It is known that thrombophilia (TP) is a risk factor for deep venous thrombosis (DVT), and that DVT predisposes to chronic venous ulceration (CVU). However, the relationship between TP and CVU has not been well studied. Review of the literature reveals that the prevalence of TP in CVU patients is high — similar to the prevalence found in patients with a history of DVT. This is despite many patients with CVU having no clear history, or duplex evidence of previous DVT. TP may predispose to CVU by leading to macro- or micro-vascular thrombosis. This association raises several issues regarding the investigation, prevention and management of patients with venous disease.

**Introduction**

Chronic venous ulceration (CVU) affects at least 1% of the adult population (life-time risk), is associated with a marked reduction in quality of life, is characterized by low healing and high recurrence rates regardless of treatment, and consumes 1–2% of health care spending in most developed countries. The pathogenesis of the condition, especially at the microvascular level, remains incompletely defined and controversial. However, at the macrovascular level, it is generally agreed that the skin changes of chronic venous insufficiency (CVI) are predominantly due to sustained ambulatory venous hypertension. This, in turn, is due to venous reflux in the superficial and/or deep venous systems and, to a lesser extent, deep venous obstruction. A significant proportion of ulcers follow a clinically apparent and clearly documented episode of deep venous thrombosis (DVT) (post-phlebitic syndrome). Almost certainly, a further significant proportion of CVU follows a sub-clinical, forgotten, undocumented or unrecognised DVT. As a result, the proportion of CVU that are deemed to be post-thrombotic varies considerably between series depending upon thoroughness with which previous DVT is sought.

Thrombophilia (TP) may be defined as an abnormality of the clotting and/or fibrinolytic cascade(s) that leads to a hypercoagulable state. TP can be acquired or inherited and may predispose to atypical and/or recurrent arterial and/or venous thrombosis at a relatively young age (Table 1). As DVT is clearly a major risk factor for CVU it is perhaps surprising that the possible link between TP and CVU has not received more attention. It seems reasonable to hypothesise that a DVT developing in the presence of TP is more likely to lead to the post-phlebitic syndrome and CVU because it may occur earlier in life, is more likely to be extensive, may be more resistant to endogenous fibrinolysis and recanalisation, may be less responsive to treatment and is more likely to recur. Furthermore, CVU is associated with microvascular thrombosis and the development of a peri-capillary fibrin cuff; both of which may reflect defective fibrinolytic capacity. The aim of this paper is to review what is known of the relationship between CVU and TP.

**Methods**

The Medline database was searched for articles using the terms: thrombophilia, venous ulceration, venous insufficiency, as well as the individual thrombophilias. All abstracts were reviewed, and full text of relevant articles retrieved. Reference lists of retrieved articles were also searched for pertinent publications.
Thrombophilia

Thrombophilia and its relationship with arterial and venous thrombosis has been extensively reviewed elsewhere. For that reason, only a short description of the common abnormalities to be discussed below in relation to CVU is given here.

**Antithrombin (AT) deficiency**

AT is synthesized by the liver and inhibits thrombin and the activated factors of the intrinsic cascade (Xa, IXa, XIa, XIIa) and kallikrein. Many (> 80) mutations of the AT gene have been reported. AT deficiency is usually inherited in an autosomal dominant manner. Type I deficiency is due to low levels of AT and type II is due to the presence of a variant AT protein. In either case, functional AT activity can be determined by its ability to inhibit Xa in a heparin cofactor assay. Other tests can be used to distinguish type I from type II deficiency, as well as different types of type II deficiency. However, the clinical significance of this is unclear and a functional test is recommended for screening. Acquired AT deficiency can occur in association with many conditions including major surgery and malignancy.

**Protein C (PC) deficiency**

Protein C (PC) is a vitamin K dependent glycoprotein that is synthesised in the liver. Approximately 60% is bound to complement (C4b) and 40% circulates as free protein. Only free PS acts as a non-enzymatic cofactor to enhance the actions of APC on Va and VIIIa. At least 70 mutations have been identified leading to type I and type II deficiencies, which are usually passed on in an autosomal dominant manner. Some patients have low functional PS activity but no identifiable mutation; either the relevant mutations is yet to be identified or another mechanism is responsible. This, so-called, type III deficiency is associated with normal total PS antigen but reduced free antigen and activity. Type I and type III deficiencies may co-exist in the same kindred. There is overlap in free PS levels between PS deficient heterozygotes and the normal population. Also, PS levels vary with age, gender, a number of medical conditions, pregnancy and hormone usage. For all these reasons, the diagnosis of PS deficiency is more difficult than for AT or PC.

