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ORIGINAL ARTICLE

Immunohistochemical Features of Fibrillary Proteins at the Dermal-Epidermal Junction in Sepsis

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Abstract

Background/Aim: Sepsis is a life-threatening condition that significantly disrupts skin function and healing, yet the underlying mechanisms remain poorly understood. This study aimed to assess the fibrous components of the epidermal-dermal junction (Integrin-β1, laminin-332 and type IV collagen) in sepsis patients to better understand the structural changes in the skin during this condition.

Methods: The study included 55 patients with sepsis (Group I) and a control group (Group II) of 10 deceased patients without infectious diseases. Patients' medical records were analysed, including clinical data, disease duration, pharmacological therapy and comorbidities. Skin biopsies were processed for histological and immunohistochemical examination to assess the expression levels of laminin-332, type IV collagen and integrin-β1. Statistical analysis was performed using SPSS 12, with p-values ≤ 0.05 considered statistically significant.

Results: Histological and immunohistochemical analyses revealed significant decreases in the expression of laminin-332, type IV collagen and integrin-β1 in sepsis patients (Group I) compared to the control group (Group II). These changes were more pronounced in older patients, indicating a correlation between age and the extent of disruption. The decrease in expression of these proteins suggests partial fragmentation of the basement membrane, leading to increased permeability, impaired epidermal-dermal attachment and disruption of regenerative processes.

Conclusion: The observed changes in the fibrous components of the basement membrane, particularly the reduction in integrin-β1 expression, highlight the skin's active role in the pathological process of sepsis. The impaired regenerative potential of the skin exacerbates its structural defects, hindering reparative processes and contributing to the progression of systemic inflammation. Pathological skin changes in sepsis are more pronounced in older individuals, likely due to the reduced activity of adaptive and compensatory mechanisms. Future research should focus on the recovery dynamics of these proteins and the potential for molecular-genetic analysis in understanding the long-term effects of sepsis on skin regeneration.

Key words: Sepsis; Epidermis; Dermis; Epidermal-dermal junction; Laminin-332; Integrin-β1; Collagen, type IV.

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Introduction

Sepsis remains one of the leading causes of death among patients in intensive care and resuscitation units.[1] Despite some progress in the study of the pathomorphological mechanisms of sepsis and improvements in the treatment of critical conditions, mortality rates in sepsis remain high-ranging from 18.4 % to 54.5 %.[2, 3] In response to infection by pathogenic microbes, severe systemic inflammation may develop in the body, often leading to death.[4] It has been empirically established that sepsis disrupts the integrity of skin functions and impairs its healing.[5] However, the mechanisms underlying these changes are poorly described or remain hypothetical.

The basement membrane, located at the boundary between the epidermis and dermis, plays a key role in maintaining the mechanical strength of the skin and regulating the lifecycle of keratinocytes.[6-8] Its structural foundation consists of laminin-332 and type IV collagen, which form a molecular network that ensures the adhesion of skin layers through specific interprotein interactions.[9, 10] The dermal-epidermal junction (DEJ), also known as the cutaneous basement membrane zone, is the specialised area where the epidermis (outer skin layer) and dermis (middle skin layer) connect. It acts as a crucial interface, providing both structural support and functional roles in skin integrity and cellular interactions.

To date, there is a notable lack of research specifically addressing the roles of laminin-332, integrins and type IV collagen in the pathogenesis of sepsis. As a result, most assumptions regarding their dysfunction in this condition must currently be extrapolated from data obtained in studies of other pathological processes such as genetic syndromes, wound healing, or inflammatory skin diseases.

Laminin-332 is a critical component of the dermal-epidermal junction.[11] Its loss leads to a disruption of skin integrity and a reduction in the lifespan of keratinocytes.[12] This protein links basal keratinocytes to the extracellular matrix through interactions with integrins α6β4 (in hemidesmosomes) and α3β1 (in ZO contacts).[8, 10] Although mutations in the genes LAMA3, LAMB3 and LAMC2 have been associated with defects in laminin-332 function, their role in the pathophysiology of sepsis remains largely hypothetical and unconfirmed in clinical settings.[13]

Integrins, especially α3β1 and α6β4, mediate the connection between the extracellular matrix and the cytoskeleton.[14, 15] Their expression, normally confined to the basal layer, changes under pathological conditions, which may serve as a diagnostic marker.[16, 17]

