Atherosclerosis 223 (2012) 378–383

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

# Epicardial adipose tissue and idiopathic deep venous thrombosis: An association study

Gianluigi Mazzoccoli [a,*,1], Massimiliano Copetti [b,1], Mariangela Pia Dagostino [a], Massimo Grilli [a], Andrea Fontana [b], Fabio Pellegrini [b,c], Antonio Greco [d]

[a] Unit of Internal Medicine, Department of Medical Sciences, Scientific Institute and Regional General Hospital "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy
[b] Unit of Biostatistics, Scientific Institute and Regional General Hospital "Casa Sollievo della Sofferenza", S. Giovanni Rotondo, Italy
[c] Unit of Biostatistics, Laboratory of Clinical Epidemiology of Diabetes and Chronic Diseases, Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy
[d] Unit of Geriatrics, Scientific Institute and Regional General Hospital "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy

ARTICLE INFO

*Article history:*
Received 10 March 2012
Received in revised form
15 May 2012
Accepted 28 May 2012
Available online 12 June 2012

*Keywords:*
Epicardial fat
Venous thrombosis
Atherosclerosis
Cardiovascular risk
Aging

ABSTRACT

*Objective:* Epicardial fat (EpiF) reflects abdominal visceral adiposity and visceral fat plays an important role in the development of an unfavorable metabolic and atherosclerosis risk profile. An increased cardiovascular risk has been evidenced in patients with deep venous thrombosis (DVT). Advancing age is characterized by alterations of body fat mass and function In this study we studied the association between EpiF, DVT, age, obesity and other atherosclerosis risk factors.
*Methods and results:* 77 patients were recruited: 44 men and 33 women, 38 without DVT (65.9 ± 16.3 years, range 26–92 years) and 39 with DVT (65.4 ± 17.2 years, range 28–90 years). The study design was balanced for established atherosclerosis risk factors (gender, obesity, smoking habits, dyslipidemia, diabetes mellitus, arterial hypertension), for previous cardiovascular events, for use of statins and platelet anti-aggregating agents. Multivariate regression model and RECPAM regression tree were used to study the association between EpiF thickness and the other potential risk factors. Patients with DVT showed a thicker EpiF with respect to those without DVT (12 ± 2 mm *vs.* 9 ± 2 mm respectively, $p < 0.001$). Multivariate linear regression model showed that DVT, obesity and age were positively associated with EpiF thickness after adjusting for the established atherosclerosis risk factors. Furthermore, the RECPAM analysis was performed to evaluate interactions between DVT, age and obesity: four main distinct and homogeneous subgroups of patients in terms of EpiF thickness were identified. The most important variable in partitioning patients was represented, as expected, by DVT ($p < 0.001$) followed by age ($p = 0.004$), while obesity did not contribute to the model as well as the other atherosclerosis risk factors. Patients with DVT and older than 41 years of age had higher EpiF thickness in respect of patients with DVT and younger than 41 years of age. In patients without DVT the estimated cut-off age was 50 years, and older patients had thicker EpiF in respect of patients younger than 50 years of age. Conclusion: DVT should be considered as strongly associated with EpiF thickness. *Advancing age* (with or without spontaneous DVT) is significantly associated with an increased EpiF thickness. The measurement of EpiF thickness, a valuable marker of cardio-metabolic risk, may represent a useful and reliable method to evaluate cardiovascular risk in patients with idiopathic deep phlebothrombosis.


## 1. Introduction

The adipose tissue that surrounds the internal organs (e.g., heart, intestines) in the cavities of the body, called visceral fat, predicts an unfavorable cardiovascular and metabolic risk profile. The epicardial fat (EpiF) is metabolically active, produces free fatty acids, adiponectin and inflammatory cytokines and is strongly correlated to visceral adiposity [1–4]. Advancing age is associated to altered body fat mass and function [5]. Clinical imaging studies have demonstrated a strong direct correlation between abdominal visceral adiposity and epicardial adipose tissue, and multislice whole body magnetic resonance imaging would be the gold standard technique to accurately measure visceral adiposity [6].

Waist circumference and body mass index are surrogate measures of visceral abdominal obesity and markers of an adverse

* Corresponding author. Tel.: +39 (0)882835321; fax: +39 (0)882410255.
*E-mail addresses:* g.mazzoccoli@tin.it, g.mazzoccoli@operapadrepio.it (G. Mazzoccoli).
[1] These two authors contributed equally to this study.

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http://dx.doi.org/10.1016/j.atherosclerosis.2012.05.033

metabolic profile associated with high cardiovascular risk, but waist circumference seems to quantify subcutaneous fat better than visceral fat, and might be a not reliable measure in older individuals. Direct measurement of EpiF thickness via transthoracic two-dimensional (2D) guided M-mode echocardiography is a valuable, affordable and reliable method to evaluate visceral adiposity [7–15].

Thrombosis in the arterial and venous compartment have always been considered different pathologies, but indicators of atherosclerosis and/or arterial thromboembolic events have been associated to venous thrombosis by epidemiological studies, highlighting the role of venous thrombosis as a long-term risk factor for cardiovascular events [16–27].

The aim of our study was to investigate the association between EpiF thickness and idiopathic Deep Venous Thrombosis (DVT), and to evaluate how they interact in patients with or without DVT characterized by the same risk factors for atherosclerosis (age, gender, obesity, cigarette smoking, dyslipidemia, diabetes mellitus, arterial hypertension).

