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BRIEF ARTICLE

High prevalence of nonalcoholic fatty liver in patients with idiopathic venous thromboembolism

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Abstract

AIM: To assess the prevalence of nonalcoholic fatty liver disease (NAFLD) in patients with idiopathic venous thromboembolism (VTE).

METHODS: In a case-control study, after excluding subjects with well-consolidated risk factors for VTE, idiopathic VTE was documented in 138 consecutive patients who were referred to our department. Two hundred and seventy-six healthy sex/age/body-mass-index-matched subjects, without any clinical/instrumental evidence of VTE, served as controls. All underwent a clinical/laboratory/ultrasound assessment for the presence of metabolic syndrome and NAFLD.

RESULTS: NAFLD was detected in 112/138 cases (81%) and in 84/276 controls (30%) [risk ratio: 2.7, 95% confidence interval (CI): 2.2-3.2, $P < 0.0001$]. Metabolic syndrome and smoking habit were more prevalent in patients with idiopathic VTE. The high prevalence of NAFLD in VTE was also confirmed after adjustment for inherited thrombophilia. NAFLD was clearly predicted by VTE (odds ratio: 1.8, 95% CI: 1.2-2.7, $P < 0.0001$).

CONCLUSION: NAFLD was independently associated with idiopathic VTE.

Key words: Thromboembolism; Metabolic syndrome; Nonalcoholic fatty liver disease

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INTRODUCTION

Venous thromboembolism (VTE) has an annual incidence of 1-2 events/1000 people in the general population, and is considered to be an emerging health problem[1,2]. Arterial and venous thromboses have been historically considered as distinct entities due to thrombus composition and different response to antiplatelet or anticoagulant drugs[3]. Metabolic syndrome (MS), which affects > 20% of the whole population[4,5], increases cardiovascular risk[6] by a blood hypercoagulability-related mechanism. This phenomenon is the result of abnormally high plasma levels of plasminogen activator inhibitor-1 (PAI-1), fibrinogen and factors Ⅶ, Ⅷ and von Willebrand, as well intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1[7-12]. Indeed, antiphospholipid syndrome and hyperhomocysteinemia predispose to venous and

cardiovascular events[13-15]. Ageno *et al*[16] have reported an association between idiopathic VTE and MS, which has been confirmed by Ay *et al*[17]. Arterial hypertension is a cardiovascular risk factor for VTE[18,19]. In addition, type 2 diabetes is associated with several coagulation and fibrinolysis alterations that lead to a procoagulant, thrombogenic predisposition, and is likely to have a significant impact on VTE occurrence[20]. Abdominal obesity is currently accepted as an independent risk factor for VTE[21].

Nonalcoholic fatty liver disease (NAFLD) has been strictly associated with MS[22]. Insulin resistance is reckoned to be the major mechanism. NAFLD refers to a wide spectrum of liver damage, which ranges from simple steatosis to nonalcoholic steatohepatitis, advanced fibrosis and cirrhosis.

In a series of patients with idiopathic VTE, we tried to assess the prevalence of NAFLD, further expression of MS, comparing the data with those achieved in control subjects.

MATERIALS AND METHODS

Inclusion criteria

One hundred and thirty-eight patients with recent (< 6 mo) objective diagnosis of idiopathic VTE were enrolled in the study. One hundred and twenty patients had deep vein thrombosis (DVT), of which, 21 were associated with superficial vein thrombosis, nine were suffering from isolated pulmonary embolism (PE), and 16 with PE plus DVT. DVT was confirmed by Doppler ultrasonography (DUS). PE was documented by computed tomography.

VTE was defined as idiopathic in the absence of pregnancy or puerperium, known active malignancies, recent (< 3 mo) surgery or trauma, fracture, immobilization, lack of prophylaxis, acute medical disease, use of oral contraceptives, long-distance travel, a history of VTE or repeated birth loss. In contrast, when at least one of the previous risk factors was present, VTE was defined as secondary and the patients were excluded from the study.

As many as 276 healthy sex/age/body mass index (BMI)-matched subjects served as controls. In all of them, exclusion of DVT was based on clinical examination, use of D-dimer testing, and clinical pretest probability and, in some uncertain cases, by two DUS examinations within 1 wk of each other.

Exclusion criteria

Cases and controls who presented with unstable medical conditions were excluded. Other exclusion criteria were a history of infectious chronic diseases including hepatitis B and C, autoimmune and storage diseases, drug-induced hepatic steatosis, and prior use of medication known to affect inflammation, glucose metabolism or blood lipids. Alcohol abuse was ruled out, according to the DSM-IV diagnostic criteria, by means of screening tests such as MAST (Michigan Alcohol Screening Test) and CAGE (Cut down, Annoyed, Guilty, and Eye opener), as well as random tests for blood alcohol concentration and the use of a surrogate marker, e.g. mean corpuscular volume. Patients on antihypertensive therapy maintained a balanced medical regimen throughout the study.

