Factor XIII and Endothelial Dysfunction in Patients with Systemic Sclerosis

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Hamostaseologie 2023;43:411–417.

Abstract

Systemic sclerosis (SSc, scleroderma) is a severe autoimmune connective tissue disease which affects the skin and internal organs. There has been evidence that coagulation factor XIII (FXIII) has a positive impact on clinical results in patients with SSc. In a single-center cohort study, we investigated the relationship between coagulation FXIII, endothelial dysfunction, and skin infection in SSc. Fifty-six patients could be included and were divided into two groups (with and without scleroderma). Markers of inflammation, coagulation, and endothelial dysfunction like C-reactive protein, leucocytes, fibrinogen, FVIII, VWF-Ag (von Willebrand factor antigen), D-dimers, and vascular endothelial growth factor were analyzed as well as MRSS (modified Rodnan skin scores) data were evaluated. Reduced daily activities were evaluated by the Scleroderma Health Assessment Questionnaire (SHAQ). There were no significant correlations between FXIII activity, MRSS, and SHAQ score. There were correlations between FXIII activity and Raynaud's phenomenon–related symptoms and a weak but not significant positive correlation with the level of pain. A significant correlation between VWF-Ag and lung-associated complaints ($n = 56$; $p = 0.41$, $p < 0.0001$) was found. Moreover, the study showed a correlation between VWF-Ag and MRSS (r [$N = 48$] $= 0.4$, $p = 0.01$), which means that higher VWF-Ag levels come along with more severe skin involvement. A trend toward a negative correlation between FXIII activity and VWF-Ag as marker of endothelial dysfunction was found (r [$N = 56$] $= -0.20$, $p = 0.15$). In our cohort, there is no FXIII deficiency in patients with SSc. FXIII might have a role in improving cutaneous manifestations indirectly by means of a moderating influence on endothelial dysfunction. Further clinical evaluation is needed.

Keywords
- factor XIII
- transglutaminases
- scleroderma
- endothelial cells
- von Willebrand factor

Introduction

Systemic sclerosis (SSc, scleroderma) is a severe autoimmune connective tissue disease which affects the skin and internal organs. Unfortunately, it may result in changes to the skin, blood vessels, and internal organs.[1,2] Symptoms include areas of thickened skin, stiffness, fatigue, and Raynaud's fingers.[3] Risk factors include family history, mutations, and even exposure to silica.[4–6] Diagnosis is based on symptoms, supported by a skin biopsy or blood tests.[2] Currently, treatment can only improve symptoms.[3] Outcome depends on the

received
July 19, 2022
accepted after revision
December 31, 2022

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-2018-7014.
ISSN 0720-9355.

severity of disease.[4] Patients with a localized disease generally have a normal life expectancy.[7] In those with systemic disease, the life expectancy is reduced.[4]

About 3 out of 100,000 people per year develop the systemic form.[4] The condition most often begins in middle age.[1] Women are more often affected than men.[1]

As a coagulation factor in hemostasis, plasmatic transglutaminase FXIII increases the stability of the fibrin clot. However, FXIII also plays a role in various repair processes that are also important in the disease of scleroderma. These include the endothelial barrier function,[7–10] wound healing,[11,12] and vascular regeneration,[13,14] as well as the interaction with involved cells such as fibroblasts, monocytes,[12,15] and endothelial cells.[13,14]

Marzano et al[16] reported significantly higher von Willebrand factor antigen (VWF-Ag) levels in scleroderma patients compared to an age- and sex-matched control group as well as significantly lower VWF-Ag levels in FXIII-treated patients.

This might be induced by the endothelial dysfunction and hypercoagulation state caused by alteration in VWF:Ag.

Previous studies, which have tested the effects of substitution with FXIII in patients with scleroderma, report positive effects on clinical findings[17–21] without critical adverse events.

Dickneite et al[22] provided a tabulated overview of studies of FXIII concentrate treatment in patients with SSc. Eight articles published between 1975 and 1995 described positive effects of FXIII supplementation up to 37 months. Main findings have been improvement of arthralgia, improvement in Raynaud's phenomenon, and amelioration of cutaneous symptoms.

