist circumference ≥ 102 cm for men and ≥ 88 cm for women;
- Triglycerides ≥ 150 mg/dL;
- HDL-cholesterol levels for men < 40 mg/dL and for women < 50 mg/dL.
- Glucose ≥ 100 mg/dL, on drug treatment for elevated glucose, or a diagnosis of diabetes;
- Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or on antihypertensive therapy;

Case ascertainment

Study participants were followed for VTE (deep vein thrombosis (DVT) or pulmonary embolism (PE)) endpoints through 2001 in CHS and 2002 in ARIC. Hospitalizations were identified by participant or proxy report via annual telephone calls and surveillance of community hospitals in ARIC (16) or via alternating clinic visits and telephone contact every 6 months and by search of Health Care Financing Administration records in CHS (18). For all hospitalizations, ICD-9-CM discharge codes were recorded and were used to identify medical records of possible VTE event (21). Medical records were obtained and reviewed by two physicians. VTE events were classified independently, and differences resolved through discussion. VTE required objective evidence from imaging or autopsy. DVT was nearly always defined as a positive duplex ultrasound or venogram, but rarely in the earliest years, by a positive Doppler ultrasound or impedance plethysmography. PE nearly always was defined by a ventilation-perfusion scan with multiple segmental or subsegmental mismatched defects, or a positive pulmonary angiogram or computed tomography. Idiopathic VTE events were defined as VTE excluding obvious precipitants (e.g. surgery, trauma, recent hospitalization, or severe immobility) (21).

Statistical analysis

Of the 15,792 ARIC participants and 5,888 CHS participants, we excluded from the analyses those with a history of VTE before baseline (n=477), who used warfarin at baseline (n=185), or who developed cancer-related VTE during follow-up (n=125). We further excluded 933 individuals with non-fasting blood specimens and other missing data. Seventy-two individuals were excluded because they were not white or African American, leaving 20,374, including 11,429 women and 8,945 men.

All analyses were conducted using the statistical software package SAS, version 9.1 (SAS Institute; Cary, NC). Follow-up time was calculated as time from baseline to incident VTE, death, last follow-up contact, or through 2001 for CHS and 2002 for ARIC, whichever occurred first. Means and proportions were computed to describe baseline characteristics of participants by metabolic syndrome status and for those who did or did not develop VTE. Hazard ratios were calculated, adjusted for age, race, sex, and other covariates, using proportional hazards regression models. After assessing for potential effect modification by race or sex, regression models were stratified by sex ($p_{interaction}$=0.001). The relations for idiopathic VTE cases only were also evaluated. In sensitivity analysis, we assessed whether adjustment for lipid medication use changed study findings.

RESULTS

Over 56% of the LITE cohort was female and 23% African American. At baseline, study participants were average age 58.9 (10.1) years. For women and men, the average BMI (SD)

was 27.6 (5.9) and 27.2 (4.1) kg/m^2, and 62% and 70% were overweight or obese, respectively. Almost 34% of women and 30% of men had MetSyn at baseline. Mean levels of risk factors were greater among individuals with MetSyn than among those without MetSyn (Table 1). Similar findings were observed when risk factors were stratified by abdominal obesity instead of MetSyn (data not shown).

As shown in Table 2, the prevalence of metabolic syndrome among women who did or did not develop incident VTE was similar (both 34%), however, the prevalence of MetSyn was greater among men who developed incident VTE than among those who did not (44% vs. 30%, p<0.001). Abdominal obesity was significantly greater among both men and women who developed VTE than among those who did not. Interestingly, more women who did not develop VTE had low HDL-cholesterol than women who did develop VTE, whereas, there was no significant difference between groups for men.

Over an average 12.5 years of follow-up, there were 358 incident non-cancer related VTE events, including 195 idiopathic events. While most components of the MetSyn were not significantly related to VTE, abdominal obesity was significantly and positively related to VTE risk in both men and women (Model 1, Table 3). Compared with those free of Metsyn, MetSyn was associated with a higher risk of incident VTE among men (HR=1.84, 95% CI 1.30-2.59), but not women (Model 2, Table 3). HRs were smaller (1.59; 95% CI 1.02, 2.47) for the relationship between MetSyn and idiopathic than secondary VTE in men (Model 2, Table 3). Further adjustment for fibrinogen and factors VIIc and VIIIc in statistical models only slightly attenuated associations (data not shown). Results were similar after excluding individuals who were taking lipid-lowering medication (data not shown). In LITE, the major race group is Caucasian (77%). Race was not an effect modifier or a significant confounding factor in the statistical models. When we analyzed the data excluding African Americans, similar results were observed for whites as when both races were included in the model. For white men only the HR for risk of developing VTE was 2.02 (95% CI 1.38, 2.94) and for white women only, the HR for risk of developing VTE was 0.88 (95% CI 0.62, 1.25).

