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CLINICAL MANIFESTATIONS OF NECROBIOSIS LIPOIDICA AND CONTEMPORARY TREATMENT STRATEGIES

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Necrobiosis lipoidica is considered one of the diabetes-associated cutaneous manifestations of diabetes mellitus. The disease is characterized by granulomatous inflammation with pathological signs of collagen necrobiosis and inflammation of the dermis. The purpose of the study was to examine patients in order to collect data on the epidemiology of necrobiosis lipoidica in Azerbaijan, to visually assess changes in the appearance of necrobiosis lipoidica lesions, and to compare lipid-profile, carbohydrate-metabolism and coagulation-profile parameters before and after the proposed treatment. Various clinical forms of necrobiosis lipoidica, its association with diabetes mellitus, disease duration and concomitant diseases were assessed; histomorphological examination of biopsy specimens was performed. A drug based on sweet clover was included in the treatment regimen. Before and after treatment, necrobiosis lipoidica lesions were objectively examined, and trends in lipid-profile, carbohydrate-metabolism and coagulation-profile parameters were compared. The use of a drug based on sweet clover in combination with traditional treatment helped to reduce the diameter of the lesion, a change in lesion color to pale yellow or skin-colored, disappearance of inflammation of the peripheral rim, regression of subjective complaints, and favorable changes in carbohydrate metabolism, lipid metabolism and coagulation-profile parameters.

Key words: necrobiosis lipoidica, a drug based on sweet clover, cutaneous lesions, carbohydrate metabolism, lipid profile, coagulation profile.

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КЛІНІЧНІ ПРОЯВИ ЛІПОЇДНОГО НЕКРОБІОЗУ ТА НОВІ НАПРЯМКИ У ЛІКУВАННІ ЦІЄЇ ПАТОЛОГІЇ

Ліпоїдний некробіоз вважається одним із шкірних проявів цукрового діабету. Захворювання характеризується гранулематозним запаленням із патологічними ознаками колагенового некробіозу та запаленням дерми. Метою дослідження було обстеження пацієнтів з метою збору даних про епідеміологію ліпоїдного некробіозу в Азербайджані, візуальної оцінки змін зовнішнього вигляду уражень при ліпоїдному некробіозі та порівняння показників ліпідного профілю, вуглеводного обміну та коагуляційного профілю до та після запропонованого лікування. Було оцінено різні клінічні форми ліпоїдного некробіозу, його зв'язок із цукровим діабетом, тривалість захворювання та супутні захворювання; проведено гістоморфологічне дослідження біоптатів. До схеми лікування було включено препарат на основі буркуну лікарського. До та після лікування було об'єктивно досліджено вогнища ліпоїдного некробіозу та порівняно зміни показників ліпідного профілю, вуглеводного обміну та системи згортання крові. Застосування препарату на основі буркуну лікарського у поєднанні з традиційним лікуванням сприяло зменшенню діаметра вогнища ураження, зміні кольору вогнища ураження на блідо-жовтий або колір шкіри, зникненню запалення периферичних відділів, регресу суб'єктивних скарг та сприятливим змінам у вуглеводному обміні, ліпідному обміні та параметрах коагуляційного профілю.

Ключові слова: ліпоїдний некробіоз, препарат на основі буркуну лікарського, шкірні ураження, вуглеводний обмін, ліпідний профіль, коагуляційний профіль.

Profound metabolic disturbances and the development of various syndromes in diabetes mellitus (DM) lead to progressive systemic damage, which substantially increases the frequency and severity of abnormal cutaneous manifestations [3].

Diabetes-associated skin lesions are commonly divided into groups caused by metabolic, vascular, neurological and immune disturbances related to diabetic pathogenesis, as well as diseases of unclear pathogenesis. The frequency of disorders of unclear pathogenesis in patients with DM is approximately 2.5-20 %; these include diabetic dermopathy, diabetic skin infiltration, diabetic erythema, diabetic bullae, lipodystrophy, lipohypertrophy, pyoderma and necrobiosis lipoidica (NL). The nosology of NL is interpreted differently by different authors: some classify it among granulomatous conditions with connective-tissue degeneration or among dermatoses specific to DM. Other researchers consider NL to be a specific cutaneous lesion caused by diabetic angiopathy. NL is also regarded as a "latent state" of DM, when the disease may proceed almost asymptomatically. NL is most often associated with DM (in 0.3-1.2 % of patients), especially type 1 diabetes mellitus (T1DM), although the disease may also occur independently [1, 6, 14]. The reciprocal relationship between the frequency of NL development and DM is still being studied, and the etiology of the disease remains a matter of debate and requires further clarification [3]. Establishing a clear etiopathogenesis of this condition is complicated by the lack of randomized controlled trials, since NL may be regarded as an orphan disease [4].

NL is characterized by granulomatous inflammation with pathological signs of collagen necrobiosis and dermal inflammation. Hyperlipidemia and dyslipidemia, observed in most patients with NL, cause damage to the vascular wall and formation of a lipoprotein barrier around the peripheral capillary circulation, thereby impairing oxygen diffusion. These disorders trigger hypoxia, lead to vascular insufficiency, and contribute to the

development of macro- and microangiopathy with lipid deposition and thickening of blood-vessel walls [5, 7, 14]. As a dermatological disorder, NL is manifested predominantly on the lower legs as well-demarcated, telangiectatic, brownish-red plaques with atrophic yellowish centers and a tendency to ulceration [5, 8, 12]. Although in most patients the disease is relatively asymptomatic, in others it progresses to debilitating manifestations accompanied by pruritus, dysesthesia and pain [14].