Despite these results, FXIII administration has so far not been evaluated broadly as a new treatment option. This might have been due to strict regulations with respect to plasma/placenta-derived products related to HIV infections at that time.

The aim of this study was to investigate if there is evidence of a correlation between FXIII activity, markers of endothelial dysfunction (including VWF:Ag), and the severity of skin infection in patients with SSc. Furthermore, the study assesses if there are any anomalies in FXIII activity in patients with SSc.

Methods

Study Design

The study was a single-center cohort study. Data on 56 patients with systemic scleroderma were assessed. Patients in the cohort study consented in writing to participate in the study. Blood was drawn and 52 patients completed the Scleroderma Health Assessment Questionnaire (SHAQ). The study protocol was approved by the Ethics Committee of the Medical University of Frankfurt/Main, file number 14/10 of 03/15/2010) and followed Good clinical practice.

Study Population

The study population consisted of patients aged 25 to 74 years, requiring outpatient services at the Division of Rheumatology, Medical University of Frankfurt/Main. Written informed consent was obtained from the patients. Exclusion criteria were nonage or surgical procedure less than 6 months ago.

Scores and Questionnaire

Modified Rodnan Skin Thickness Score

In 1979, Rodnan et al[23] demonstrated by skin biopsies of scleroderma patients compared to healthy individuals that there is a highly significant increase in skin thickness during the indurative phase of SSc, which is proportional to the increase in collagen content in the skin.

Due to this observation, a scoring system that uses standardized palpation to determine the severity of skin involvement was developed, without taking skin biopsies.

Seventeen body regions (face, abdomen, and thorax, as well as right and left hands, fingers, upper arm, forearm, upper and lower leg, and feet) are assessed by palpation and assigned the values 0 (normal skin thickness), 1 (weak skin thickening), 2 (moderate skin thickening), and 3 (severe skin thickening) depending on the severity of the sclerosis. The sum of the 17 values gives the modified Rodnan skin score (MRSS), which ranges from 0 to a maximum of 51.

Scleroderma Health Assessment Questionnaire

SHAQ is a health questionnaire for scleroderma patients recording the patient's subjective assessment of his/her daily impairments. Two scores are determined, the "disability index (DI)" and the visual analog scale (VAS) score, and from these the SHAQ score is formed.

The Disability Index

Questions were divided into eight areas using a verbal rating scale regarding the extent of activities of daily living. The questions cover areas such as dressing and grooming, walking, eating, reaching, and grasping, as well as general activities.

Four answer categories ("without difficulty," "with some difficulty," "with great difficulty," "unable") are available. If six or more of the eight categories are answered, the answers may be evaluated.

The **SHAQ** contains four questions on the impairment of activities of daily living by:

- Raynaud's symptoms.
- Finger ulcerations.
- Pulmonary involvement.
- Gastrointestinal involvement.

In addition, there are questions on impairment of daily living due to scleroderma and a question on perceived pain. These questions are to be answered using a VAS score.

The left border of the scale stands for "no impairment" or "no pain," and the right border stands for "severe impairment" or "exceptionally severe pain."

For the evaluation of the VAS score, the 10-cm straight line on which the answer was marked by the patient is converted per question into a scale corresponding to a maximum of

three achievable points: 1 cm on the scale thus corresponds to 0.3 points.

The two scores, DI and VAS, enter the total SHAQ score with equal weighting by taking the arithmetic mean of VAS and DI:

$$(\text{VAS} + \text{DI}) = \text{SHAQ score}.$$

Diffusing Capacity of the Lung for Carbon Monoxide

Diffusing capacity of the lung for carbon monoxide (DLCO) allows conclusions to be drawn about the ability of the lung to diffuse oxygen across the alveolocapillary membrane.

