Factor XIII-deficiency in the Blood of Venous Leg Ulcer Patients

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Pericapillary fibrin cuffs are probably involved in the pathogenesis of venous leg ulcers. Factor XIII (Fibrin stabilizing factor) is of importance in wound healing. Its activity, which may affect ulceration, was found to be significantly reduced in the blood of venous leg ulcer patients and in post-phlebitic patients, compared with healthy controls. ***Key word: Pericapillary fibrin.***

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Burnand et al. (1) and Browse & Burnand (2) have suggested that unrelieved venous pressure leads to a leakage of fibrinogen into the dermis, with consequent formation of pericapillary fibrin layers. The pericapillary fibrin 'cuff' so formed is believed to impede oxygen diffusion between the blood and the adjacent tissue. A low oxygen uptake can be assessed by positron emission tomography (3); transcutaneous oxygen tension is low in the edges of venous ulcers (4). Falanga et al. (5) were able to demonstrate that pericapillary fibrin can be found in the dermis adjacent to venous ulcers.

Systemic implications of the pericapillary fibrin deposition have not been investigated hitherto. Factor XIII (F.XIII) plays a crucial role in wound healing and has a close relationship to fibrin (6–9). It is activated in the plasma in the presence of thrombin and calcium (8) and transforms the urea-soluble fibrin clot into an insoluble form by the oxidation of the gamma-amino group of lysine to an aldehyde which subsequently forms interchains (10). Stabilized fibrin is essential for the growth of fibroblasts in vitro. An increased tensile strength of wounds in animals treated with F.XIII has been observed (6, 9).

Impaired wound healing was found clinically in patients with congenital F.XIII-deficiency (11).

The aim of this study was to investigate the activity of F.XIII in the blood of patients with venous leg ulcers, to compare it with non-venous leg ulcers and to check whether F.XIII-deficiency precedes venous ulceration in post-phlebitic syndromes.

PATIENTS AND METHODS

Only leg ulcers that did not respond to conventional conservative therapy within 6 months were included in this study. Five leg ulcer groups were defined as follows: Patients with post-phlebitic leg ulcers (PPU) (n = 39) had phlebographically proved post-phlebitic deep vein damage. Patients with varicose leg ulcers (VU) (n = 23) showed primary varicosis, perforator incompetence and intact deep veins.

The group of patients with mixed leg ulcers (MU) (n = 30) had either primary varicosis and perforator incompetence or post-phlebitic vein damage. The ankle/arm occlusive pressure ratio in this group which was determined in all patients was < 0.8.

In patients with leg ulcers of non-venous etiology (NVU) (n = 11), a concomitant venous disease was excluded phlebographically. The ulcer etiology in this group was partially traumatic (n = 6), partially hematogenous (n = 1), partially arterial (n = 2), partially vasculitic (n = 1) and partially spinocellularcancerous (n = 1).

The post-phlebitic group consisted of patients (PP) (n = 19) with a post-phlebitic vein damage in the phlebogram but without previous or actual leg ulceration.

Patients with diseases of the liver or kidneys, rheumathoid arthritis, leukemia or colitis ulcerosa were excluded from the study, as also were patients who had undergone an operation within 6 months of the study. Drugs influencing coagulation, such as acetylsalicylic acid, heparin or dicoumarol also warranted exclusion.

From the recumbent, fasting patient, blood was drawn from the cubital vein after a tourniquet for venous puncture had been placed as briefly as technically possible. F.XIII was measured by the coagulation f.XIII rapid reagent (12) (Behring^R). One part of citrated buffer solution and 9 parts of venous blood were drawn into a sterile syringe and carefully mixed, avoiding formation of foam. The mixture was then transferred to a clean centrifuge tube and centrifuged for 10 min at 3000 rpm. The supernatant plasma was removed by aspiration. 0.05 ml diluted plasma and 0.1 ml Ca-thrombin-kaolin solution were mixed immediately and incubated for exactly 10 min at 37°C. 1 ml of 5% monochloracetic acid was added immediately. Clots were detached from the tube wall by vigorous shaking. After incubation for a further 2 min at 37°C, the results were read. Normal F.XIII-activities vary between 70 and 130%.

