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Original Article

Factor XIII: More than just a fibrin stabilizer for the burn patient? A matched-pair analysis

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ABSTRACT

Background: Acquired factor XIII deficiency is an underestimated risk in patients with large surface burns, which potentially exposes these patients to prolonged bleeding and delayed wound healing if undetected.

Methods: A retrospective matched-pair analysis of the burn registry of the Department of Plastic, Aesthetic, Hand, and Reconstructive Surgery of Hannover Medical School was performed from 2018 to 2023.

Results: A total of 18 patients were included. Acquired factor XIII deficiency was not statistically significant correlated with age, sex, or body mass index. Patients who developed acquired factor XIII deficiency had a significantly longer hospital stay (72.8 days) compared with those in the matched group (46.4 days), although burn depths, total body surface area, and Abbreviated Burn Severity Index were not statistically correlated with factor XIII deficiency.

Conclusions: Little is known about acquired factor XIII deficiency in patients with burns. Factor XIII supplementation may improve hemostasis, wound healing, and general outcome while reducing the patient's exposure to blood products.

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Introduction

The global incidence, severity, and mortality of burn injuries have decreased; however, large surface burns represent devastating wounds that have a huge impact on the patient's health and quality of life.[1] In particular, large surface burns covering more than 30% of the total body surface area (TBSA) account for roughly 10% cases of burns and are associated with high overall mortality.[2] Over the years, surgical techniques have improved, including necrosectomy with skin grafting and modern methods of intensive care measurements. Despite these advances, surgical therapy is associated with substantial blood loss and requires frequent blood transfusions.[3] Hemostatic techniques, such as the use of tourniquets, subcutaneous epinephrine infiltration, fibrin sealant, and systemic therapies, have been well established in specialized burn centers throughout the world.[4–6] Further, the increasing availability of fast and reliable laboratory coagulation tests has shifted the interest to correcting coagulation abnormalities in patients with burns pre- and postsurgery. However, for such patients, there is little to no evidence regarding treatment algorithms guided by rotational thromboelastography, such as ROTEM, or deficiencies in clotting factors, such as factor XIII deficiency.[7] Factor XIII functions within the coagulation cascade by stabilizing the process of blood clot formation. As a heterotetrameric proenzyme, it is converted into a transglutaminase by thrombin and calcium. Once activated, it catalyzes the linkage between the fibrin monomers and a2-antiplasmin with fibrin during the process of clot formation.[8] Within the coagulation cascade, factor XIII consecutively participates in the common pathway by modulating the thrombin-catalyzed cleavage of fibrinogen into fibrin, which gives interlocking strength to a blood clot. These bonds dissolve during clot retraction caused by fibrinolysis and destruction of factor XIII crosslinks.[9] In addition to playing an important role in the coagulation cascade, factor XIII controls the maintenance of pregnancy, angiogenesis, cardiac protection, and wound healing.[10] The positive effects of factor XIII on wound healing can be attributed to its antiapoptotic effects and its role in cell migration into the wound and subsequently in fibrin and collagen synthesis modulation.[11–14] Factor XIII deficiency can be classified as congenital or acquired. Patients with burns are diagnosed almost exclusively with the latter form, resulting from increased consumption of factor XIII due to surgical bleeding and decreased synthesis due to the pathophysiology of large burns.[15] In the case of factor XIII deficiency, routine coagulation tests, such as the international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time (APTT), can provide physiological values, indicating the necessity to perform special factor XIII activity tests.[14] If a deficiency is detected, 15–20 IU/kg of recombinant factor XIII should be administered.[16] The literature currently lacks relevant information regarding the incidence of and treatment recommendations for acquired factor XIII deficiency in patients with burns. Thus, this retrospective study used matched-pair analysis to determine the influence of factor XIII application on patients with large surface burns.

Methods

Study design

A retrospective descriptive analysis of the burn registry of the Department of Plastic, Aesthetic, Hand, and Reconstructive Surgery of Hannover Medical School was performed from January 1, 2018, to January 1, 2023. Patients with acquired factor XIII deficiency requiring recombinant factor XIII supplementation were matched with patients exhibiting normal factor XIII activity based on key variables and shared characteristics. The data of all patients who were admitted and treated at the burn inten-

sive care unit of the department were anonymously collected using an online data collection portal. The patients or their legal representatives signed the informed consent form, allowing the use of their anonymous data. As this study is a retrospective analysis of an anonymous database, approval from the local ethics committee was not required.

