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METABOLIC RISK FACTORS FOR DISORDERS IN LOCALIZED SCLERODERMA

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Localized scleroderma is a relatively common chronic inflammatory connective tissue disorder, yet the mechanisms underlying its progression remain insufficiently understood, underscoring the need to investigate metabolic risk factors and develop appropriate therapeutic approaches. In this study, a comprehensive examination and treatment were performed in 78 patients with localized scleroderma, including assessment of endothelial function, endogenous intoxication, and prooxidant–antioxidant balance, as well as comparison of the efficacy of standard and proposed therapies. It was demonstrated that patients with focal scleroderma develop an unfavorable toxic-metabolic profile. Based on the obtained results, an improved comprehensive treatment method was developed: in addition to standard therapy, patients in the main group received an endothelial-protective agent, a sorbent, an antioxidant agent, and ultrasound-mediated hyaluronidase (ultraphonophoresis). The proposed treatment regimen led to significant reductions in endothelin-1, VEGF-A, VCAM-1, and protein carbonyl levels, along with increased activity of superoxide dismutase, glutathione reductase, and increased reduced glutathione content. These findings support the rationale for incorporating endothelial-protective and antioxidant agents into comprehensive treatment schemes to enhance current therapeutic approaches and optimize patient management.

Key words: localized scleroderma, risk factors, metabolic disorders, oxidative stress, morphea.

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МЕТАБОЛІЧНІ ФАКТОРИ РИЗИКУ РОЗВИТКУ ВОГНИЩЕВОЇ СКЛЕРОДЕРМІЇ

Вогнищева склеродермія є доволі поширеним хронічним запальним захворюванням сполучної тканини, але механізми її прогресування залишаються недостатньо з'ясованими, що зумовлює актуальність вивчення метаболічних чинників ризику та пошуку відповідних терапевтичних підходів. Під час дослідження було проведено комплексне обстеження та лікування 78 пацієнтів із вогнищевою склеродермією з оцінкою показників ендотеліальної функції, ендогенної інтоксикації та прооксидантно-антиоксидантного балансу, а також порівнянням ефективності стандартної та запропонованої терапій. Доведено, що у хворих на вогнищеву склеродермію формується несприятливий токсично-метаболічний патерн. На підставі отриманих результатів дослідження розроблено удосконалений спосіб комплексного лікування хворих, а саме: на тлі стандартної терапії пацієнти основної групи додатково отримували ендотеліопротекторний препарат, сорбент, препарат з антиоксидантною дією та ультрафонофорез з гіалуронідазою. Встановлено, що запропонована схема лікування сприяла достовірно більшому зниженню рівнів ендотеліну-1, VEGF-A, VCAM-1, карбонільних груп білків та збільшенню активності супероксиддисмутази, глутатіонредуктази та вмісту відновленого глутатіону. Отримані результати обґрунтовують доцільність включення ендотеліопротекторних і антиоксидантних засобів до комплексних схем лікування для вдосконалення сучасних терапевтичних підходів і оптимізації ведення пацієнтів.

Ключові слова: вогнищева склеродермія, чинники ризику, метаболічні порушення, оксидативний стрес, морфея.

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Localized scleroderma (LS) is a chronic inflammatory connective tissue disease characterized by progressive fibrosis of the skin and underlying tissues, marked clinical heterogeneity, and an unpredictable course. The first descriptions of skin induration date back to ancient medical writings; however, a systematic understanding of scleroderma developed only in the eighteenth and nineteenth centuries. Subsequent advances in clinical medicine, pathology, and immunology led to the recognition of scleroderma as a distinct group of fibrosing disorders with diverse clinical manifestations [3, 8].