In scleroderma, diffusion impairment is often found as a result of interstitial pulmonary fibrosis.[19] In relation to scleroderma patients, Medsger et al[24] demonstrated in 2003, based on a case–control study, a predictive value of DLCO with respect to the development of pulmonary fibrosis.

Blood Sample Acquisition

Blood samples were drawn and transported to the coagulation laboratories within 1 hour.

Analyses

Berichrom FXIII chromogenic assay (Siemens, Marburg, Germany) and VWF-Ag test kits (BCS, Siemens) were used according to the manufacturer's instructions to measure the factor levels. BCS from Siemens Healthcare Diagnostics Products GmbH (Marburg, Germany) is a fully automated analyzer for clotting, chromogenic, and immunologic assays.

Fibrinogen was measured using the Clauss method on the STA according to the manufacturer's instructions (STA-Fibrinogen 5; Roche Diagnostics, Mannheim, Germany). Endothelin-1 was measured using QuantiGlo Human Endothelin-1 Chemiluminescent ELISAs (QET00B; R&D Systems, Abingdon, Great Britain). The microplate reader was from TECAN infinite M200 (Magellan V 6.5, USA).

To determine vascular endothelial growth factor (VEGF), QuantiGlo Chemiluminescent ELISAs Human VEGF (QVE00B; R&D Systems) and the microplate reader (TECAN infinite M200; Magellan V 6.5, USA) were used.

FXIII Activity

FXIII activity was determined using Berichrom FXIII and the Fickenscher photometric method.[25] Added thrombin activates FXIII, which catalyzes "the cross-linking of a peptide substrate with glycine ethyl ester."[25] In the subsequent reaction, the ammonia formed is converted by the glutamate dehydrogenase with consumption of NADH. The decrease in NADH can be determined via the extinction at 340 nm and is proportional to the FXIII activity in the plasma to be examined.

von Willebrand Factor Antigen

The sample containing the VWF:Ag is mixed with the reagent and aggregate small polystyrene particles coated with antibodies. The specific antibodies are connected to the particles by covalent bonds. The aggregation is examined turbidimetrically. The turbidity acts directly proportional to the level of antigen in the sample.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics for Linux, Version 22.0 (Armonk, United States: IBM Corp.), and BiAS, Version 9 (Hochheim–Darmstadt: Epsilon-Verlag). Correlations were calculated using the Spearman correlation. Strength and direction of the correlation are determined by the Spearman correlation coefficient *r*. *P*-value of <0.05 was considered significant.

Results

Study Population

The cohort of the laboratory study evaluating markers of inflammation, coagulation, and endothelial dysfunction consisted of 56 patients. The cohort that completed the SHAQ consisted of 52 patients. MRSS data were available from 48 patients.

Patient Demographics

The mean age was 52.9 years (minimum: 25.2; maximum: 74.5). Fifty (89.3%) patients were female and six (10.7%) were male.

FXIII Levels

Elevated levels of FXIII greater than 140% were found in 16 of 56 patients. Elevated level of VWF:Ag greater than 150% was found in 30 of 56 patients (►Fig. 1).

Correlations

See ►Table 1.

Correlations between FXIII and Endothelial Dysfunction

There were no significant correlations between FXIII activity and markers of inflammation and endothelial dysfunction like C-reactive protein ($r\ [N=55]=0.02$, $p=0.88$), lactate dehydrogenase ($r\ [N=55]=0.18$, $p=0.18$), blood sedimentation rate ($r\ [N=54]=-0.16$, $p=0.26$), leucocytes ($r\ [N=55]=0.18$, $p=0,19$), fibrinogen ($r\ [N=56]=0.15$, $p=0.26$), FVIII ($r\ [N=56]=-0.08$, $p=0.58$), D-dimers ($r\ [N=51]=-0.03$, $p=0.84$), VEGF ($r\ [N=55]=0.14$, $p=0.29$), and endothelin-1 ($r\ [N=50]=-0.12$, $p=0.41$).

The negative correlation between FXIII activity and VWF-Ag as marker of endothelial dysfunction (VWF-Ag; $r\ [N=56]=-0.20$, $p=0.15$) just missed the level of significance.