Type IV collagen, synthesised by keratinocytes and fibroblasts, forms the structural framework of the basement membrane.[18] Mutations in this collagen are associated with Alport syndrome, which manifests as a disruption of the barrier function.[19] To date, very few studies have systematically evaluated the role of type IV collagen in sepsis-associated cutaneous pathology.[20]

In cases of injury, the activation of repair processes involves an increased expression of laminin-332 and the migration of keratinocytes.[21, 22] Studying the changes in these components during sepsis is particularly important, as current knowledge is limited. Expanding this line of research may offer novel insights into the pathogenesis of skin involvement in systemic inflammation and help identify potential diagnostic or therapeutic targets in sepsis.

Aim of the study was assessment of the fibrous component of the dermal-epidermal junction (integrin-1, laminin-332, type IV collagen) in sepsis.

Methods

The study sample consisted of patients (n = 55) receiving inpatient treatment. Medical records were used for analysis: surgical intervention protocols, discharge summaries and clinical data, specifically evaluating complaints, the severity of symptoms, anamnesis, disease duration, details of pharmacological therapy (medications, doses, frequency, duration and regularity), comorbidities, as well as the dynamics of laboratory parameter changes.

According to clinical and morphological criteria, two groups were formed in the study:

Group I – deceased patients with pathologically confirmed complications of the underlying disease: sepsis/septic shock, according to the Sepsis-3 consensus and multiple organ dysfunction syndrome (n = 45).

Inclusion criteria for patients in Group I: age range 18 – 45 years, clinically and morpho-

logically verified signs of internal organ hypoperfusion, serum lactate levels > 4 mmol/L, oliguria, altered consciousness.

Group II – deceased patients due to causes unrelated to infectious diseases (n = 10).
Inclusion criteria for patients in Group II: age range 18–45 years, absence of clinically and morphologically verified sepsis criteria.

Exclusion criteria for patients in both groups were: pregnancy, presence of oncological diseases, nosocomial infection, hereditary and acquired diseases affecting the skin and/or connective tissue (Marfan syndrome, Ehlers-Danlos syndrome, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, ankylosing spondylitis, psoriasis, follicular hyperkeratosis, etc), chronic liver disease, renal failure, bullous diseases (acquired and hereditary), immunosuppressive and hormonal therapy and history of haemostasis disorders.

Additionally, for a more detailed analysis, the patients in the sepsis group (Group I) were further subdivided into age subcategories: 18–24 years, 25–34 years and 35–45 years, with 15 individuals in each subgroup. In the control group (Group II), the respective age subgroups included 3, 3 and 4 individuals.

Histological examination

For general histological examination for light microscopy, skin fragments were collected from visually unaltered abdominal skin within 6 hours after the confirmation of biological death., skin fragments measuring 1.0×1.0×0.5 cm were fixed in a 10 % buffered formalin solution (pH 7.2 – 7.4) at room temperature for 24 hours; dehydrated in ascending concentrations of alcohol; cleared in xylene; embedded in paraffin blocks; serial sections of approximately 2 – 3 µm thickness were prepared using a Leica RM 2255 microtome; and stained with Mayer's haematoxylin and eosin.

Immunohistochemical examination

Immunohistochemical analysis was performed on serial paraffin sections of 2–3 µm thickness, placed on adhesive slides coated with poly-L-lysine. Using this indirect immunohistochemical method, the main proteins of the fibrous component of the dermal-epidermal junction (laminin-332, integrin-ß1, collagen IV) were identified (Table 1). The expression of laminin-332 and collagen IV was assessed based on the intensity and distribution of staining. An intensity reaction scale (IRS) was used: 0 – no reaction; 1 – 3 – weak; 4 – 6 – moderate; 7 – 10 – strong.

The number of integrin-positive cells in the epidermis was counted in 10 random fields of view at ×400 magnification (in %). All image evaluations were performed by an independent expert blinded to group allocation. Quantification of protein expression was conducted using ImageJ software (version 1.51), allowing for standardised and objective assessment of staining intensity and cell counts.