Clinical, laboratory and imaging data

Sex, age, BMI, waist circumference, history of symptomatic atherosclerosis (i.e. ischemic stroke, transient ischemic attack, acute myocardial infarction, angina, intermittent claudication), arterial hypertension or use of antihypertensive drugs, diabetes mellitus or use of antidiabetic drugs, hyperlipidemia or use of statins or clofibrate, smoking habit (daily consumption of $\geqslant$ 1 cigarette), current use of heparin, oral anticoagulant or antiplatelet drugs were recorded. Subsequently, all patients underwent liver ultrasound (US), measurement of blood pressure, fasting glucose, transaminases and γ-glutamyl transferase activity, high-density lipoprotein (HDL) cholesterol and triglyceride levels. MS was diagnosed by the presence of at least three criteria (National Cholesterol Education Adult Treatment Panel Ⅲ) on the basis of abdominal obesity (waist circumference > 102 cm for men and > 88 cm for women), triglycerides $\geqslant$ 150 mg/dL, HDL-cholesterol < 40 mg/dL for men and < 50 mg/dL for women, blood pressure $\geqslant$ 130 mmHg and/or $\geqslant$ 85 mmHg, and fasting glucose $\geqslant$ 100 mg/dL. Obesity was recognized as a BMI $\geqslant$ 30.

The classification of "bright liver" or hepatic steatosis grade was based on the following scale of hyperechogenity at US: 0 = absent, 1 = light, 2 = moderate, 3 = severe, pointing out the difference between the densities of the liver and the right kidney[23]. Diagnostic criteria for DVT were observation of an intraluminal venous thrombus, loss of compressibility, and lack of flow at DUS.

Statistical analysis

We observed how many times the event of interest, i.e. NAFLD occurred in the experimental group or cases (VTE) and in controls. Statistical confidence was increased by taking two controls per case. The RR and 95% CI was the ratio of the proportions of cases with a positive outcome in the two groups. Patients' clinical characteristics were compared using Student's *t* test (continuous variables) and the χ^2 test (dichotomous variables). A logistic regression (stepwise model) was adopted, in which NAFLD was the dependent variable and sex, anthropometric parameters (BMI, waist circumference), metabolic features (serum HDL-cholesterol, triglycerides and glucose), systolic blood pressure, diastolic blood pressure, smoking habit and finally VTE were employed as independent variables. MS as entity was not considered in prediction, to avoid multicollinearity. The same tool (enter method) was carried out to predict VTE presence the by US grade of steatosis. Statistical analysis was performed with MedCalc® 11.2.

RESULTS

The mean age in the cases and controls was 41.8 ± 13.0 and 43.4 ± 15.7 years, and the mean BMI in the two groups was 30.4 ± 4.1 and 29.6 ± 3.9 (P = 0.79 and P

Table 1 Prevalence of clinical and laboratory findings and smoking in the whole population

	Cases (138) yes/not	Controls (276) yes/not	RR (95% CI)	*P*
Smoking habit	81/57	108/168	1.5 (1.2-1.8)	0.000
Fasting glucose ⩾ 110 mg/dL	84/54	110/166	1.5 (1.25-1.9)	0.000
Abdominal obesity	98/40	107/169	1.8 (1.5-2.2)	< 0.0001
Hypertriglyceridemia	72/66	131/145	1.1 (0.8-1.3)	0.35
Low HDL-cholesterolemia	91/47	146/130	1.2 (1.1-1.5)	0.008
Hypertension	94/44	111/165	1.7 (1.4-2.0)	< 0.0001

RR: Risk ratio; CI: Confidence interval; HDL: High-density lipoprotein.

= 0.81, respectively). Sex distribution between the two groups did not show significant differences (χ^2, $P = 0.95$).

Among the 138 VTE patients, 112 (81%) had concomitant NAFLD, whereas 84 out of 276 (30%) controls suffered from NAFLD (RR = 2.7, 95% CI: 2.2-3.2, $P < 0.0001$). The RRs of smoking habit and single components of MS are shown in Table 1.