**Activated protein C resistance (APCR) and factor V leiden (FVL)**

Activated PC resistance (APCR) is caused in the great majority (90%) of cases by a single base (Leiden) mutation in the factor V gene (FVL). This mutation renders Va resistant to the action of APC. Other factor V mutations (Cambridge, Hong Kong) and

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**Table 1. The prevalence of thrombophilia and the relative risk for venous thrombosis.**

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Estimated prevalence in general &quot;Western&quot; population (%)</th>
<th>Estimated prevalence in unselected patients with a first DVT (%)</th>
<th>Estimated relative risk for DVT</th>
</tr>
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secondary causes, such as antiphospholipid antibodies (APLA), account for the remaining cases of APCR. FVL is common in Europeans (5–10%), uncommon in people from North India and the Middle East and absent in the indigenous people of Asia, America and Australasia. FVL heterozygotes may have a survival advantage through a reduction in intra- and post-partum haemorrhage. The commonest test for APCR involves measuring the prolongation of the APTT following the addition of APC (APC ratio). However, there are a number of problems associated with using this test as a screening tool and most authorities also recommend a polymerase chain reaction (PCR)-based “genetic” test to specifically identify the FVL mutation.12

Hyperhomocystinaemia

Hyperhomocystinaemia (HHcy) has been implicated in the development of arterial and venous thrombosis through a range of incompletely understood mechanisms.14–16 Homocysteine is a metabolic breakdown product of methionine, which is itself metabolised through remethylation (vitamin B12 dependent) or transulphuration (B6 dependent) pathways. HHcy, due to a heterozygous deficiency of one of several enzymes involved in these pathways, is present in approximately 1% of the population. More commonly, HHcy is due to a deficiency of B12, B6 and folate in the diet. Such HHcy is frequently defined as >15 μmol/l; this being the level found in about 5% of the population. Hcy can be measured in number of different ways; in our laboratory we use high-pressure liquid chromatography.

Elevated factor VIII levels

Elevated factor VIII (FVIII) levels (>150 IU/dl) are associated with an almost five fold increase in DVT risk and are present in just over 10% of the normal population. Affected patients are particularly prone to recurrent thrombosis.17 The reasons for high FVIII are unclear but there does appear to be a hereditary component, possibly linked to the X-chromosome.16 FVIII can also arise as part of an acute phase response and it is recommended that C-reactive protein (CRP) be measured at the same time.

Elevated factor XI levels

Factor XI (FXI) is a component of the intrinsic system with direct procoagulant and indirect antifibrinolytic activity.19 Elevated FXI levels (>90th centile) are associated with a doubling of thrombotic risk.20 As yet, it is unclear whether the elevated level is due to specific genetic mutations.

Prothrombin G20210A variant

Prothrombin is a vitamin-K dependent glycoprotein. A single base mutation (A to G at position 20210) of the prothrombin gene is found in approximately 1–3% of the general European population but is rare in people of African and Asian descent.21 The mutation is associated with increased prothrombin blood levels and activation, which presumably explains the increased thrombotic risk.22 This may be due to increased gene expression. The mutation can be readily detected by means of PCR.

Antiphospholipid antibodies

There are two distinct types of APA; lupus anticoagulant (LA) and anticardiolipin antibodies (ACLA).23 LAmay inhibit the T-TM complex dependent activation of PC upon the EC surface. ACLA are commoner than LA in the general population and may be IgM or IgG or, rarely, IgA molecules. IgG is generally held to be the most pathogenic. ACLA appear to promote thrombosis through a number of different, incompletely defined, mechanisms including stimulation of platelet aggregation, inhibition of APC and AT, and up-regulation of tissue factor. APLA are frequently detected transiently in patients with autoimmune and viral conditions and those on certain drugs. It is recommended, therefore, that patients positive for LA or ACLA should be restated after a period of at least three months.

Other thrombophilias

New information regarding various putative inherited and acquired risk factors for venous thrombosis is accruing rapidly.

The multifactorial nature of thrombophilic risk and its management

In an otherwise young and fit individual, heterozygosity for a single inherited TP does not usually confer a significant increase in the risk of primary or recurrent thrombosis24 or of pulmonary embolism.25
However, where one or more such abnormalities co-segregate and/or where they are accompanied by one or more acquired TP, then risk of DVT can increase dramatically. This is especially so in older individuals. For example, a FVL-positive women taking hormone replacement therapy undergoing venous surgery for a post-thrombotic CVU may present an exceptionally high risk for recurrent thrombosis. At the present time, there are insufficient data to provide a firm evidence base for the management of thrombophilic patients. However, it must be remembered that oral anticoagulation to a target INR of 2.5 is associated with one major and 0.25 fatal haemorrhages per 100 patient treatment years.