To determine if abdominal obesity was the sole predictor of VTE rather than the cluster of MetSyn components, a model was run that included abdominal obesity, a variable representing the cluster of MetSyn components but without abdominal obesity, and the previously identified confounding factors (Model 3, Table 3). Abdominal obesity was associated with incident VTE in men (HR 2.10 95% CI 1.51, 2.93) and women (HR 1.70, 95% CI 1.24, 2.34), but not 'MetSyn without abdominal obesity' in men (HR 1.28, 95% CI 0.92, 1.79) or women (HR 0.84, 95% CI 0.63, 1.12). The HRs relative to abdominal obesity or 'MetSyn without abdominal obesity' were similar for idiopathic VTE and for total VTE.

DISCUSSION

Over 12 years of follow-up, MetSyn was associated with 84% increased risk of developing non-cancer related VTE among men, but not women. Moreover, the cluster of the MetSyn components minus abdominal obesity was not related to VTE risk, so that only abdominal obesity, but not MetSyn, *per se* was associated with increased risk of VTE. Results were similar for idiopathic VTE events.

Some investigators suggest a link between VTE and atherosclerosis through common risk factors (2,7), including obesity and abdominal obesity, diabetes, HDL-cholesterol, high blood pressure, smoking (1-3,5,6,22), and most recently MetSyn (10,11); however, study findings have not consistently shown that these factors are risk factors for VTE (4,7,22). Two case-control studies demonstrated higher prevalence of the MetSyn in idiopathic DVT or recurrent VTE patients than controls (10,11). However, in our prospective study of over 20,000 male

and female participants, abdominal obesity was the only component of MetSyn related to incident VTE, and not the cluster of other components of the MetSyn.

Even though diabetes, a known risk factor for VTE (4,7,22), is accompanied by increased coagulation factors (23) and increased platelet reactivity (24), elevated glucose levels were not related to VTE risk in our study. The evidence is less consistent for hypertension associating with VTE (3,4,7), and elevated blood pressure (defined as SBP≥130 mmHg or DBP≥85 mmHg) was not related to incident VTE in the current study or others (22).

Low HDL-cholesterol is a strong risk factor for atherosclerotic events, however, it was related to VTE in only one case-control study (5), but not in prospective studies (4). In the current study, low HDL-cholesterol (<40 mg/dL in men and <50 mg/dL in women) was not significantly related to incident VTE. Furthermore, the prevalence of low HDL-cholesterol was higher among women who did not develop VTE than those who did develop incident VTE. High triglyceride concentrations (≥ 150 mg/dL), another component of the MetSyn, also was not related to VTE in LITE.

Our results are consistent with those in other studies of abdominal obesity. In men born in 1913, waist circumference greater than 100 cm was associated with a three-fold increased risk of VTE compared to a waist size less than 100 cm (1). One meta-analysis, including 4 case-control studies and the LITE study, evaluated the effect of obesity (BMI>30 kg/m^2) on VTE and reported an increased odds ratio of 1.84 (95% CI 1.55, 2.18) (22). In the current analysis, abdominal obesity doubled the risk of developing VTE in both men and women; whereas, MetSyn was related to VTE in men only. Analogously, previous studies have sometimes found gender-specific differences in the association between MetSyn and arterial disease (25).

It is biologically plausible that risk of VTE in abdominally obese individuals is mediated by a state of hypercoagulability and endothelial cell injury, two of three components of Virchow's triad involved in the pathogenesis of VTE (7,22-24,26,27). Several studies have demonstrated elevated hemostatic factors in abdominal obesity, including factor VII, fibrinogen, von Willebrand factor (vWF), and PAI-1 (14,27-30), and these markers are sometimes elevated in VTE, especially vWF (13,31,32). In the current study, individuals with MetSyn and abdominal obesity had higher levels of fibrinogen and factors VIIc and VIIIc than those without MetSyn or abdominal obesity.

A major strength of this investigation is the prospective study design examining the relation between MetSyn and VTE. The study followed a large number of primarily white and African American middle-aged and elderly men and women over 12 years. We measured and adjusted for several VTE risk factors but it is possible there was residual confounding by unaccounted for factors associated with both MetSyn and VTE. A limitation of the study is that MetSyn was defined several years before the VTE event, therefore, if there were acute effects of MetSyn they could have been missed.

MetSyn is associated with chronic disease, including coronary heart disease (8,12,20,30), and type 2 diabetes (8,12,20), but not with incident VTE in this prospective study. Abdominal obesity, an established VTE risk factor was important, but not the cluster of other MetSyn components.

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Table 1

Adjusted mean (SE)* baseline levels of risk factors in relation to metabolic syndrome (MetSyn), LITE Study