Factor V G1691A and/or prothrombin G20210A polymorphisms (major determinants) were not detected in 80 out of 138 cases (58%) and in 188 out of 276 controls (68.1%). A higher prevalence of NAFLD in patients with VTE but without inherited thrombophilia versus controls was also confirmed on the basis of this further selection; 62 patients in cases and 61 in controls (RR = 2.4, 95% CI: 1.9-3, $P < 0.0001$). When predicting NAFLD, VTE played an important role, which confirmed the aforementioned findings, but also smoking habit and some MS components gave a good prediction (Table 2). In contrast, age, BMI and sex did not enter the model, because their significance was > 0.1. The presence of VTE was well predicted by grade of steatosis, as revealed by US (OR = 1.9, 95% CI: 1.05-3.8, $P < 0.0001$).

DISCUSSION

Our main finding was a significantly higher prevalence of NAFLD in idiopathic VTE patients than in controls, which was confirmed after adjusting for inherited thrombophilia. Although these results were partially expected, they were highlighted for the first time in the present study. What is more, this report extends previous data[16] on MS. In a recent report[24], rather than considering "all-or-nothing" definitions for MS, the additive effect of having more than one of the MS features has been considered. This is a controversial point. However, what if physicians use an indirect parameter of MS presence, e.g. NAFLD? The present study supports a significant correlation between every single component of MS and VTE, even though the strictest association was demonstrated between NAFLD, a further expression of MS as a whole[22], and VTE, which by-passes the restrictive criteria of MS.

These data lend credence to the possibility that VTE is an early clinical event in a generalized vascular disease

Table 2 Prediction of nonalcoholic fatty liver disease

	OR (95% CI)	*P*
Venous thromboembolism	1.8 (1.2-2.7)	< 0.0001
Fasting glucose ⩾ 110 mg/dL	1.0 (1.0-1.02)	0.04
Abdominal obesity	1.7 (1.14-2.5)	0.0001
Hypertension	1.02 (1.0-1.04)	0.03
Smoking habit	1.6 (0.8-2.3)	0.0002

Method: Stepwise; variable entered if $P < 0.05$, and removed if $P > 0.1$. OR: Odds ratio; CI: Confidence interval.

that involves venous and arterial circulation. Our results support the need for further studies to evaluate the risk of subsequent cardiovascular events in VTE patients without MS, but with NAFLD.

In trying to establish the complex interaction between VTE and NAFLD, we stress that they share common mechanisms. First of all, we should pinpoint the role of PAI-1. In fact, abdominal fat, liver steatosis and serum triglycerides levels have been shown to be significant and independent determinants of PAI-1 plasma level in an unselected sample of male adults upon adjustment for age and therapy[25]. Additionally, the pro-angiogenic factor, vascular endothelial growth factor, which is generally thought to be the main factor that determines VTE in patients with cancer[26], plays a key role in NAFLD[27]. Recent evidence has substantiated that NAFLD is associated with elevated circulating levels of ICAM-1, which throws further light on inflammation-related liver damage[28]. Another intriguing link is represented by smoking, which is a plain risk factor for the development of VTE. Indeed, this relationship could be justified by the presence of NAFLD. In fact, Yuan *et al*[29] have provided novel evidence to demonstrate that tobacco smoke exposure can accelerate the development of experimental NAFLD.

The limitations of the present study are as follows. Our control group comprised individuals who were referred for signs or symptoms initially suggestive of VTE, and it may not adequately represent a general healthy population. However, the prevalence of MS in our control group was comparable to that reported in the general Italian population[5], which suggests that, with a differently selected control group, our findings could have been comparable to those reported in the previous study. Although patients with cancer were excluded from our study, some VTE patients might have had occult cancer at the time of investigation. The impact of occult cancer on the components of MS is unknown; however, its impact on the results of our analysis was likely to have been low. With regard to the definition of idiopathic VTE, we have defined it as VTE that occurs in patients without the most common known risk factors. Based on our definition, other risk factors might have been missed, but this is unlikely to have significantly influenced our results. Another potential point of criticism relates to the size of the study, which was not very large.

In conclusion, an eventual association between VTE and NAFLD should be always pursued.

COMMENTS

Background

Venous thromboembolism (VTE) with an annual incidence of 1-2 events/1000 people in the general population is considered to be an emerging health problem.

Research frontiers

Metabolic syndrome affects > 20% of the whole population, and increases the cardiovascular risk by a blood hypercoagulability-related mechanism.

Innovations and breakthroughs

This is believed to be the first evidence to show a strict link between idiopathic VTE and nonalcoholic fatty liver disease (NAFLD). Smoking could increase the risk of VTE by worsening NAFLD.

Applications

Patients suffering from MS should be warned against their increased risk of VTE.

Peer review

In this paper, research on the prevalence of NAFLD in idiopathic VTE is presented, which is an interesting topic.

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