In 44 patients, leg ulcer biopsies were taken on the day of blood sampling for F.XIII determination. The specimens were stained with Weigert's fibrin and the Picro-Mallory staining and investigated for pericapillary fibrin cuffs.

RESULTS

In the post-phlebitic ulcer group, 20 of 39 patients had a pathologically decreased F.XIII activity of ≤ 50%. The mean F.XIII activity was 66.67 ± 5.11%. Only 3 out of 23 patients in the primary varicosis ulcer group had a F.XIII deficiency (≤ 50%). The mean F.XIII activity in this group was 90.20 ± 6.38%. F.XIII deficiency was also frequent in the mixed ulcer group (11 of 30 patients). The mean F.XIII activity in this group was 76.30 ± 4.99%. Five of these F.XIII deficient patients had phlebographic evidence of postphlebitic deep vein damage.

In the group of non-venous ulcers, only 1 patient with an arterial ulcer had a F.XIII activity of 37.5%. The mean F.XIII activity in this group was 89.80 ± 8.40%. Eleven of 19 patients with a post-phlebitic syndrome without leg ulceration had F.XIII activities of ≤ 50% (mean 69.8 ± 5.75%). Venous-healthy control patients did not have F.XIII deficiency (mean 125.00 ± 9.41%).

Statistical analysis of the various leg ulcer groups showed a significant difference in F.XIII activity between those patients with either post-phlebitic syndromes, post-phlebitic ulcers, varicose leg ulcers or mixed leg ulcers and those patients without venous disease. There was no significant difference between patients with non-venous leg ulcers and healthy controls ($p > 0.10$). In 20 out of 44 biopsies from leg ulcer edges, pericapillary fibrin cuffs (PCF+) were found, while 24 did not show any signs of PCF (PCF−). The mean Factor XIII activity was 76.90 ± 40.82% in the PCF+-group and 72.40 ± 33.98% in the PCF−-group.

Statistical evaluation showed no significant differences between the two groups ($p = 0.949$).

DISCUSSION

F.XIII plays an important role in wound healing (6–10) and is intimately related to fibrin. It could therefore be expected that chronic leg ulcers might be associated with a F.XIII deficiency.

In a study of 148 patients we found a significantly reduced F.XIII activity in the blood of venous leg ulcer patients and patients with a post-phlebitic syndrome, compared with venous healthy controls, while there was no significant difference between non-venous leg ulcer patients and healthy controls. In chronic venous disease, pericapillary fibrin deposition contributes to the pathogenesis (1, 2). Hypothetically, this might induce a fibrin consumption.

The consumption of fibrin during wound healing is associated with an activation of thrombin (8). Thrombin causes an activation and consumption of F.XIII (8). Therefore, any process that inaugurates thrombin activation might lead to a F.XIII activation and consumption. Other fibrin-consuming diseases, such as ulcerative colitis, are also known to be associated with F.XIII deficiency (10). In chronic venous disease the process of fibrinogen leakage is not restricted to the ulcer area but involves the whole lower limb. Falanga et al. (5) described pericapillary fibrin cuffs in the skin adjacent to venous leg ulcers. Burnand et al. (1) and Browse & Burnand (2) found PCF in dermato-liposclerotic skin. This might explain why we found no significant difference between the non-venous leg ulcer group and healthy controls.

We could not find any statistically significant correlation between the F.XIII activity and the existence of pericapillary fibrin cuffs which could be attributed to a sample error, insofar as we took only small punch biopsies. Venous ulceration in post-phlebitic patients might be preceded by F.XIII deficiency. So far we have not investigated whether these F.XIII deficient patients are prone to wound healing problems in other areas.

In general surgery it was reported that patients with an F.XIII deficiency developed significantly more postoperative wound healing problems than their healthy controls (13, 14). Therefore the clinical relevance of the observed F.XIII deficiency in venous leg ulcer patients requires further investigation.

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