Correlations between FXIII, Skin Infection, and Other Clinical Results

There were no significant correlations between FXIII activity and MRSS as a measure of skin infection ($r\ [N=48]=0.16$, $p=0.84$; see ►Fig. 2). Yet a significantly positive correlation between FXIII activity and Raynaud's phenomenon–related symptoms was noticed ($r\ [N=52]=0.27\ p=0.05$), and there is a weak but not significant positive correlation with the level of pain perceived by the patients ($r\ [N=52]=0.22$, $p=0.11$).

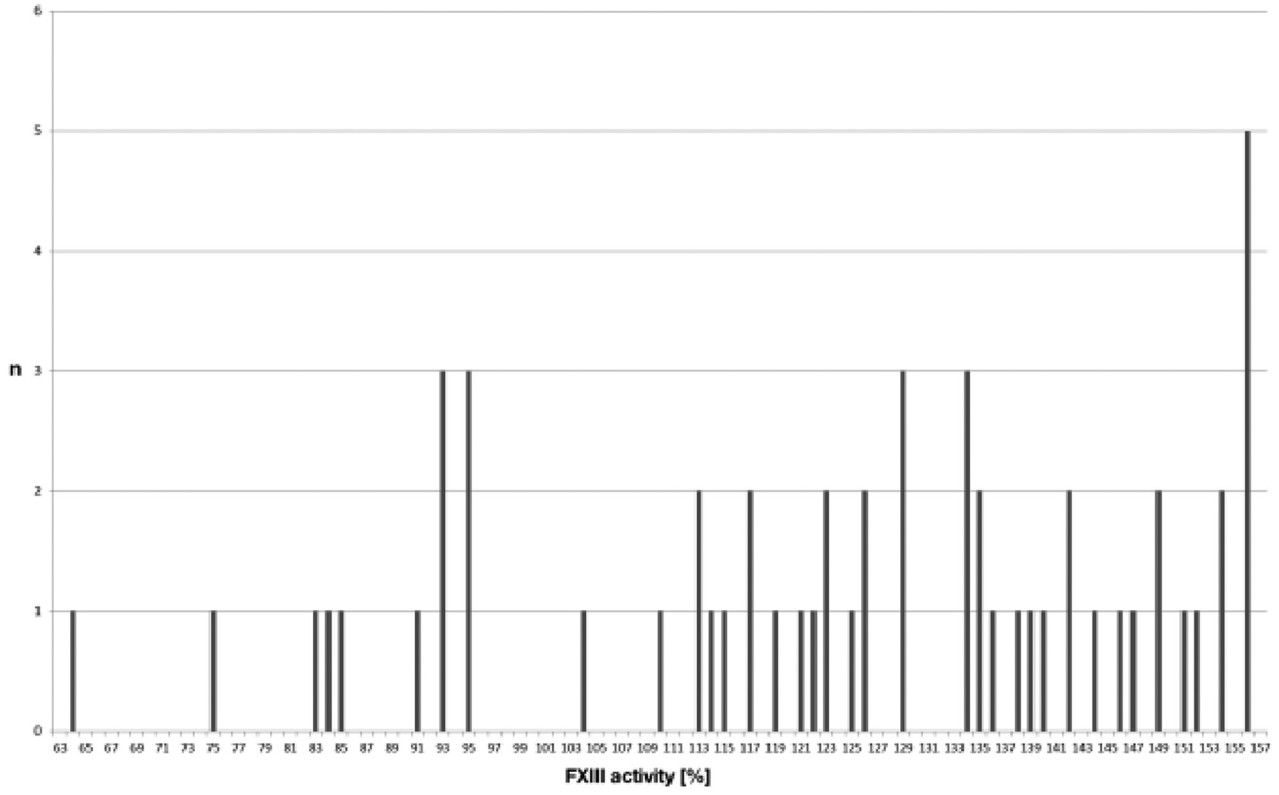

Fig. 1 Distribution of FXIII activity in 56 patients with systemic sclerosis.