Statistical analysis

The data obtained from the calculations were processed using SPSS 12 for Windows (IBM Analytics, USA). The results are presented as the mean value ± SD (standard deviation). The Shapiro-Wilk test was used to assess the normality of data distribution. For comparisons between groups with non-normal distribution, the Kruskal-Wallis test was applied, followed by the Dunn post-hoc test. Multiple comparisons were made using the Mann-Whitney U test. A p-value of ≤ 0.05 was considered statistically significant.

Table 1: Used antibodies, their clones and brief characteristics

Antibodies	The clone	Specificity and characterisation
Laminin-332 1:100	Clone 5HCLC Leica Biosystems Newcastle Ltd	Glycoprotein; normally visualised in the basement membrane of the skin epidermis.
Integrin-ß1 1:500	Clone 1G9-B0-F5 Leica Biosystems Newcastle Ltd	Integral antigen; normally found in the basal layer of keratinocytes.
Collagen IV 1:100	Clone EPR20966 Leica Biosystems Newcastle Ltd	Fibrillar antigen; normally visualised in the basement membrane of the epidermis.

Results

In Group I, males predominated, with a median age of 41 years and the majority died on day 4. Laboratory data revealed elevated body temperature (37.1 ± 1.1 °C), creatinine (7.5 ± 0.5 mg/L) and CRP (191.1 ± 12.2 mg/dL). The primary entry sites were predominantly the lungs (Figure 1) and the most common pathogen was *Staphylococcus aureus* (Figure 2). All patients received antibacterial and infusion therapy according to the etiological factor and the severity of sepsis.

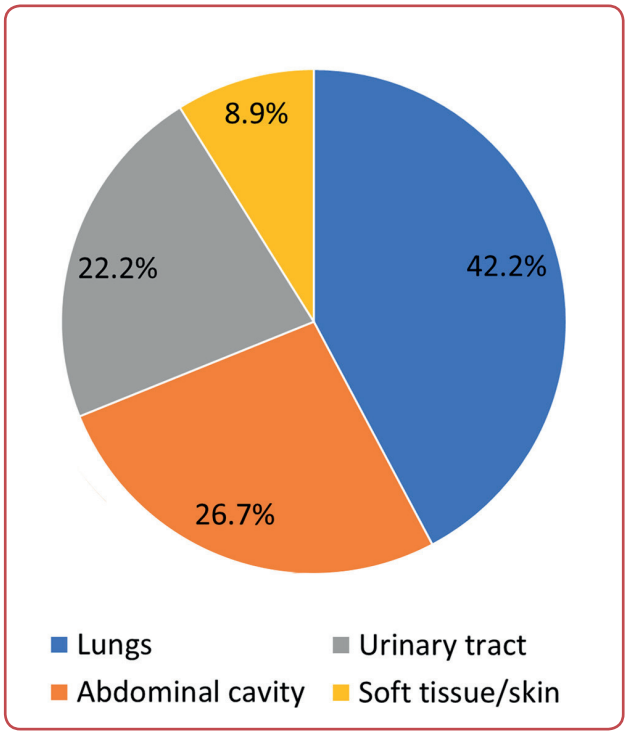

Figure 1: Localisation of infectious foci

Histological examination

Histological examination of the skin in sepsis patients revealed thinning of the epidermis, moderate perivascular inflammatory infiltration and local areas of mild oedema. Despite this, no significant disruptions in the histoarchitecture of the skin were found: all layers of the epidermis maintained clear differentiation and the dermal structure showed no signs of significant destructive changes (Figure 3a).

Microscopic examination of skin samples from Group II patients shows a normal histological picture. The basement membrane is visualised as a clearly defined homogeneous band at the epidermal-dermal junction, providing a strong connection between the stratified squamous keratinising epithelium and the underlying loose, unorganised fibrous connective tissue of the papillary dermis (Figure 3b).

In certain areas of the skin in sepsis patients, pronounced inflammation with abundant cellular infiltration (neutrophils, lymphocytes, etc) was observed, which may also lead to local disruptions in the integrity of the fibrous structures of the dermis and basement membrane (Figure 4).