Study population

Patients included in this retrospective matched-pair analysis came to the burn center of our facility as a primary referral or secondary transfer via ambulance or helicopter. Current German burn guidelines require patient referral to a specialized burn center for partial burns with >10% TBSA; full-thickness burns; burn injury of the hand, face, or genitalia; electrical injuries; chemical burns; inhalation injuries; or burn injury in pediatric patients.[17] Patients with acquired factor XIII deficiency were matched with those who showed normal factor XIII activity based on the shared key characteristics, such as sex, age, body mass index (BMI), TBSA, percentage of partial- and full-thickness burns, location of burns, and Abbreviated Burn Severity Index (ABSI).

Statistical analysis

Statistical analysis was conducted using GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA), Microsoft Excel (Microsoft, Redmon, WA, USA), and Numbers (Apple, CA, USA). Descriptive statistics are presented as numbers (percentage) and medians (interquartile range). The number of patients and their characteristics were compared using Student's t-test. A p-value of <0.05 was considered statistically significant.

Results

A total of 18 patients were included in this study. They were classified into two equal groups according to similar characteristics (such as sex, age, BMI, TBSA, percentage of partial- and full-thickness burns, location of burns, and ABSI). The study cohort consisted of 12 male and 6 female patients, with a mean age of 48.8 years (16–77 years, standard deviation [SD] 15.02 years). The unaffected patient group was borderline normal weight, with BMI of 24.7 kg/m^2 (11.7–29.4 kg/m^2, SD 6.4 kg/m^2), whereas the patient group with acquired factor XIII deficiency was slightly overweight, with BMI of 26.3 kg/m^2 (20.7–35.1 kg/m^2, SD 4.3 kg/m^2). Patient characteristics are summarized in Table 1.

There were no significant differences between the study groups in terms of sex (p=0.3559), age (p=0.7480), and BMI (p=0.7307) (Figure 1).

Various mechanisms, including flames, deflagration, scalds, electricity, and explosions, caused burn injuries, with a mean TBSA of 39% (12%–77%, SD 22.8%) for patients who developed factor XIII deficiency and 38.1% (12%–66%, SD 21%) for their corresponding matched pairs. Regarding burn depth, patients with acquired factor XIII deficiency (mean burn depth: 2a° 5.2%, 2b°12%, and 3° 39%) as well as matched patients with physiological values (mean burn depth: 2a° 12.4%, 2b°12.6%, and 3° 38.1%) mainly exhibited partial- and full-thickness burns requiring surgical treatment. The overall mean ABSI was 9.11 (4–13, SD 2.6), and the index was slightly higher for patients with acquired factor XIII deficiency (mean ABSI = 9.22 [4–13, SD 3]). Matched patients with physiological factor XIII values presented a slightly lower mean ABSI of 9 (5–12, SD 2.3). There were no significant differences between the two groups in terms of ABSI, TBSA, and extent of partial- and full-thickness burns (Figure 1).

The mean length of hospital stay was significantly lower for unaffected patients, with a mean length of 46.4 days (9–90 days, SD 31.1 days) compared with 72.8 days in affected patients (14–162 days, SD 54 days) (p=0.0354). However, the mean number of surgical interventions was 6.5 (1–18, SD 5), which was not statistically significant based on the comparison between the groups (p=0.8855) (Figure 1).

The routine coagulation test results were within the physiological range for both patient groups, and there were no significant differences between the two groups. The mean APTT was 36.4 seconds (29–46 seconds, SD 5.8 seconds) for patients with acquired factor XIII deficiency compared with

