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Full Length Article

Body size measures, hemostatic and inflammatory markers and risk of venous thrombosis: The Longitudinal Investigation of Thromboembolism Etiology

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ABSTRACT

Objective: Obesity is an important venous thrombosis (VT) risk factor but the reasons for this are unclear.
Materials and methods: In a cohort of 20,914 individuals aged 45 and older without prior VT, we calculated the relative risk (RR) of VT over 12.6 years follow-up according to baseline body size measures, and studied whether associations were mediated by biomarkers of hemostasis and inflammation that are related to adiposity.
Results: Greater levels of all body size measures (weight, height, waist, hip circumference, calf circumference, body-mass index, waist-hip ratio, fat mass and fat-free mass) were associated with increased risk of VT, with 4th versus 1st quartile RRs of 1.5–3.0. There were no multiplicative interactions of biomarkers with obesity status. Adjustment for biomarkers associated with VT risk and body size (factors VII and VIII, von Willebrand factor, partial thromboplastin time, D-dimer, C-reactive protein and factor XI) only marginally lowered, or did not impact, the RRs associated with body size measures.
Conclusions: Greater body size, by multiple measures, is a risk factor for VT. Associations were not mediated by circulating levels of studied biomarkers suggesting that body size relates to VT because of physical factors associated with blood flow, not the hypercoagulability or inflammation associated with adiposity.

1. Introduction

Obesity is epidemic worldwide, with little evidence of improvement in recent years [1]. Other than age, obesity is the major atherosclerotic risk factor associated with risk of venous thrombosis (VT) [2–9]. In 2008 the United States Surgeon General called for more research on the reasons for an association of obesity with VT [10] yet few studies have comprehensively assessed obesity as a VT risk factor by including evaluation of many body size measures or by assessing mediating factors for associations of obesity with VT.

Mechanisms linking obesity to VT are speculative. The association may be due to physical factors related to obesity such as impaired venous return, biochemical effects of adipose tissue such as enhanced inflammation or hypercoagulability, or venous vessel wall alterations.

In the Longitudinal Investigation of Thromboembolism Etiology (LITE) we previously reported that obesity (BMI >30 kg/m^2) was associated with a 2-fold higher risk of future VT [4]. With longer follow-up and >200 additional VT events, we report here more detail on associations of body size measures, hemostasis and inflammation with VT. We hypothesized that several measures of body size are positively associated with VT risk and that the body fat component is more strongly related than non-fat mass. Under a hypothesis that adipose tissue directly influences the inflammatory and procoagulant state, we expected some degree of mediation of associations of body size by levels of hemostasis and inflammation markers.

2. Methods

2.1. Subjects

LITE is a prospective population-based study of 21,680 participants of the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk in Communities (ARIC) study [11]. Both studies examined risk factors at baseline and followed participants for cardiovascular diseases. Detailed methods have been published [11]. In 1987–89, 15,792 men and

Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMI, body-mass index; CHS, Cardiovascular Health Study; VT, venous thrombosis.

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women 45–64 years of age were enrolled in ARIC; 27% were African American. In 1989–90, 5201 men and women age 65–100 were enrolled in CHS, and 687 African American participants were enrolled in 1992–93. Six communities are represented in LITE: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pennsylvania. All participants provided written informed consent with methods approved by local institutional review committees.

At baseline, extensive information was collected using standardized methods, including medical history, medication use, measured height, weight, waist circumference, and hip circumference. BMI was calculated as weight in kg / height in m^2, and waist-hip ratio was calculated. ARIC also measured calf circumference at the widest point of the right calf while the participant sat high enough that their feet did not touch the floor. CHS measured fat mass and fat-free (lean) mass using bioelectric impedance with participants in the supine position wearing standard clothing [12]. Resistance was measured with a TVI-10 Body Composition Analyzer (Danninger Medican Technology Inc., Columbus, OH) at 50 kHz. Fat-free mass was estimated using the formula of Deurenberg: $6710 * \text{height}^2 / (R + 3.1 * S + 3.9)$, where R is resistance in ohms and S is sex (0 for women, 1 for men) [13]. Fat mass was calculated as the difference between weight and fat-free mass. Obesity status was categorized as normal, overweight, obese and severely obese by BMI <25, 25–30, 30–40, and 40 + kg/m^2, respectively. The latter two categories were combined for some analyses. Elevated waist circumference was defined as ≥88 cm in women and ≥102 cm in men. Waist and hip circumferences, waist-hip ratio, fat and fat-free mass and calf circumference were also analyzed as continuous variables or in sex-specific quartiles of the distribution. Race was categorized as black and non-black. Diabetes was defined as fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, use of diabetes medications or self-reported diabetes.

The two studies maintained longitudinal contact with participants to identify all hospitalizations. Potential cases of hospitalized VT were identified from ICD discharge codes and validated by medical record review by two physicians as previously reported [11]. VT events included deep vein thrombosis (DVT) and pulmonary embolism (PE). Classification as VT required positive imaging. VT cases ascertained in both cohorts with complete follow-up through the end of 2001 (when CHS follow up for VT stopped) were included in this analysis. Cases were defined as provoked if they were associated with cancer, major trauma, surgery or marked immobility, and as unprovoked otherwise.