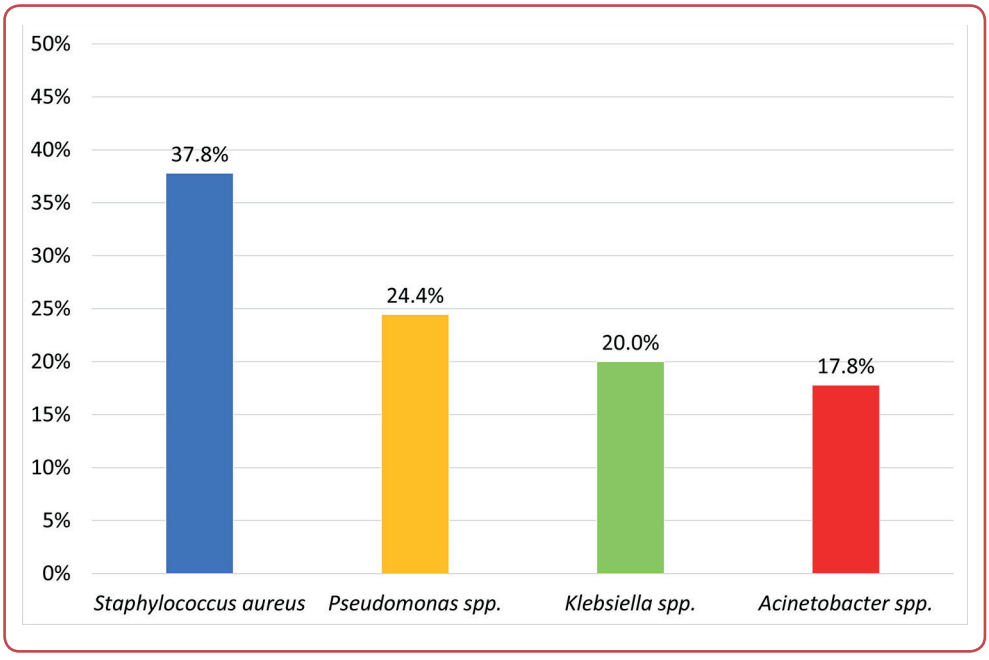

Figure 2: Pathogens of infectious diseases that led to sepsis

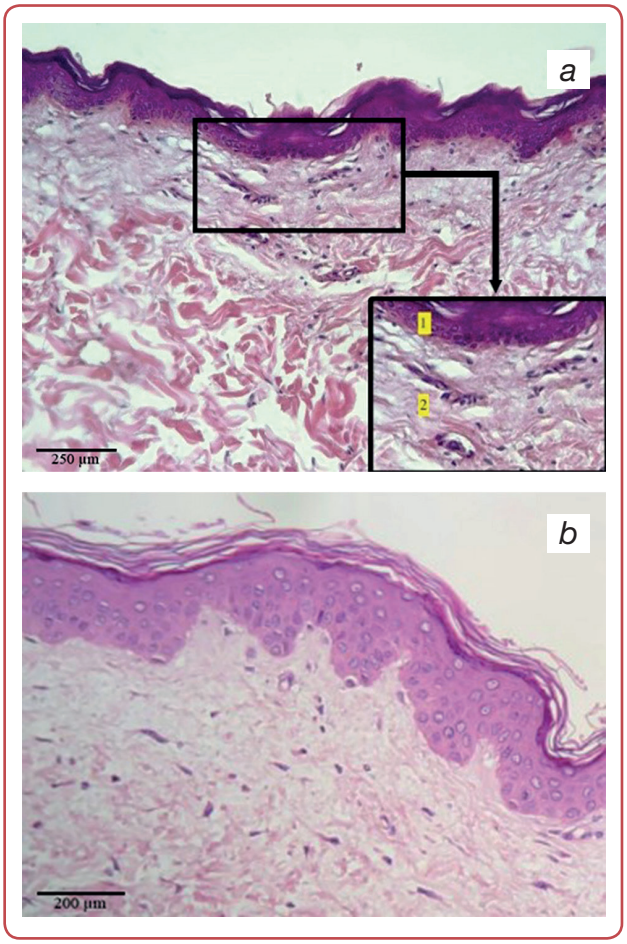

Figure 3: Skin in sepsis (a) and control group (b). Staining: haematoxylin and eosin. Magnification ×200, inset – magnification ×400. Skin layers: 1 – epidermis, 2 – dermis

Immunohistochemical examination

The basement membrane is a specialised extracellular structure located between epithelial, endothelial, or muscle cells and the underlying connective tissue. It consists of two main layers: the light layer (*lamina lucida*), adjacent to the cells and the dense layer (*lamina densa*), which is in contact with the connective tissue.