Modern concepts distinguish two fundamental forms of scleroderma: systemic sclerosis and LS. Systemic sclerosis is a generalized autoimmune disease involving the skin and internal organs, whereas localized scleroderma is primarily confined to the skin and subcutaneous tissues without progressive visceral involvement [3, 10]. Despite this distinction, accumulating evidence indicates partial overlap in immunological mechanisms and vascular abnormalities between the two forms, which complicates differential diagnosis and therapeutic decision-making [8, 9].

According to current classifications, LS includes morphea and lichen sclerosus, both of which represent inflammatory dermatoses that may lead to irreversible sclerosis [10]. Morphea presents with

several clinical variants, including plaque, linear, deep, nodular, and mixed forms, with linear scleroderma particularly prevalent in pediatric populations [4, 12]. The disease often shows a chronic relapsing course, with progression over several years followed by partial spontaneous regression, although residual atrophy and cosmetic defects frequently persist [1, 4].

Recent studies emphasize the important role of immune dysregulation, endothelial dysfunction, and fibroblast activation in the pathogenesis of LS. Abnormal vascular responses, altered growth factor expression, and excessive collagen deposition have been observed in affected tissues, suggesting that microvascular injury may represent an early trigger in the disease process [7, 9]. Additionally, comorbid autoimmune conditions have been increasingly reported in patients with localized scleroderma, further supporting the systemic immunological background of this disorder [2].

Despite significant progress in understanding the clinical spectrum of LS, the mechanisms underlying disease persistence, progression, and response to therapy remain insufficiently elucidated. Current treatment strategies, including phototherapy, immunomodulatory agents, and biologic therapies, are often based on limited evidence and show variable efficacy [1, 5, 6]. Therefore, further investigation into pathogenic mechanisms, particularly metabolic and endothelial factors, is essential to optimize therapeutic approaches and improve patient outcomes. This necessity determines the relevance of the present study, which focuses on metabolic disturbances and endothelial dysfunction in patients with localized scleroderma.

The purpose of the study was to optimize the diagnosis and management of localized scleroderma by assessing endothelial dysfunction, endotoxin-associated changes, and prooxidant metabolic disorders.

Materials and methods. The study was conducted on the basis of the National Pirogov Memorial Medical University, “Vinnytsia Regional Clinical Skin and Venereological Center of the Vinnytsia Regional Council”, “RAK Medical & Health Sciences University, UAE” and “Ministry of Health of Jordan”. Jordanian physicians affiliated with the Ministry of Health contributed to data review, laboratory result classification, and scientific interpretation within an approved academic collaboration. A physician from the United Arab Emirates also assisted in reviewing and classifying the collected data and laboratory analyses as part of the research collaboration.

The study was based on prospective observation and analysis of examination results from 78 patients with LS who received inpatient treatment at the Vinnytsia Regional Clinical Dermatovenerologic Center of Vinnytsia Regional Council from 2022 to 2025.

All participants were divided into two groups: the main group (78 patients, 69%), including 40 patients in the combination therapy subgroup and 38 patients in the standard (basic) therapy subgroup, and the control group (35 patients, 31%). The mean age of patients in the main group was 43.2±7.28 years (range 10–81 years), whereas in the control group, the mean age was 39.5±8.10 years (range 27–55 years). According to gender distribution, females predominated among the study participants (73 individuals, 64.6 %) compared to males (40 individuals, 35.4 %).

Study inclusion criteria: presence of LS in patients with an established diagnosis (typical erythema, edema, and induration); absence of signs of systemic involvement; written informed consent to participate in the study in accordance with the principles of the Helsinki Declaration on patients’ rights.

Study exclusion criteria: history of malignancy; psychiatric disorders; pregnancy or lactation; decompensated diseases; traumatic injuries of the central nervous system and psychiatric disorders; acute infectious diseases; use of medications that could significantly affect the course of the underlying disease; history of adverse reactions to therapy or development of new adverse effects during ongoing treatment; current or past substance abuse; withdrawal of consent or refusal to participate in the study for any reason.