## 2. Materials and methods

### 2.1. Patients

The study was approved by the local Scientific and Ethical Committee and was conducted on consecutive patients hospitalized in the Department of Internal Medicine. We enrolled 77 Caucasian subjects, 44 men and 33 women, 38 without DVT (23 men and 15 women) and 39 with DVT (21 men and 18 women), assessed through the compression ultrasonography (CUS) of lower limb veins.

This case series was the result of the analysis of 327 consecutive patients with spontaneous DVT followed at our Institute. Most patients not enrolled had exclusion criteria, although 3 eligible patients did not give informed consent, and 59 were lost to follow-up. All the other patients meeting inclusion criteria were studied.

Subjects gave written informed consent and the investigation conformed to the principles outlined in the Declaration of Helsinki. Exclusion criteria included pregnancy, cancer, concomitant infection, leg trauma or bone fracture, cast therapy, surgical procedures in the last 90 days, condition of being chronically ill, *bedridden* or non ambulatory and treatment with prothrombinogenic agents (steroids, estrogens). Subjects were chosen to obtain two matched groups homogeneous with respect to the common risk factors for atherosclerosis, (age, male gender, obesity, current cigarette smoking, dyslipidemia, diabetes mellitus, arterial hypertension), with respect to previous cardiovascular diseases (stable and unstable angina, myocardial infarction, cerebrovascular accident such as nonhemorrhagic stroke, peripheral vascular disease) and with respect to medication history (use of statins, antihypertensive agents and platelet anti-aggregating agents) and biochemical parameters (total, LDL and HDL cholesterol, triglycerides, plasma glucose and erythrocyte sedimentation rate, ESR). Patients with DVT were selected in the acute phase (within two weeks from onset) of disease and heparin was administered to the patients with venous thrombosis after the ultrasonographic evaluations in the form of low-molecular-weight heparin (enoxaparin, at a dosage of 1 mg/kg twice a day). Patients without DVT were diagnosed as functional dyspepsia, irritable bowel syndrome, musculoskeletal disorder such as low back pain.

### 2.2. Clinical and biochemical risk variables

In all enrolled subject weight in kilograms and standing height in centimeters were measured at the clinic examination by standard protocols. Level of overweight was measured by body mass index (BMI). Questions were asked on number of cigarettes smoked per day and duration of smoking; responses to these questions provided the foundation for the definitions of smoking status and pack-years of smoking. Blood pressure was measured in both groups using the same protocol. Three measurements were taken with a random-zero sphygmomanometer, and the mean of the last 2 of 3 measurements was used.

In all enrolled subjects, a venous blood sample was drawn after an overnight fast for the determination of lipid parameters (total, LDL and HDL cholesterol, triglycerides), plasma glucose and erythrocyte sedimentation rate (ESR). Plasma glucose, total cholesterol (milligrams per deciliter) and triglyceride levels (milligrams per deciliter) were measured by enzymatic methods and low-density lipoprotein (LDL) cholesterol (milligrams per deciliter) was calculated indirectly using the Friedewald equation. High-density lipoprotein (HDL) cholesterol was measured after precipitation of the other lipoprotein fractions by dextran sulfate.

The following cut-off values were considered: systolic arterial pressure $> 140$ mmHg and diastolic arterial pressure $> 90$ mmHg for definition of arterial hypertension or a history of or treatment for arterial hypertension, a total cholesterol level $> 200$ mg/dl, a low-density lipoprotein (LDL) cholesterol level $> 100$ mg/dl, a high-density lipoprotein (HDL) cholesterol level $< 40$ mg/dl for male subjects or $< 50$ mg/dl for female subjects and a triglyceride level $\geq 150$ mg/dl for definition of dyslipidemia. BMI $\geq 30$ for definition of obesity. Diabetes mellitus was defined at baseline as fasting glucose levels of 126 mg/dL (7 mmol/L) or higher, nonfasting glucose levels of 200 mg/dL (11.1 mmol/L) or higher, or a history of or treatment for diabetes. Impaired fasting glucose level was defined as 110 mg/dL (6.1 mmol/L) or higher but lower than 126 mg/dL (7 mmol/L). ESR $\geq 20$ mm/h was considered for definition of inflammation in the body.

The screening for mutations and conditions associated with thrombophilia (antithrombin III, protein C or protein S deficiency, factor V Leiden, prothrombin G20210A mutation, hyperhomocysteinemia and lupus-like anticoagulants) was performed in all the subjects and the subjects with alterations of these factors were excluded from the study.

### 2.3. Echocardiographic study of epicardial adipose tissue

Each subject underwent transthoracic two-dimensional (2D) guided M-mode echocardiogram. Echocardiograms were performed with an Esaote MyLab TM Gold Cardiovascular instrument (Esaote, Genova, Italy) by standard techniques with subjects in the left lateral decubitus position. Echocardiograms were recorded on videotape. The echocardiographic study required the recording of 10 or more cycles of 2D parasternal long- and short-axis views and 10 or more cycles of M-mode with optimal cursor beam orientation in each view. Echocardiograms were performed by the same expert sonographer (MPD), who was blinded to the subjects' clinical data and anthropometric features. The ultrasonographic evaluations have been effectuated on day 1 of their diagnosis or at enrollment. When the measurements were performed on 2 separate days in 10 patients, the within-patient difference for the measurement of the Epi F was $1.1 \pm 0.9\%$, indicating good reproducibility of the echocardiographic measurements [28]. We measured epicardial fat thickness on the free wall of the right ventricle from both parasternal long- and short-axis views. We used imaging constraints to make sure that the EpiF thickness was not measured obliquely. Measurements on M-mode strips obtained from both 2D views with longitudinal cursor beam orientation in each view were also performed. The maximum values at any site were measured, and the average value was considered.