The basement membrane is primarily composed of laminin and type IV collagen. Laminin, with its cross-shaped structure, facilitates cell adhesion and interacts with other components. Type IV collagen forms a strong network, providing mechanical stability to the membrane. The membrane also contains integrins, which ensure cell attachment. In all samples from Group I patients, immunohistochemical analysis showed positive reactions with all proteins, but the intensity varied compared to Group II.

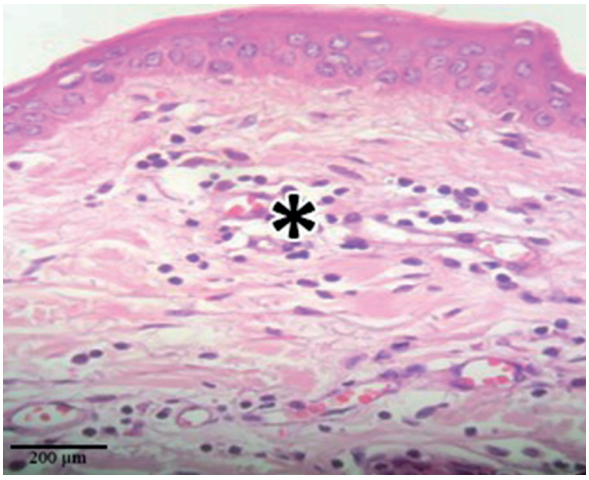

*Figure 4: Skin of a patient in sepsis; staining – haematoxylin and eosin, magnification ×400. * – moderate cellular inflammatory infiltration, predominantly lymphocytes*

Laminin-332

Immunohistochemical analysis revealed statistically significant differences ($p < 0.05$) in the inten-

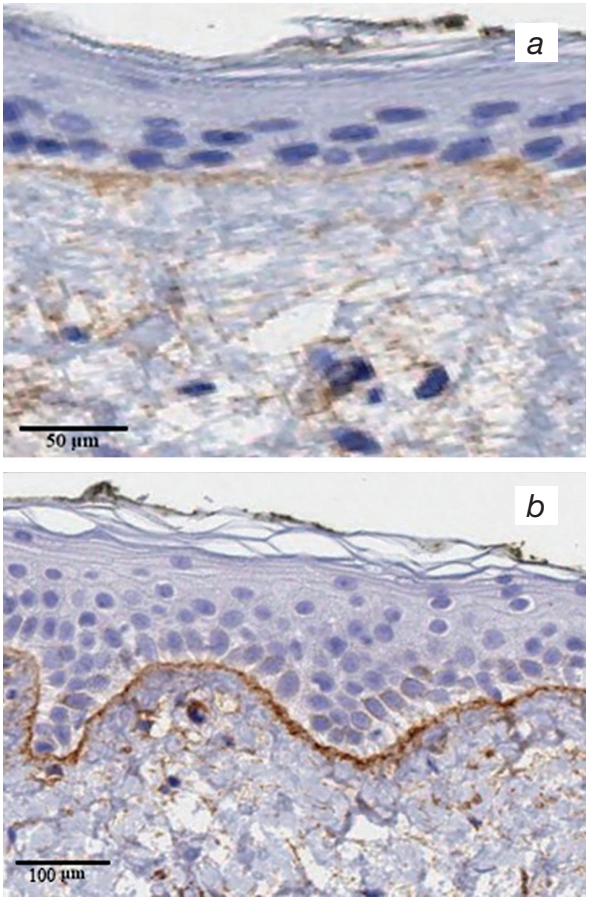

Figure 5: Skin in sepsis (a; IRS – 3 points) and control group (b; IRS – 8 points). Immunohistochemical analysis with antibodies to laminin, nuclei counterstained with haematoxylin; magnification ×400

sity of laminin-332 expression between the compared groups. In the sepsis group (Group I), the expression level was significantly lower compared to the control group. Stratification by age showed a trend toward decreasing laminin-332 expression with increasing age: the highest values were observed in patients aged 18 – 24 years, while the lowest were found in patients aged 35 – 45 years (Table 2). In the control group (Group II), expression remained stable and significantly higher compared to the sepsis group in all age subcategories. The most intense reaction was noted in the dermo-epidermal junction and in the walls of blood vessels in the dermis (Figure 5).