Table 1
Patient characteristics

Pair	Age	Sex	BMI (kg/m²)	Number of days in hospital	Number of surgeries	Number of applications of factor XIII	Mechanism of injury	Partial thickness burn (2a°)	Partial thickness burn (2b°)	Full thickness burn (3°)	Total burn area (%)	Mean APTT (seconds)	Mean value on Quick's test (%)	Mean INR
1	67	male	23.1	24	3	2	scald	0	4	20	24	45	83	1.11
2	16	male	23.5	92	4	1	flame	0	0	12	12	35	89	1.1
3	56	male	24.5	50	9	6	explosion	2	10	65	77	38	85	1.1
4	50	male	35.1	14	4	1	explosion	0	30	25	55	36	88	1.06
5	38	female	30.1	29	1	7	flame	2	3	7	12	46	44	1.74
6	62	male	24.7	36	3	2	flame	23	1	1	25	34	121	0.93
7	44	male	20.7	162	18	12	explosion	0	10	50	60	30	129	0.86
8	34	female	27.7	115	7	12	flame	10	25	1	36	35	117	0.91
9	66	female	27.7	133	14	11	flame	10	25	15	50	29	93	1.03
1	77	male	21.5	27	4		deflagration	12	5	15	32	46	70	1.21
2	17	male	11.7	81	11		electrical	0	6	6	12	30	109	0.94
3	62	male	34	13	3		flame	18	15	33	66	46	63	1.31
4	57	female	25.7	9	2		flame	23	10	20	53	83	28	2.71
5	42	male	26.3	48	3		flame	8	5	2	15	31	114	0.94
6	69	male	27.7	17	1		flame	2	5	8	15	33	91	1.05
7	34	male	20	90	14		explosion	27	15	15	57	25	104	0.99
8	57	female	29.4	60	8		scald	6	20	9	35	28	91	1.05
9	30	female	25.6	73	8		flame	16	32	10	58	29	76	1.17

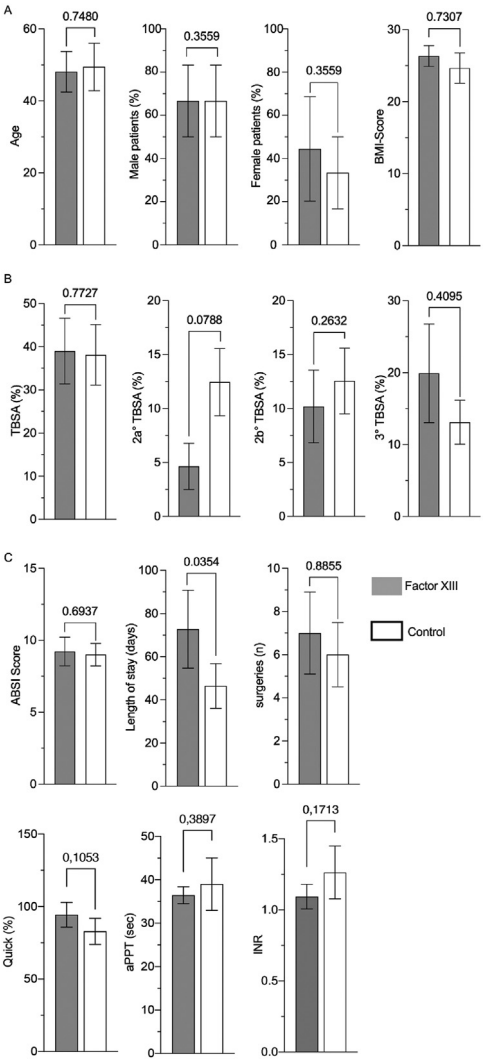

Figure 1. Matched-pairs correlations.

39 seconds (25–83 seconds, SD 18.1 seconds) for the matched pairs with physiological factor XIII (p=0.3897).

Furthermore, the mean Quick's test value for patients with factor XIII deficiency was 94.3% (44%–129%, SD 25.6%) compared with 82.8% (28%–114%, SD 27%) for the matched patients, with no significant differences between the two groups (p=0.1053). The overall INR for patients with factor XIII deficiency was 1.09 (0.86–1.74, SD 0.25) compared with 1.26 in the matched unaffected group (0.94–2.71, SD 0.55), with no significant correlation between the two groups (p=0.1713) (Figure 1).

Patients who developed acquired factor XIII deficiency received a mean of six supplementations of 1250 IU recombinant factor XIII (1–12, SD 4.7). We compared routine coagulation test values between the two groups before factor XIII supplementation, and the results did not reveal any statistically significant differences. There were no deaths in either patient cohort.

Discussion

Patients with major burns are prone to severe systemic responses involving systemic inflammation and disorders of the coagulation system, which may be associated with a worse clinical outcome.[6] Previous studies have described hypercoagulability and hyperfibrinolysis in patients with thermal injury on day 1, with persistence throughout the shock phase increasing overall mortality.[18,19] These findings suggest an important correlation between acquired coagulation disorders and burn healing outcomes.