For verification and formulation of the diagnosis, the International Classification of Diseases, 10th Revision (ICD-10) was applied. The management of LS was performed in accordance with the recommendations of the European Dermatology Forum (EDF) S1 guideline on the diagnosis and treatment of LS. Clinical evaluation included assessment of disease subtype, extent, and activity, with exclusion of systemic involvement. Therapeutic strategies were selected based on disease severity and activity following established European evidence-based recommendations.

All clinical investigations were conducted at the Research and Educational Laboratory of the Bukovinian State Medical University. Clinical blood and urine tests were performed using standardized methods. Complete blood count analysis was performed on stabilized whole blood using an automatic hematology analyzer Abacus 3CT (DIATRON MI PLC, Hungary). Biochemical analyses were carried out on citrated plasma and serum using an automatic biochemical analyzer, Diagon Coag4D (Diagon Ltd, Hungary). Laboratory diagnostics comprised a complete blood count with evaluation of leukocytosis and erythrocyte sedimentation rate, biochemical blood analysis, including C-reactive protein and total protein levels, as well as immunological testing for antinuclear factor, antinuclear antibodies, and antibodies to the scleroderma-70 antigen. To assess collagen

metabolism, blood and urinary oxyproline levels and urinary glycosaminoglycan concentrations were determined. Evaluation of internal organs was conducted only when systemic involvement was suspected. To investigate endothelial dysfunction, serum levels of endothelin-1, vascular endothelial growth factor, and cell adhesion molecules were analyzed. Oxidative stress was assessed by measuring protein oxidative modification using neutral and basic dinitrophenylhydrazones. The antioxidant defense system was evaluated by measuring the activity of superoxide dismutase, catalase, glutathione reductase, and reduced glutathione.

All analyses were performed using modern automated or semi-automated laboratory equipment: spectrophotometers (BioSpectrometer, Eppendorf) and standard biochemical analyzers (Biochem FC, Mindray). Reagents suitable for human studies were used (Sigma-Aldrich or PanReac AppliChem). Immunoenzymatic assays were performed using commercial ELISA kits following the manufacturer's protocols.

The treatment lasted 4 weeks and was conducted partially in the hospital and partially on an outpatient basis. Standard therapy included the use of antifibrotic, detoxifying, vasoactive agents, and vitamins according to established protocols, along with physiotherapy methods for patients with LS. To evaluate the efficacy of conventional therapy supplemented with endothelioprotective, detoxifying, and antioxidant agents—including L-arginine, silicon dioxide, thioctic acid, and ultrasound-mediated hyaluronidase (ultraphonophoresis)—all patients were randomly assigned to two comparable groups, formed from those meeting the inclusion criteria.

In the control group (n=38, 48.7 %), treatment followed standard clinical recommendations for this condition, including intramuscular penicillin-O (Sandoz, Austria) 1 million IU twice daily for 10 days or benzylpenicillin (Sandoz, Austria) 1 million IU twice daily for 10 days; lidase (Biopharm, Ukraine) 64 IU, 1 ml intramuscularly every other day for 10 doses; Vitreous body (Biopharm, Ukraine) 2 ml intramuscularly every other day for 10 doses or Plasmol (Biopharm, Ukraine) 1 million IU subcutaneously every other day for 10 doses; vitamins A and E (Biopharm, Ukraine), 1 capsule daily for 4 weeks; and xanthinol nicotinate (Arterium, Ukraine), 1 tablet three times daily for 4 weeks. Local therapy included hydrocortisone or Celestoderm cream (Organon, Belgium) twice daily for 4 weeks.

In the main group (n=40, 51.3 %), patients received standard therapy with the addition of Tivortin (Yuriya-Pharm, Ukraine) (1 spoon twice daily for 2 weeks), Eliminal gel (Orisil-Pharm, Ukraine) (1 stick twice daily, one hour before meals for 2 weeks), alpha-lipoic acid (Biopharm, Ukraine) 300 mg (once daily 30 minutes before breakfast for 2 weeks), and ultraphonophoresis with longidase 3000 IU once daily for 7 procedures.