Table 2: Comparison of laminin-332 expression levels in the dermal-epidermal junction ($p < 0.05$)

Age	Sepsis (I group)	Intact skin (II group)
18 – 24 years	3.9 ± 0.3	6.8 ± 0.1
25 – 34 years	2.5 ± 0.2	6.5 ± 0.2
35 – 45 years	1.8 ± 0.4	6.3 ± 0.1

Table 3: Comparison of the expression level of collagen IV dermal-epidermal junction ($p < 0.05$)

Age	Sepsis (I group)	Intact skin (II group)
18 – 24 years	3.6 ± 0.4	7.4 ± 0.5
25 – 34 years	2.8 ± 0.5	7.2 ± 0.3
35 – 45 years	1.4 ± 0.3	6.8 ± 0.4

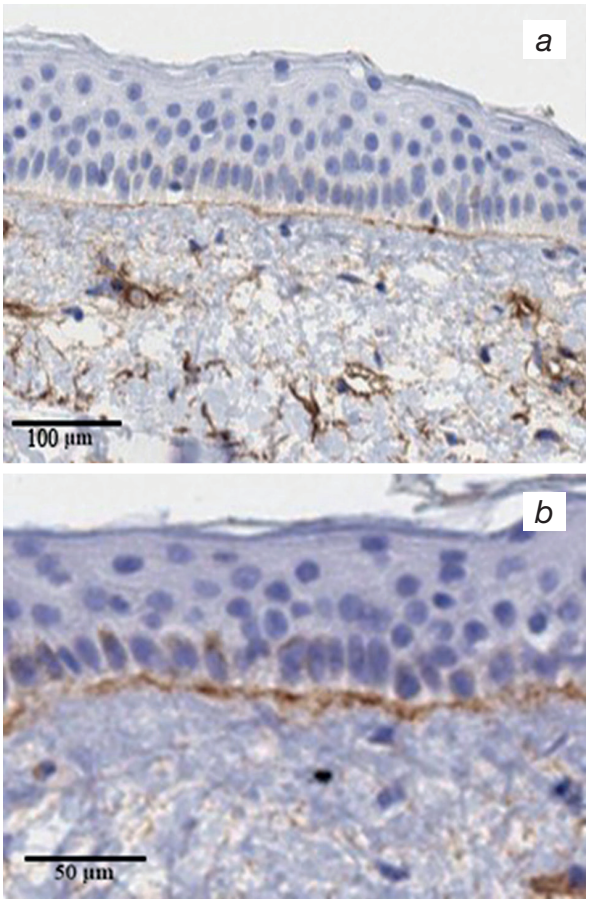

Figure 6: Skin in sepsis (a; IRS – 3 points) and control group (b; IRS – 9 points). Immunohistochemical analysis with antibodies to Collagen IV, nuclei counterstained with haematoxylin; magnification ×400

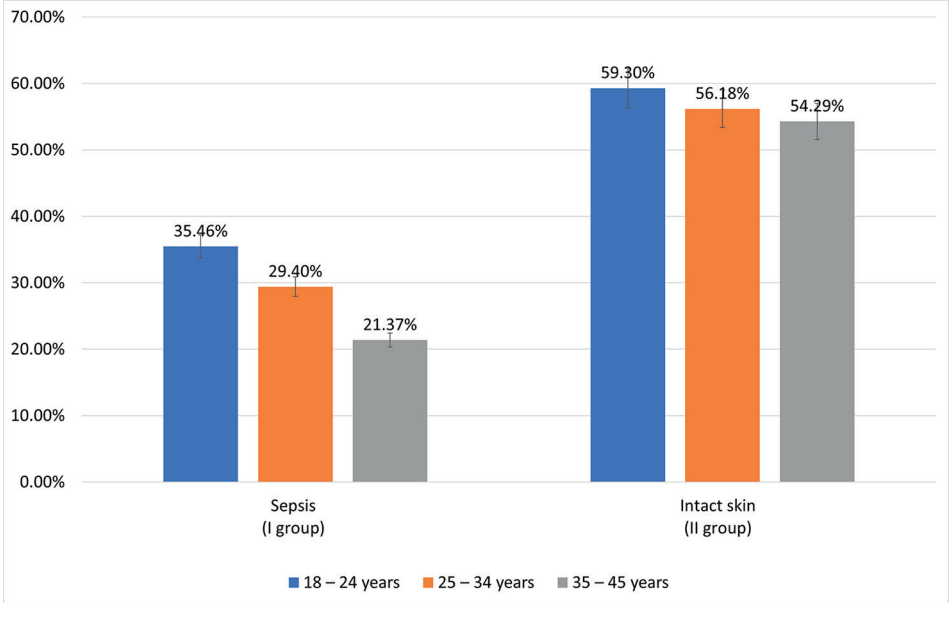

Figure 7: The percentage of integrin-ß1-positive keratinocytes in sepsis (Group I) and in the control group (Group II, normal) ($p < 0.05$)