The Prevalence of TP in CVU

**AT, PC and PS deficiency**

The first study to examine the relationship between TP and CVU was conducted by Falanga who found a reduction in PC activity/antigen, and/or PS antigen, in 5 of 19 patients with lipodermatosclerosis (LDS) and ulceration; two of which had a history of DVT. This led Falanga to propose PC deficiency as a possible risk factor for CVU. In subsequent correspondence Salmaska suggested that as PC (PS) activation requires the presence of TM, the decreased PC activity found by Falanga might be due to an endothelial cell defect related to venous hypertension rather than an actual deficiency of PC. Tsutsui described a patient with recurrent venous leg ulcers and a type II protein S deficiency who responded to warfarin. Phifer identified three siblings with chronic venous insufficiency, all of whom had AT III deficiency. A further sibling had died aged 20 years old of pulmonary embolism. More recently, however, Ribeudeau found that none of 35 consecutive patients presenting with CVU (14 of which had a history of DVT) had a deficiency in PC (antigen or activity), PS (activity and free and total antigens) or AT antigen.

**APCR and FVL**

In 1995, Munkvad and Jorgensen reported on 46 patients with CVU. Using a functional assay based upon the activated partial thromboplastin time (APTT) in the presence and absence of APC, APCR was found in 12 (26%). Of these, 25% had a history of DVT compared with eight of 34 (26%) without APCR (non-significant). Grossman reported on 29 consecutive patients with CVU. APCR was first determined by a functional assay based upon the APTT and if this was positive the FVL genetic test was performed. Although APCR was found in 11 patients, only two (7.7%, overall) were found to be heterozygous for FVL. Hafner and von Felten studied 20 consecutive patients presenting with CVU. APCR was present in four patients on the basis of the APTT test. Two of these patients had a history of DVT compared with four of 16 patients without APCR (non-significant). However, the importance of performing the FVL genetic test in all patients was quickly emphasised as it is possible to be heterozygous for FVL without an abnormality in the APTT APCR test, and not all cases of APCR are caused by FVL. Hachenjos described a 34-year-old man who had suffered recurrent CVU of both legs since childhood in association with APCR due to FVL and an intermittent factor XIII deficiency. Mitsis presented a similar report of a 25-year-old man with recurrent DVT and severe post-phlebitic syndrome. He was found to be homozygous for FVL, and heterozygous for f II 20210 G-A mutation. Maessen-Visch found that 21 of 92 patients with healed or open ulceration (54 of which had a history of DVT) were FVL positive (20 heterozygous and one homozygous) compared with four of 53 controls (7.5%) (odds ratio 3.6, 95% CI 1.2-11.2, p = 0.03). Patients with FVL were more likely to have a history of DVT (91% vs 48%, p = 0.002) and, specifically, recurrent DVT (38% vs 14%, p = 0.03) and to have had more than nine episodes of ulceration (43% vs 16%, p = 0.01). There was no relationship between FVL and age or the results of light reflection rheography. The authors concluded that the combination of DVT and FVL increased the risk of recurrent CVU. Ribeudeau also looked at the prevalence of FVL and APCR in 35 patients with CVU. APCR was present in only four of 33 patients tested, of whom one had a history of DVT. One patient with APCR, and a previous DVT, was FVL positive and also had IgG APLA. FVL was not detected in any patient without APCR. The high prevalence of FVL in CVU patients was confirmed by Gaber who studied 100 consecutive CVU patients. Of these, 53 were deemed to have a post-thrombotic ulcer, 19 of whom had FVL (36%); this compares with three of 47 CVU patients with no history of thrombosis, and 5% of healthy controls.

**Prothrombin 20210A**

To date, only one study has examined the prevalence of PT 20210A. Ribeudeau found no cases in a series of 35 patients with CVU.
Antiphospholipid antibodies

Three studies have examined the prevalence of APAs in patients with CVU. Grossman studied 29 patients presenting with CVU and found ACLA in six of 21 patients tested.35 In a series of 35 patients with CVU, Ribeadeau found that APLA of IgG class were present in three of 31 patients tested (one of whom had a previous DVT) compared with two of 23 controls.33 No patients had IgM class antibodies. IgG antibodies were associated with APCR in two patients, one of whom also had FVL. Alcaraz studied 27 CVU patients. Twelve CVU patients had APLA (five ACLA, four LA and three both), three of whom had a history of DVT.43 Unfortunately, none of the above studies performed confirmatory repeat tests, noted concomitant drug therapy or quantified the level of antibody titre.