However, in the literature, there is little evidence regarding the incidence of acquired factor XIII deficiency and its effects on patients with burns. Factor XIII is not described in the recent guidelines for burn treatment by the German Society for Burn Injuries, British Burn Association, and European Burns Association, suggesting low awareness about the effects of acquired factor XIII deficiency in patients with burns.[20–22] Consistent with the findings of the study by Kleber et al., as of February 2023, there are no ongoing clinical trials on factor XIII and patients with burns listed at clinicaltrials.gov or the European Union Clinical Trials Register.[23]

This study revealed a significant correlation between factor XIII and longer hospital stays. Consequently, acquired factor XIII deficiency in patients with burns can be considered a negative prognostic marker. This may be hypothetically explained by the fact that patients who develop an acquired factor XIII deficiency are more affected by the inflammatory and hyperfibrinolytic effects of burn injury because the coagulation factor is consumed during the acute phase. In addition, a prolonged hospital stay can be associated with additional hospital-acquired complications such as pneumonia, urinary tract infection, delirium, or infection with multidrug resistant organisms, strengthening the use of factor XIII deficiency as an adverse prognostic marker.

Neither of the assessed patient cohorts showed a statistically significant association between recombinant factor XIII supplementation and the number of surgeries required, possibly due to the relatively small size of the cohort.

The positive effect of factor XIII on wound healing has been described in both humans and experimental animal studies. The mechanism of action of factor XIII for tissue repair is pleiotropic based on its functions within the coagulation cascade.[24,25] A significant reduction in postoperative complications, such as delayed wound healing for gastrointestinal surgery or nonsurgical wounds like pressure sores or leg ulcers, has been described in the literature. In addition, small trials and case studies have identified a positive healing effect, even if applied topically to the wound.[23,26,27]

The results of this study suggest that systematic screening for factor XIII activity should be performed in patients with large surface burn injuries during admission, postoperatively, and in cases of clinically manifested bleeding complications.

The results indicate that routine coagulation tests such as INR, PT, APTT, and platelet count may show values in physiological range even in cases of acquired factor XIII deficiency, making it necessary to perform laboratory tests for factor XIII activity. Our burn center defines factor XIII activity of $<50\%$ as an indication for supplementation. We recommend initial dosing of 15–20 IU/kg of recombinant factor XIII. The safety profile of recombinant factor XIII is promising, especially in cases of trauma.[28,29] Given that recombinant factor XIII is potentially thrombogenic, studies have reported that its administration is associated with a low risk for thromboembolic events.[30] This finding is consistent with the findings of the present study as there was no case of thromboembolic complications such as deep venous thrombosis or pulmonary embolism in the patients who received factor XIII supplementation. In the case of recent thrombosis, factor XIII activity of $<45\%$ is defined as an indicator for starting supplementation at our burn center, but only in the presence of clinically manifested bleeding.

The material costs for the administration of 1250 IU recombinant factor XIII are estimated to be roughly 500 euros. However, considering the abovementioned positive effects of this treatment, this price may be justified to stop bleeding and accelerate wound healing in patients with burns.

This study has several limitations. First, it is a retrospective study and has a relatively small sample size. Second, it represents a single-center analysis of a specialized burn center in northern Germany. Thus, the data represent a large geographic area. Finally, this study does not provide insight into the efficacy of recombinant factor XIII supplementation because all patients with factor XIII deficiency received supplementation. With this article, we want to raise awareness about potential factor XIII

deficiency in burns and its role in hemostasis and wound healing because the current burn guidelines are missing this information.

Conclusion

Coagulation abnormalities represent a challenge in treating patients with large surface burns. However, little is known about acquired factor XIII deficiency in patients with burns, and recombinant factor XIII is a poorly used blood product for the treatment of these patients.

Modern state-of-the-art treatment approaches should monitor the activity of specific coagulation factors. Early goal-directed supplementation with recombinant factor XIII may improve hemostasis, wound healing, and general outcome. Further, the patient's exposure to blood products is reduced.

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Conflicts of interest: None declared.

Ethical approval: Being a retrospective analysis of an anonymous database, approval by the local ethics committee was not required.

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