Collagen IV

Immunohistochemical analysis revealed a significant decrease ($p < 0.05$) in collagen type IV expression in the dermal-epidermal junction in sepsis patients (Group I) compared to the control group. Age-stratified analysis showed a gradual reduction in expression with increasing age: the highest values were observed in the younger age group and the lowest in individuals aged 35 – 45 years (Table 3). In intact skin (Group II), Collagen type IV expression remained consistently high across all age subgroups. The most pronounced reaction was observed in the dermal-epidermal junction and in the walls of blood vessels in the dermis (Figure 6).

Intregrin-β1

Immunohistochemical analysis of integrin-β1 expression in the dermal-epidermal junction in sepsis patients (Group I) revealed a significant decrease in the number of Integrin-positive basal epidermal cells compared to the control group (Group II). Age-stratified analysis showed that integrin-β1 expression decreased with increasing age: the highest values were observed in the younger age subgroups and the lowest values in individuals aged 35–45 years (Figure 7, 8). In intact skin, Integrin-β1 expression remained consistently high with only minor age-related fluctuations.

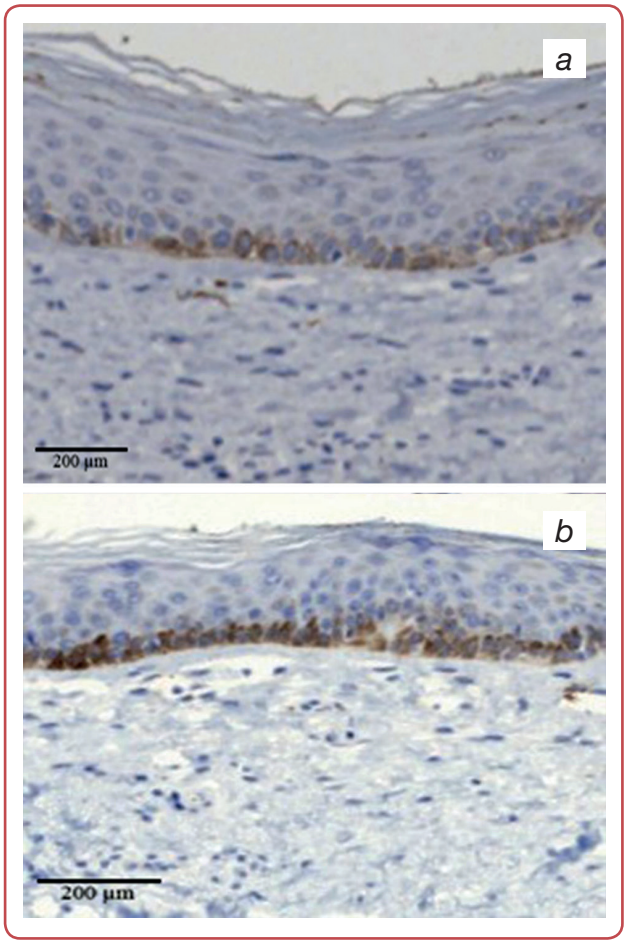

Figure 8: Skin in sepsis (a) and control group (b). Immunohistochemical analysis with integrin-ß1 antibodies, nuclear counterstaining with haematoxylin; magnification ×400

Correlation analysis with clinical parameters

No statistically significant correlations were found between the levels of protein expression (laminin-332, collagen IV and integrin-β1) and clinical parameters such as disease duration, sepsis severity, systemic inflammatory markers, serum lactate levels, or organ dysfunction scores.

Discussion

The results of this study demonstrate the critical role of the structural components of the fibrous component, primarily the basement membrane, in maintaining the integrity of the dermal-epidermal junction. The obtained data indicate a significant decrease in the expression of key basement membrane proteins in the skin of sepsis patients compared to the control group. Additionally, it is important to highlight the disruption of the differentiation of intercellular contacts in the basal layer keratinocytes.