The patient groups were comparable with respect to sex, age, and baseline clinical and laboratory parameters. Therapeutic efficacy was assessed by changes in the internationally validated Modified Localized Scleroderma Severity Index (mLoSSI) and by a global assessment using a 100-mm visual analog scale (PhysGA-A).

For statistical analysis, the obtained data were processed using the general-purpose software package Statistica for Windows, version 6.0 (StatSoft Inc., USA), and the Epi Info 2000 software package, version 3.3.2. Quantitative data with non-normal distribution were presented as median (Me) with lower (Q25) and upper (Q75) quartiles. Parameters with normal distribution were expressed as mean±standard error (M±m). Statistical processing was performed using standard parametric and nonparametric methods.

Ethical principles were observed in accordance with the Declaration of Helsinki, and a written informed consent form was obtained from all patients. No vulnerable populations, as defined by Good Clinical Practice (GCP) guidelines—including children, elderly individuals, prisoners, pregnant women, cognitively impaired persons, economically disadvantaged groups, ethnic minorities, or refugees—were included in this study.

Results of the study and their discussion. A total of 78 patients with LS who received inpatient treatment at the Vinnytsia Regional Clinical Dermatovenerologic Center of the Vinnytsia Regional Council were enrolled in the study.

The results demonstrated that the majority of cases were represented by plaque (55 patients; 70.5 %) and discoid (12 patients; 15.4 %) forms of the disease, characterized by rounded or oval skin lesions with a limited number of foci. The initial stage of the disease was marked by the appearance of pinkish-lilac macules of varying diameters, which gradually transformed into dense sclerotic plaques with a smooth, ivory-colored surface. In some patients, a persistent lilac inflammatory rim was observed, indicating ongoing disease activity.

Analysis of the skin lesions in the enrolled patients enabled determination of the stage of the cutaneous process: the majority of patients (47 individuals; 61.0 %) were in the induration stage, whereas a smaller proportion (6 individuals; 8.0 %) were in the atrophic stage.

The obtained clinical results demonstrated that patients with LS developed pronounced metabolic and toxic disturbances. A significant increase in markers of endothelial dysfunction, endogenous intoxication, and oxidative stress was detected in comparison with practically healthy individuals. In particular, endothelin-1 levels were significantly elevated in patients with LS, indicating endothelial

damage and vascular dysregulation. In LS, the level of this biomarker increased by 2.44-fold compared with that in practically healthy individuals, reaching 8.69 (6.53–10.2) pg/mL, versus 3.56 (2.69–4.53) pg/mL (Fig. 1).

Thus, in patients with LS, elevated plasma ET-1 levels may contribute to vascular damage by regulating factors that promote angiogenesis and induce vascular remodeling, representing an important mechanism in the development of skin fibrosis.

Vascular endothelial growth factor (VEGF) is a potent angiogenic peptide and a key regulator of blood vessel growth. Tissue hypoxia and ischemia lead to the expression of angiogenic growth factors, including VEGF-A. Owing to its involvement in both physiological and pathological angiogenesis, VEGF has become an attractive target for both pro-angiogenic and anti-angiogenic therapies. It is believed that VEGF and its receptors are expressed more in the skin of patients with scleroderma.

In our study, a significant increase in endothelial proliferative activity and elevated VEGF-A levels were observed in LS (445.9 (218.5–644.9) pg/mL) compared with practically healthy individuals (96.6 (99.3–110.4) pg/mL; p<0.05).