The Edinburgh and Birmingham Study

This was a prospective study of 88 patients with CVU who underwent clinical assessment, duplex ultrasound and TP screen comprising antithrombin (AT), protein C (PC) and S (PS), activated protein C resistance (APCR), factor V Leiden (FVL), prothrombin G20210A (PT 20210A), lupus anticoagulant (LA) and anticoagulopin antibodies (ACA).44 There were 35 men of median age (IQR) 61 years (45–72), and 53 women of median age 76 years (69–82); and 36% of patients had either a history or duplex evidence suggestive of previous DVT. The following abnormalities were detected: 4 AT, 5 PC and 6 PS deficiencies, APCR 14, FVL 11, PT 20210A 3, LA 8 and ACLA 12. All abnormalities were confirmed on repeat testing at three months. The presence of TP was not significantly related to previous DVT, deep reflux or disease severity (duration of disease, total area, number of episodes or level of pain). In this cohort, 41% of patients had at least one abnormality on TP screening. This is 2–30 times higher than the general population but similar to that reported for DVT patients. In a further study HHcy (>15μmol/l) was found in 23 (42%) of 55 patients with open CVU and four (25%) of 16 patients with healed CVU. This compares with 5% of the normal population (Fig. 1). There was no association between the presence, number or type of thrombophilic abnormalities and the severity of disease or the pattern or severity of reflux on duplex.

Other Thrombophilias and CVU

At the time of writing there are no published data regarding the prevalence of elevated coagulation factor levels, or the moieties listed in Table 2, and CVU. However, on-going work in our own department is addressing this area.

Discussion

The main conclusion to be drawn from the available literature is that patients with CVU appear have a prevalence of TP that is much higher than the general population but similar to post-DVT patients. This high prevalence is observed in ulcer patients with and without a documented history of DVT. It is well recognised that a patient-reported history of DVT is unreliable due to false positives and negatives. In other words, many DVTs are sub-clinical, others are misdiagnosed and patients may confuse DVT with other related conditions such as superficial...
thrombophlebitis. Duplex, as opposed to venography, is increasingly used to image patients with CVU; and duplex is much less sensitive at picking up minor post-thrombotic changes in the deep veins, particularly below the knee.\textsuperscript{45} It can be difficult, therefore, to determine whether DVR in a patient with CVU is post-thrombotic in aetiology or due to primary valvular insufficiency. The strong association between CVU and TP, regardless of whether there is clear clinical or duplex-based evidence of previous DVT, suggests that a considerably greater proportion of patients than previous thought may actually have a post-thrombotic ulcer. However, further work is required to determine if, indeed, this is the case.

Many duplex-based studies have reported CVU in association with apparently isolated superficial venous reflux. But, it remains difficult to explain why certain patients with gross superficial reflux have pristine skin while others with lesser disease suffer the full gamut of venous hypertensive skin changes. There is the suspicion that some other, as yet unrecognised factor, must be at work in such patients. It is interesting to speculate that this additional factor is distal macrovascular and/or microvascular thrombosis; in many cases this may be associated with undiagnosed TP. It may well be that a significant proportion of patients with apparently isolated superficial disease actually have infra-popliteal post-thrombotic venous pathology that is below the limit of duplex detection. In this regard it is interesting to observe that DVT occurring in association with TP is more likely to be distal than proximal.\textsuperscript{46} Furthermore, it is clear that DVT is associated with the development of superficial reflux.\textsuperscript{47} This may be post-thrombotic due to direct LSV damage but other, as yet ill-defined, mechanisms may be involved. It is also suggested that varicose veins may be a risk factor for DVT, especially in older patients.\textsuperscript{48}

At the level of the microcirculation, CVU patients are recognised to have a hypercoagulable diathesis characterised by depressed fibrinolytic activity, increased red cell aggregation, endothelial cell damage, expression of adhesion molecules and cytokine release. In this regard it is interesting to observe that long after the acute inflammatory phase of DVT has passed there is evidence of chronic thrombin and fibrin formation as manifest by PF\textsubscript{1+2} and D-dimer; and that this may predict recurrent thrombotic events.\textsuperscript{47,49}

**Future Work**

TP is clearly an important risk factor for a large proportion, perhaps the great majority of CVU. Cross-sectional and longitudinal studies are needed to answer several important clinical questions relating to the prevention and treatment of CVU. Is TP a risk factor for the progression of simple varicose veins to CVI and, eventually, ulceration? If so, would anti-thrombotic treatment in thrombophilic patients with uncomplicated varicose veins slow, even prevent, disease progression? Should patients with DVT in association with TP be offered more prolonged anti-thrombotic treatment, either with Warfarin\textsuperscript{50,51} or low molecular weight heparin,\textsuperscript{52} in order to prevent the development of CVU? Would long-term anti-thrombotic treatment of thrombophilic patients with CVU augment healing and reduce recurrence?\textsuperscript{53}

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