Laminin-332, being the main structural component of anchor fibrils, plays a key role in maintaining the stability of the dermal-epidermal junction.[23] In sepsis patients, a decrease in its expression was observed, indicating partial fragmentation of the basement membrane, which leads to increased permeability of the epidermis and dermis.[24] The obtained data are consistent with the results of other studies, demonstrating a connection between the disruption of basement membrane integrity and the development of oedema in sepsis, which may also correlate with the frequency of fatal outcomes.[25] It is important to note that the deficiency of key basement membrane proteins leads not only to mechanical instability, but also to the formation of defects and disruption of basement membrane regeneration processes, similar to the development of pressure ulcers.[26]

Of particular interest is the observed decrease in the expression of type IV collagen, which forms the structural framework of the basement membrane. This is consistent with current concepts of the cascade nature of dermal-epidermal junction formation during regenerative processes, where the initial deposition of laminins precedes the polymerisation of type IV collagen, involving both keratinocytes and fibroblasts.[27, 28] Type IV collagen ensures a strong connection between the epidermis and dermis, providing barrier function. The observed weak expression in sepsis confirms the involvement of the skin in the systemic process, which, similar to laminin, may lead to the development of oedema correlating with mortality.[29]

Particular attention should also be given to the intercellular communication protein – integrin-β1, which not only ensures the mechanical adhesion of keratinocytes but also participates in regulating their proliferation and differentiation.[20] The observed partial disruption of integrin in sepsis may indicate a disturbance in both the attachment of the epidermis to the dermis and in regenerative processes, which collectively impair skin functions, including its barrier function. The obtained data support the concept that the level of integrin-β1 expression serves as an important regulatory mechanism controlling the migration of keratinocytes from the basal layer.

Although the present study demonstrates a significant decrease in the expression of laminin-332, collagen IV and integrin-β1, the underlying mechanisms remain to be clarified. It is currently unclear whether this reduction results from a lower number of protein-producing cells, suppressed synthesis within keratinocytes, or enhanced proteolytic degradation under systemic inflammatory conditions.[30, 31] Additionally, post-translational modifications, which may alter protein function without affecting expression levels, were not assessed.[32] These factors should be considered in future studies to better understand the functional consequences of reduced marker expression in sepsis.

It should be noted that the issue of morphofunctional changes in the skin during sepsis of varying severity and aetiology has been studied for a long time. Even more interesting is the lack of data on age-related changes over time, which makes presented study provide a new perspective on the problem. The changes we observed, according to age-periodisation, point to the role of regulatory and integrating systems that ensure adaptive and compensatory mechanisms, which are more pronounced in younger individuals. At the same time, in the older age group, these mechanisms are less pronounced, indicating a higher likelihood of an unfavourable prognosis.

The obtained data suggest that the skin should be considered not only as a target organ in sepsis but also as an active participant in the pathological process. This is because the disruption of its structural integrity contributes to the progression of systemic inflammation by enhancing transepidermal fluid loss, impairing local immune surveillance and creating conditions for secondary infection.

A promising direction for future research could be the study of the dynamics of fibrous component protein expression recovery in the basement membrane of patients who have undergone sepsis, taking into account data on the prolonged (up to 3 months) persistence of changes, including the use of molecular-genetic analysis.[33]

Conclusion

In sepsis patients, a significant reduction in the expression of the intercellular communication protein – integrin-β1 – is of particular importance. This leads to impaired adhesive properties of keratinocytes and affects their proliferation and differentiation through the modulation of intracellular signalling pathways. The combination of morphological and immunohistochemical changes, as well as the qualitative and quantitative deviation of laminin and collagen type IV, creates conditions for the formation of a vicious circle, where the disruption of the skin's regenerative potential exacerbates its structural defects and these, in turn, hinder the normal course of reparative processes. Pathological changes in the skin during sepsis are particularly pronounced in older individuals, possibly due to the decreased activity of adaptive and compensatory mechanisms.

Ethics

The Bioethics Commission of the Peoples' Friendship University of Russia named after Patrice Lumumba in accordance with the National Bioethics Committee, approved this study (Protocol No 11), dated 14 May 2019.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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