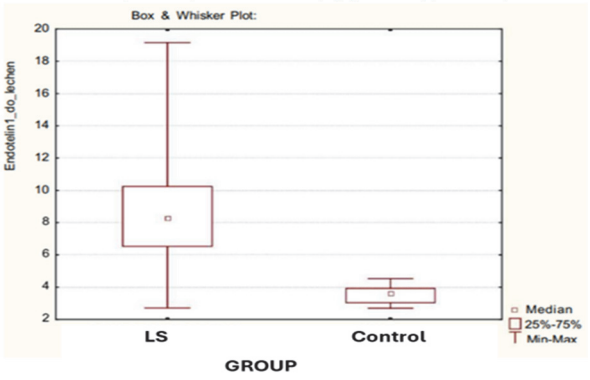

Fig. 1. Endothelin-1 content in patients with localized scleroderma and control subjects, pg/mL.

A U-shaped age-related pattern of disease course was also noted: high VEGF-A levels were detected in patients under 20 years of age – 424.3 (229.3–662.9) pg/mL – followed by a 2.82-fold decrease in angiogenic factor levels among patients aged 20–35 years – 150.3 (77.5–163.7) pg/mL – and a subsequent 2.62-fold increase in patients aged 35–55 years – 393.6 (108.8–703.9) pg/mL. The highest vascular endothelial growth factor levels in LS were observed in patients older than 55 years – 490.0 pg/mL (226.9–659.9) (p<0.05).

Vascular cell adhesion molecule-1 (VCAM-1) has been reported to play a role in the pathogenesis of scleroderma. Through VCAM-1, pro-inflammatory cytokines such as IL-1β and TNF-α are induced, promoting monocyte adhesion to activated and damaged endothelial cells. In cases of excessive expression, these adhesion molecules can be detected in the circulation in soluble form and are considered markers of underlying endothelial activation and injury. We identified a significant elevation of this biomarker in the cutaneous form of scleroderma (683.4 (499.4–880.1) pg/mL) compared with practically healthy individuals (339.7 (305.9–358.3) pg/mL; p<0.05) (Fig. 2).

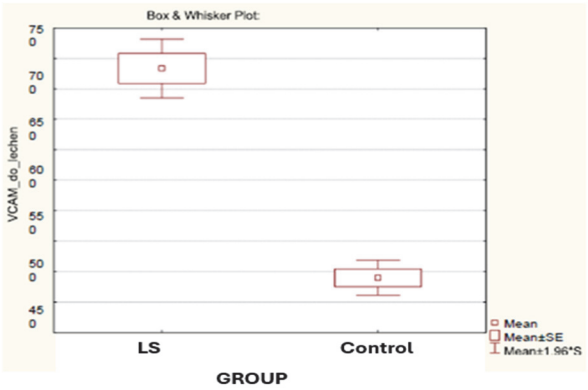

Fig. 2. Serum VCAM-1 levels in patients with LS and control subjects, pg/mL.

Thus, the pathogenesis of LS is determined, on the one hand, by characteristic microcirculatory disturbances and various manifestations of endothelial dysfunction, and, on the other hand, by autoimmune alterations in the cytokine profile. In this context, the immune system is a source of reactive oxygen species (ROS) and contributes to oxidative stress.

The level of protein oxidative modification was markedly increased. The concentration of neutral dinitrophenylhydrazones reached 4.36±0.43 nm, while basic dinitrophenylhydrazones amounted to 32.0±3.0 nm, compared to 1.67±0.43 nm and 16.3±0.81 nm, respectively, in the control group (p<0.05). These data indicate excessive formation of reactive oxygen species and the development of oxidative stress in LS. An age-related dependence of oxidative modification of proteins (OMP–carbonyl groups) was also established in patients with LS, with a significant increase in neutral and basic dinitrophenylhydrazones observed in patients older than 70 years (p<0.05).

Thus, pathological activation of the immune system in LS generates ROS, contributing to oxidative stress and placing strain on the antioxidant defense system. To better understand these processes, the levels of superoxide dismutase (SOD) and catalase (CAT) in erythrocytes, the SOD/CAT ratio, as well as plasma glutathione reductase and reduced glutathione, were assessed in patients with LS compared with practically healthy individuals.