Correlation between VWF-Ag and Lung Involvement

A significantly positive correlation between VWF-Ag and lung-associated complaints (single question in the SHAQ) ($r\,[N=56]=0.41$, $p=0.00$) was found.

Correlations between VWF and Skin Infection

This study showed a highly significant correlation between VWF-Ag and MRSS ($r\,[N=48]=0.4$, $p=0.01$), which means that higher WWF-Ag levels come along with more severe skin involvement.

Table 1 Median, IQR, number of cases (*n*) of the correlated variables

	Median	IQR	*n*	Standard range
FXIII (%)	126.75	33	56	70–140
VWF-Ag (%)	170.65	85.3	56	60–200
FVIIIc (%)	133.5	37	56	60–150
D-dimer (µg/dL)	0.49	0.49	5	<0.5
Fibrinogen (mg/dL)	366.5	93	52	150–450
Leucocytes (/nL)	6.73	3.17	55	4.2-9-07
Blood sedimentation rate (mm)	9	12	54	<30
C-reactive protein (mg/dL)	0.35	0.32	55	<0.5
Lactate dehydrogenase (U/L)	201	46	55	<247
Vascular endothelial growth factor (pg/mL)	223.71	173.78	56	47–666
Endothelin-1 (pg/mL)	1.1	0.5	51	0.401–2.83
Modified Rodnan skin score	4.0	5	49	–
Raynaud's phenomenon–related symptoms (in SHAQ)	3.8	5	53	–
Level of pain (in SHAQ)	3	5	53	–
Lung-associated complaints (in SHAQ)	0.2	4	53	–

Abbreviations: IQR, interquartile range; SHAQ, Scleroderma Health Assessment Questionnaire; VWF-Ag, von Willebrand factor antigen.