2.2. Laboratory methods

For some hemostasis and inflammation factors, levels were measured in all participants of both cohorts. For others, a nested case-control study was used to randomly select two controls per case, frequency-matched to the cases by 5-year age group, sex, race (African-American, white), follow-up time, and study (ARIC, CHS) [14].

In ARIC and CHS, fasting morning blood samples were obtained at baseline. Blood was centrifuged at 4 °C, and plasma frozen at −70 °C until analysis in central laboratories. Baseline levels of fibrinogen, factor VII and VIII coagulant activity (FVIIc, FVIIIc), and were measured, and in ARIC only, the activated partial thromboplastin time (aPTT), protein C and von Willebrand factor were measured, as previously described [15,16]. Both studies measured white blood count at laboratories near each field center. In CHS only, baseline C-reactive protein (CRP) and interleukin-6 (IL-6) were measured in the full cohort with high-sensitivity assays [17]. In the nested case-control sample D-dimer was measured by immunoturbidimetry using the Liatest D-dimer assay on the STAR analyzer (Diagnostica Stago) and factor XI by sandwich enzyme-linked immunoassay using reagents with affinity purified polyclonal antibodies from Enzyme Research Laboratories (South Bend, IN).

2.3. Statistical methods

We excluded 729 participants reporting either prebaseline VT (n = 590) or baseline warfarin use (n = 185). Incidence rates were estimated as the number of VT events divided by the total number of person-years at risk. Some analyses only included one study (ARIC or CHS) if variables of interest were only available in one study. Spearman correlation coefficients among study variables were calculated in the full cohort (or control group only for D-dimer and factor XI). In the full cohort, Cox regression models were used to estimate adjusted relative risks (hazard ratios) and 95% confidence intervals of VT associated with body size measures. In the nested case-control study, logistic regression was used to calculate odds ratios as estimates of relative risk. All models were adjusted for baseline age, sex and race. To assess whether biomarkers mediated the relationship of body size with VT we first ruled out presence of interactions between biomarkers and body size by using interaction terms in each model (all p interaction >0.05; Supplementary table). We then used multivariable models adding the biomarkers and examined change in relative risk for the body size measure. Stratification was used for some analyses by whether the VT was provoked or unprovoked and by type of VT (DVT or PE ± DVT). Differences in associations of body size measures by whether the outcome was DVT versus PE were assessed using the method of van Langervelde [18], concluding that associations were larger for PE than DVT if the RR_{PE}/RR_{DVT} was >2.0 and that they were larger for DVT than PE if this ratio was <1.0.

3. Results

With a median 12.6 years of follow-up the incidence rate of first VT was 1.8 per 1000 person-years. Table 1 shows baseline characteristics of the 448 participants with first-time VT (269 in ARIC, 179 in CHS) and the 20,466 participants without VT. Older age and diabetes were more prevalent among cases and each body size measurement was larger among cases on average, except height, which was similar. Fig. 1 shows the crude incidence rates for ARIC and CHS separately by categories of body size. There was a monotonically greater incidence of VT across BMI categories and quartiles of weight, waist circumference in ARIC, waist-hip ratio, and calf circumference (measured in ARIC only), but not height in either cohort and not waist circumference in the older CHS cohort, for which there was a J-shaped relationship. In the younger ARIC participants VT rates ranged from 0.7 to 1.0 per 1000 person years in the bottom category of each factor to 1.7 to 2.6 per 1000 in the top category. Corresponding rates in the older CHS participants were 2.3 to 2.5 per 1000, up to 3.3 to 6.2 per 1000. The inset in Fig. 1 shows that VT incidence rates in CHS also increased across categories of fat mass and fat-free mass, although for fat mass the rate was lower in the 3rd quartile than the 1st and 2nd.

Table 1
Baseline characteristics of study participants, LITE.

Characteristic, mean (SD) or %	Incident VT (n = 448)	No VT (n = 20.466)
Age, years	63 (10)	59 (10)
Sex, female	55%	56%
Race, black	26%	24%
Diabetes	18%	13%
Weight, kg	81.3 (17.0)	76.9 (16.4)
Height, cm	168 (10)	168 (9)
BMI, kg/m^2	28.8 (5.2)	27.4 (5.2)
Obesity	37%	25%
Waist circumference, cm	100 (14)	96 (14)
Elevated waist circumference	63%	51%
Hip circumference, cm	106 (11)	104 (10)
Waist-hip ratio	0.94 (0.08)	0.93 (0.08)
Calf circumference, cm[a]	38.5 (3.9)	37.4 (3.7)
Fat-free mass, kg[b]	41.5 (9.9)	39.6 (9.4)
Fat mass, kg[b]	35.3 (12.4)	32.8 (10.7)

[a] ARIC only.
[b] CHS only.