Assessment of the antioxidant defense system revealed signs of functional exhaustion. A significant decrease in SOD levels (by 12.6 %, p<0.05), a 2.17-fold increase in catalase activity (p<0.05), and a reduction in the SOD/CAT ratio to 5.71±1.17 U (normal level approximately 14 U; 13.9±2.68, p<0.05) were identified. Patients with LS also demonstrated a marked decrease in the natural antioxidant reduced glutathione (1.47±0.08 vs.

2.22±0.09 μmol/L in controls; a 51.0 % reduction, p<0.05) and its associated enzyme glutathione reductase (4.03±0.54 vs. 8.50±1.83 Ucat/L Hb; 2.11-fold decrease, p<0.05). The severity of oxidative stress and endothelial dysfunction increased with longer disease duration, greater clinical severity, and older patient age.

Therefore, tissue ischemia and cytokine imbalance in LS promote the formation of reactive oxygen species, enhanced generation of activated oxygen metabolites, and the development of oxidative stress. In turn, ROS induces endothelial cell damage, further contributing to proliferative, vasomotor, and adhesive endothelial dysfunction. The development of oxidative stress and endotoxicosis in LS provides a rationale for the use of antioxidant and detoxification therapy, which reduces matrix protein expression and intracellular ROS production while correcting microcirculatory disturbances. In this regard, nitric oxide donors (L-arginine), natural antioxidants (alpha-lipoic acid), and agents with detoxifying properties (Eliminal-gel) are of particular interest.

Following treatment, a significant reduction in neutral dinitrophenylhydrazones was observed in both the basic therapy group (by 47.5 %, from 4.47±0.42 to 3.03±0.40 nm, p<0.05) and the combination therapy group (by 71.6 %, from 4.36±0.40 to 2.54±0.37 nm, p<0.05). Basic dinitrophenylhydrazones decreased by 40.7 % in the comparison group after 6 months (from 31.8±3.24 to 22.6±2.04 nm, p<0.05) and by 73.5 % in the main group (from 32.1±3.23 to 18.5±2.18 nm, p<0.05).

Evaluation of total antioxidant activity in patients receiving different therapies also demonstrated positive effects of combination therapy, with significant increases in SOD, CAT, and glutathione reductase activity. In particular, compared with the comparison group, the main group exhibited a 15.4 % increase in SOD activity (from 37.7±4.38 to 43.5±2.21 mmol/s·g Hb, p<0.05), whereas the basic therapy group showed only a 1.3 % increase (p>0.05). Catalase activity decreased by 68.2 % in the main group (p<0.05) compared with 46.6 % in the comparison group (p<0.05). Glutathione reductase levels increased by 29.5 % in the comparison group and by 64.3 % in the main group after 6 months of therapy (p<0.05). Thus, endothelial-protective agents included in the combination treatment of LS exert additional antihypoxic and antioxidant effects, reducing free radical production and restoring antioxidant enzyme activity.

A reduction in endothelin-1 levels was also observed 6 months after treatment in both the comparison group (from 8.22 (5.99–10.9) pg/mL to 5.45 (4.99–6.26) pg/mL) and the main group (from 8.24 (6.96–10.2) pg/mL to 3.61 (2.42–4.84) pg/mL). The decrease was 50.8 % with basic therapy and 128 % with combination therapy (p<0.05). After 6 months, VEGF levels decreased by 185.3 % in the main group (from 422.0 (195.0–662.8) pg/mL to 147.9 (118.5–192.5) pg/mL) and by 78.9 % in the comparison group (p<0.05). Thus, in terms of vascular endothelial growth factor levels, combination therapy including basic treatment plus endothelial-protective, antioxidant, and detoxifying agents was nearly three times more effective than basic therapy alone.