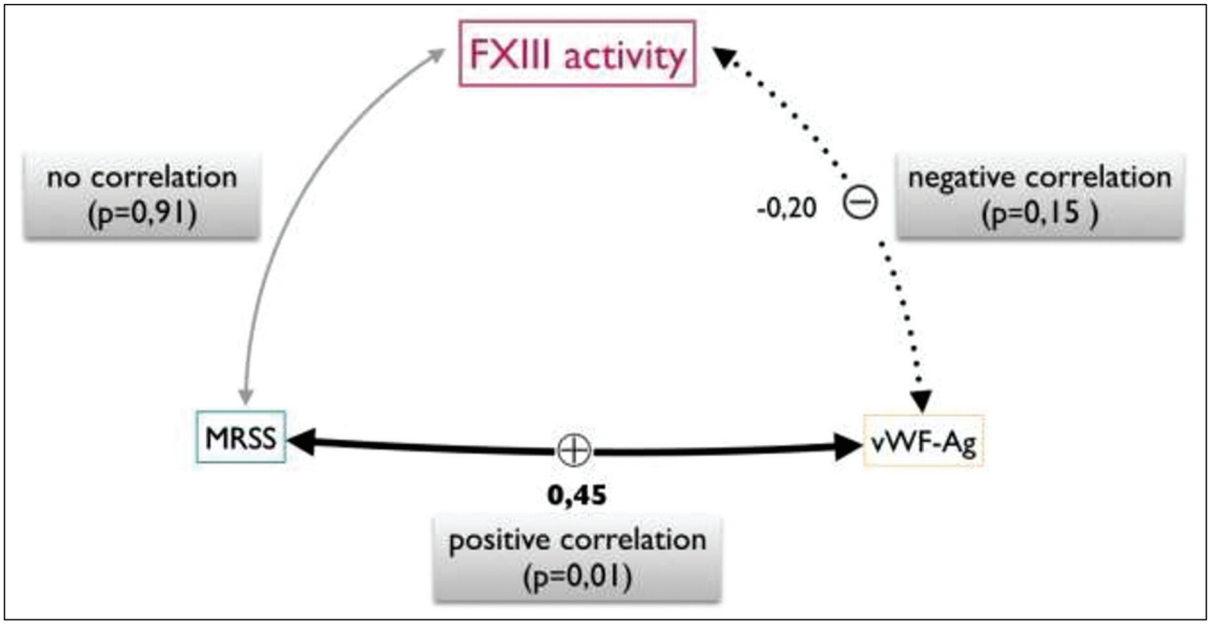

Fig. 2 Correlation between FXIII, VWF-Ag, and modified Rodnan skin score (MRSS). Numbers = correlation coefficient Spearman's rho (*r*); black line = correlation (significant); dotted line = correlation (not significant).

Discussion

In a small study with 22 patients, Marzano et al had measured an increased FXIII activity in three scleroderma patients, and none of the investigated patients had a FXIII deficiency.[16] Our study confirms these observations with a higher number of patients.

A reduced FXIII activity in scleroderma patients would have been an explanation why FXIII substitution to patients with scleroderma improved their clinical outcomes, especially ulcers in former interventional studies.[17,19,20,26,27]

However, the results of our present study could not establish any evidence of an increased occurrence of FXIII deficiency in scleroderma patients. As shown by Marzano et al, 16 patients (28.6%) had an increased FXIII activity greater than 140%, while only 1 patient had FXIII deficiency.

Nevertheless, especially in France, treatment of scleroderma skin lesions using a FXIII concentrate was common. A review by Jullien et al[27,28] described encouraging initial results in terms of skin sclerosis, musculoskeletal involvement, and weakness. Several studies and case series were published and even a standard treatment regimen (3-week intensive course followed by 6-month maintenance) has been proposed. Jullien et al[27] concluded that "FXIII is one of a very limited number of drugs which can clearly improve the quality of life in a large number of patients."

In fact, the first report of FXIII use in the treatment of scleroderma originated from 1975 and the assumed therapeutic rationale was stabilization/immobilization of soluble collagen molecules. These molecules are produced in very high amounts in scleroderma. However, the real mechanism of action remained unclear at that time.[5]

Another mode of action proposed by Marzano et al[16] was an influence of FXIII on endothelial damage. The investigator determined VWF:Ag levels as a marker of endothelial injury in a group of 22 patients suffering from SSc and 20 age- and sex-matched individuals. The VWF:Ag plasma levels were significantly higher in the SSc patients compared to the controls. Moreover, the SSc patient group consisted of 9 patients who were treated with FXIII and 13 patients were without FXIII treatment. Comparing the VWF:Ag levels between these two groups revealed significantly higher values in patients without FXIII treatment, supporting a role of FXIII in improving/preventing endothelial damage. This finding was similar to our current study; we noticed a correlation of the VWF:Ag with lung involvement and skin infection (MRSS) supporting endothelial damage as relevant.

More recently a proangiogenic effect of FXIIIa was established by Dardik et al,[29] using in vitro and in vivo models. This effect was associated with downregulation of thrombospondin 1 (TSP-1, one of the best-characterized antiangiogenic factors). In detail, the following hypothesis was suggested: "during tissue repair processes, plasma FXIII and FXIII exposed on the surface of platelets or macrophages are activated and subsequently induce endothelial cell migration and proliferation at the site of injury. The associated downregulation of TSP-1 may be responsible, at least in part, for the complex multifactorial process of new vessel formation required for remodeling and wound repair in this paradigm."

In a review, Maekawa et al[26] highlighted the role of vascular injury in sclerosis. They described that vascular injury is an early event in scleroderma which precedes fibrosis and involves small vessels. Paucity of small blood vessels is described as a characteristic finding in later stages of scleroderma.

Similarly, Greenblatt and Aliprantis[25] reported that skin biopsies from SSc patients have fewer blood vessels, providing further evidence for decreased angiogenesis in SSc. Despite defective angiogenesis in SSc, they paradoxically

recognize upregulation or increased expression of a large number of proangiogenic mediators. From the finding that SSc patients with fingertip ulcers have increased serum levels of VEGF as compared with healthy individuals (but lower than in SSc patients without fingertip ulcers), a functional deficit of VEGF in SSc patients is suggested. This deficit might be overcome if the levels of VEGF exceed an individual threshold.