Characteristic	Women (n=11,429)*†	
	With MetSyn (n=3859)	***Without MetSyn (n=7570)***
BMI, kg/m^2	30.7 (0.08)	26.0 (0.06)
Waist circumference, cm	104 (0.22)	90 (0.15)
Glucose, mg/dL‡	118	96
HDL-cholesterol, mg/dL	47 (0.24)	64 (0.17)
Triglycerides, mg/dL‡	162	93
Systolic blood pressure, mmHg	131 (0.30)	122 (0.21)
Diastolic blood pressure, mmHg	74 (0.17)	70 (0.12)
Fibrinogen, mg/dL	325 (1.17)	308 (0.69)
Factor VIIc, %	135 (0.49)	123 (0.35)
Factor VIIIc, %	140 (0.64)	128 (0.45)
	Men (n=8,945)*‡	
	With MetSyn (n=2684)	***Without MetSyn (n=6261)***
BMI, kg/m^2	29.9 (0.07)	26.0 (0.05)
Waist circumference, cm	106 (0.2)	95 (0.1)
Glucose, mg/dL‡	121	101
HDL-cholesterol, mg/dL	37 (0.24)	49 (0.2)
Triglycerides, mg/dL‡	183	103
Systolic blood pressure, mmHg	131 (0.3)	123 (0.2)
Diastolic blood pressure, mmHg	78 (0.2)	74 (0.1)
Fibrinogen, mg/dL	312 (1.2)	300 (0.8)
Factor VIIc, %	119 (0.5)	109 (0.3)
Factor VIIIc, %	130 (0.7)	123 (0.5)

*Adjusted for age, race, field center, education, smoking, and hormone replacement therapy (women)

†All means are significantly different between metabolic syndrome categories, p<0.001

‡Geometric means

Table 2

Frequency of metabolic syndrome components among study participants who did or did not develop venous thromboembolism (VTE), LITE Study

Characteristic	**Women (n=11,429)***	
Metabolic Syndrome Components	***Developed VTE (n=210)***	***Did not develop VTE (n=11,226)***
Abdominal obesity, n (%)	152 (72%)	6854 (61%) †
High glucose, n (%)	45 (19%)	2347 (21%)
Low HDL-cholesterol, n (%)	58 (29%)	3924 (35%) †
High triglycerides, n (%)	50 (22%)	2847 (25%)
Elevated blood pressure, n (%)	136 (57%)	5810 (52%)
MetSyn, n (%)	71 (34%)	3788 (34%)
	Men (n=8,945)*	
Metabolic Syndrome Components	***Developed VTE (n=149)***	***Did not develop VTE (n=8798)***
Abdominal obesity, n (%)	75 (51%)	2833 (32%) ‡
High glucose, n (%)	65 (47%)	2387 (40%) †
Low HDL-cholesterol, n (%)	50 (35%)	3491 (32%)
High triglycerides, n (%)	96 (57%)	2791 (52%)
Elevated blood pressure, n (%)	55 (36%)	4562 (27%)
MetSyn, n (%)	65 (44%)	2619 (30%) ‡

MetSyn = metabolic syndrome defined according to the ATP III guidelines

MetSyn w/o abdominal obesity = metabolic syndrome defined as 2 or more components excluding abdominal obesity

* Adjusted for age, race, field center, education, smoking, and hormone replacement therapy (women)

† $p \leq 0.05$

‡ $p < 0.001$

Table 3

Hazard ratios (95% confidence intervals) of non-cancer related venous thromboembolism in relation to metabolic syndrome and its components, LITE study

	Total non-cancer VTE events (n=358)		*Idiopathic VTE events (n=195)*	
Characteristic	**Women (n=11,429)**	**Men (n=8,945)**	**Women (n=11,333)**	**Men (n=8,863)**
VTE case, n	209	149	113	82
Model 1*				
MetSyn Components				
Abdominal Obesity	1.75 (1.27, 2.41)	2.14 (1.49, 2.93)	1.91 (1.23, 2.95)	2.42 (1.53, 3.81)
High glucose	0.94 (0.66, 1.33)	1.26 (0.89, 1.79)	0.92 (0.57, 1.49)	1.06 (0.65, 1.72)
High triglycerides	0.81 (0.57, 1.15)	0.88 (0.61, 1.27)	0.80 (0.49, 1.29)	0.79 (0.48, 1.32)
Low HDL-cholesterol	0.80 (0.59, 1.09)	1.29 (0.90, 1.84)	0.59 (0.37, 1.04)	1.57 (0.98, 2.52)
Elevated blood pressure	1.30 (0.95, 1.78)	1.17 (0.82, 1.68)	1.29 (0.85, 1.98)	0.83 (0.52, 1.33)
***Model 2**†*				
MetSyn	0.93 (0.70, 1.25)	1.84 (1.30, 2.59)	0.76 (0.51, 1.15)	1.59 (1.02, 2.47)
***Model 3**†*				
MetSyn w/o abdom obesity	0.84 (0.63, 1.12)	1.28 (0.92, 1.79)	0.76 (0.51, 1.13)	1.19 (0.76, 1.87)
Abdominal obesity	1.70 (1.24, 2.34)	2.10 (1.51, 2.93)	1.84 (1.19, 2.84)	2.31 (1.48, 3.62)

MetSyn = metabolic syndrome

*Model 1 includes all metabolic syndrome components adjusted for age, race, field center, education, smoking, and hormone replacement therapy (women)

†Model 2 includes the indicator variable metabolic syndrome (yes/no) adjusted for age, race, field center, education, smoking, and hormone replacement therapy (women)

‡Model 3 includes 2 indicator variables: abdominal obesity (yes/no) and the metabolic syndrome components without abdominal obesity (yes/no) adjusted for age, race, field center, education, and smoking