Also, we showed that VCAM-1 levels decreased in the comparison group from 686.9 (524.2–852.4) pg/mL to 460.5 (410.6–538.6) pg/mL (49.1 %, p<0.05) and in the main group from 669.5 (484.5–882.1) pg/mL to 353.4 (329.3–390.8) pg/mL (89.5 %, p<0.05).

Regarding clinical outcomes, the total number of scleroderma lesions decreased by 12.9 % in the comparison group (p<0.05) and by 78.3 % in the main group (p<0.05). According to the validated Modified Localized Scleroderma Severity Index (mLoSSI), treatment effectiveness was 31.1 % in the basic therapy group and 106.2 % in the combination therapy group (p < 0.05). Overall, most patients in both groups reported a reduction in the skin disease's impact on quality of life. The results obtained confirm that LS is associated not only with localized skin inflammation but also with systemic metabolic and vascular disturbances. Endothelial dysfunction appears to play a key role in disease progression, promoting tissue ischemia, cytokine imbalance, and fibroblast activation. These mechanisms contribute to excessive collagen production and the development of sclerosis.

The pronounced oxidative stress observed in patients supports the concept that reactive oxygen species are central mediators of endothelial injury and immune activation in LS. The detected depletion of antioxidant defense mechanisms further aggravates endothelial damage and promotes disease persistence. The presence of autoantibodies typical of systemic sclerosis in the majority of patients suggests overlapping pathogenetic pathways between localized and systemic forms of the disease, although without clinically significant involvement of internal organs.

The findings justify the inclusion of endothelioprotective, detoxifying, and antioxidant agents in comprehensive treatment regimens, which may help slow disease progression and improve clinical outcomes.

Limitations. This study has several limitations. The small sample size and single-center design may limit generalizability. Lack of randomization and blinding could introduce bias. The six-month follow-up assesses only short-term effects, not long-term outcomes or sustained changes in endothelial and oxidative stress. Larger, multicenter, randomized studies with longer follow-up are needed to validate these findings.

Conclusions

1. It has been established that patients with LS develop an unfavorable metabolic and toxic pattern characterized by endothelial dysfunction, endogenous intoxication, increased oxidative stress, and depletion of antioxidant defense mechanisms. The most pronounced changes are observed in patients with longer disease duration, greater clinical severity, and older age.

2. The levels of endothelial dysfunction, endogenous intoxication, and imbalance of the prooxidant–antioxidant system, as well as the effectiveness of their correction during complex treatment, were evaluated in patients with LS. Thus, a significant reduction in neutral and basic dinitrophenylhydrazones were observed; evaluation of total antioxidant activity in patients receiving different therapies also demonstrated positive effects of combination therapy, with significant increases in SOD, CAT, and glutathione reductase activity (the main group exhibited a 15.4 % increase in SOD activity (from 37.7±4.38 to 43.5±2.21 mmol/s·g Hb, $p<0.05$), catalase activity decreased by 68.2 % in the main group ($p<0.05$), glutathione reductase levels increased by 64.3 % in the main group after 6 months of therapy ($p<0.05$); endothelin-1 levels decrease reached 50.8 % with basic therapy and 128 % with combination therapy ($p<0.05$); VEGF levels decreased by 185.3 % in the main group; VCAM-1 levels decreased for 49.1 %, and in the main group for 89.5 %.

3. A pronounced clinical efficacy of comprehensive, differentiated treatment of focal scleroderma was demonstrated – over the entire period of controlled observation, the reduction in the number of scleroderma lesions was 78.3 % in the main group versus 12.9 % in the comparison group ($p<0.05$). Treatment efficacy measured by the mLoSSI index was 106.2 % versus 31.1 % ($p<0.05$), and by PhysGA-A dynamics – 80.7 % versus 46.3 % ($p<0.05$).

4. The inclusion of endothelioprotective, detoxifying, and antioxidant agents in complex therapy is pathogenetically justified and allows correction of the detected metabolic and vascular disorders, contributing to optimization of patient management.

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