Regarding to FXIII, we consider a systemic FXIII deficiency in scleroderma patients as unlikely. However, this observation does not allow any statement about a possible local or relative FXIII deficiency. Cutolo et al suggested that "[patients with scleroderma] have a local factor XIII deficiency in relation to elevated tissue levels of collagen and fibronectin."[30] Today, the downregulation of antiangiogenic factor thrombospondin-1 would be a suggested mechanism.

With respect to symptoms, there were no significant correlations between FXIII activity and clinical results such as MRSS as a measure of skin infection (r [$N = 48$] = 0.16, $p = 0.84$) and SHAQ score (r [$N = 52$] = 0.19, $p = 0.19$). The median of MRSS is the same in the 16 patients with increased FXIII activity as in the scleroderma patients with normal FXIII activity.

Thus, it cannot be deduced that plasma FXIII activity is associated with altered severity of skin involvement in non–FXIII-treated patients. However, the separate consideration of the individual complaints queried in SHAQ (Raynaud symptoms, finger ulcers, indigestion, lung complaints, perceived pain) shows correlation with FXIII activity: A significantly positive correlation between FXIII activity and Raynaud's phenomenon–related symptoms was noticed (r [$N = 52$] = 0.27, $p = 0.05$), that is, patients with higher FXIII activity are more likely to have circulatory disorders in their hands. Furthermore, there is a weak but not significant correlation with the level of pain perceived by the patients (r [$N = 52$] = 0.22, $p = 0.11$). Potentially patients with higher FXIII activity may be in greater pain.

In addition, the study revealed a highly significant correlation between VWF-Ag and MRSS (r [$N = 48$] = 0.4, $p = 0.01$) which means that higher VWF-Ag levels come along with more severe skin involvement. The negative correlation between FXIII activity and VWF-Ag as marker of endothelial dysfunction (VWF-Ag) (r [$N = 56$] = −0.20, $p = 0.15$) just missed the level of significance.

Summarizing the observations described in those studies and our findings, a role of FXIII in scleroderma seems likely based on:

- FXIII supports angiogenesis.[14]
- FXIII substitution relieves the infected skin in scleroderma patients.[17,20,21,27,28]
- Scleroderma patients have significantly lower VWF-Ag levels after FXIII substitution.[16]
- The present study finds a highly significant correlation between endothelial dysfunction (VWF-Ag) and skin involvement (MRSS).

This is currently addressed in a single-center, double-blind, randomized, placebo-controlled study to investigate efficacy of intravenous factor XIII treatment in patients with SSc (ClinicalTrials.gov Identifier: NCT02551042).[31]

Limitations

One limitation of the study certainly was a relatively low number of patients with ulcers due to the single-center setting. Furthermore, we could not ignore that therapeutic effects influenced the levels of FXIII, VWF:Ag, and the other parameters.

Furthermore, we had no possibility to measure the factor XIII level with a second method like FXIII-A:Ag.

In conclusion, our results confirm that there is no general FXIII deficit in patients with SSc and no correlation between low factor XIII levels and ulcers.

Considering the potential role of FXIII in angiogenesis, a consecutive increase in FXIII levels might be assumed. It could be shown that FXIII might improve cutaneous manifestations indirectly by means of a moderating influence on endothelial dysfunction. Our study is the first study that focused on the relationship between FXIII, endothelial dysfunction, and cutaneous manifestations in scleroderma. Further studies are needed, particularly with regard to a substitution therapy of FXIII in SSc aiming to broaden the therapeutic options of the disease.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgment

S.A. designed the study and contributed substantially to writing of the manuscript. C. Dockhorn and H.A. collected data of the manuscript. W.M. and M.W. provided valuable support for performing the study and critically revised the manuscript. Thanks to all the patients, the staff of the laboratories, and the ambulatory.

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