The diagnosis of NL is established on the basis of the medical history (long disease course and concomitant pathology), the clinical presentation of cutaneous lesions, histopathological examination, and assessment of lipid and carbohydrate profiles and coagulation parameters [8, 13, 14].

Dermoscopic examination of NL lesions reveals diffuse, structureless yellowish areas with clearly visible vessels showing branching and serpentine morphology, sometimes accompanied by ulcers with yellowish crusts, brown reticular structures, and other findings [15].

Resistance to therapy, an unpleasant cosmetic appearance, painful ulcers and a prolonged course represent major challenges in treatment. First-line therapies include topical corticosteroids, calcineurin inhibitors (tacrolimus and pimecrolimus), phytotherapy, cyclosporine, fumaric-acid esters, biologic agents (adalimumab, etanercept and infliximab), immunosuppressants, Janus kinase (JAK) inhibitors, combination therapy and several other treatment options [4, 10, 11].

Given the increasing prevalence of diabetes, the risk of diabetes-related skin lesions is expected to rise. Therefore, discussion of the clinical manifestations and treatment methods of NL, aimed at improving awareness among health-care professionals and enabling early intervention and appropriate patient care, remains a relevant topic of investigation.

The purpose of the study was to examine patients in order to collect data on the epidemiology of necrobiosis lipoidica in Azerbaijan, to visually assess changes in the appearance of necrobiosis lipoidica lesions, and to compare lipid-profile, carbohydrate-metabolism and coagulation-profile parameters before and after the proposed treatment.

Materials and methods. The study was conducted from 2018 to 2023 at the Republican Dermatovenereology Center (Department of Dermatovenereology, Azerbaijan Medical University) and at the Baku Health Center clinic (Baku). A total of 36 patients with NL were examined (mean age 58.7±2.2 years). Various forms of NL, association with DM, disease duration and concomitant diseases were assessed; histomorphological examination of specimens was performed.

The drug Semelil, Pars Roos Pharmaceutical Co., Iran), was included in the treatment regimen. The medicinal product does not have an International Nonproprietary Name (INN), as it is a phytotherapeutic preparation. The drug has systemic and topical effects. Its beneficial effect in the treatment of pressure ulcers and diabetic foot ulcers, whose pathogenesis is similar to that of NL, has been confirmed in several studies [2]. The regimen was outpatient treatment for 2 months: one tablet twice (100 mg) daily and local application of a thin layer of the ointment form to the affected skin areas twice daily [8].

The drug is obtained from the plant Melilotus officinalis (yellow sweet clover), which is recommended for gout, non-healing wounds, opening of abscesses and other conditions. Semelil contains coumarin derivatives (hydroxycoumarin), flavonoids, 7-oleanene glucuronide, which exert anti-inflammatory, antioxidant and angiogenic effects, as well as selenium. Selenium also demonstrates antioxidant and anti-inflammatory properties. Preclinical and clinical studies have shown the safety of Semelil [2].

To assess treatment outcomes, patients were divided into three groups of 12 patients each (33.3 %). Group I received systemic Semelil (Angipars) monotherapy for 2 months. Group II received a combination of Semelil with conventional therapy, which included Detralex® oral suspension (Servier, France), one sachet daily; the proteolytic agents Rudaza® rectal suppositories (Cydonia Phytopharmaceuticals, Bosnia and Herzegovina), one suppository every 5 days, and Longidaza® rectal suppositories (NPO Petrovax Pharm), one suppository once daily at bedtime for 10 days; the hepatoprotector Hepacaps® capsules (RealCaps), one capsule twice daily; and Cardiomagnyl® tablets (AstraZeneca, Sweden), one tablet once daily after meals. Group III received conventional treatment only. Before and after treatment, NL lesions were objectively examined with respect to localization, number, diameter, color, inflammatory rim and subjective sensations. Trends in lipid-profile, carbohydrate-metabolism and coagulation-profile parameters were compared. Carbohydrate metabolism was assessed using standard biochemical tests: fasting blood analysis, oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c), glucose and insulin.

Glucose levels were measured using the Cobas c311 automated chemistry analyzer (Roche Diagnostics, Switzerland), whereas serum insulin concentrations were determined using the Cobas e411 electrochemiluminescence immunoassay analyzer (Roche Diagnostics, Switzerland). Quantitative determination of lipid-metabolism parameters, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C), was performed by colorimetric photometry using the Cobas c311 automated chemistry analyzer (Roche Diagnostics, Switzerland).

Coagulation parameters, including activated partial thromboplastin time (APTT), international normalized ratio (INR), prothrombin time (PT), prothrombin index (PTI), fibrinogen, and thrombin time (TT), were assessed using clotting methods with the Sysmex CA-600 automated coagulation analyzer (Sysmex Corporation, Japan).

Statistical analysis was performed using Statistica 16.0, the SPSS statistical package for Windows (StatSoft Inc., USA) and the StatTech program. Quantitative variables were presented as arithmetic mean (M) and standard deviation (±m). Quantitative variables with a distribution different from normal were compared using the Mann-Whitney U test. Categorical data were described as absolute values and percentages. Absolute values in multi-field contingency tables were compared using Pearson's chi-square test (chi2) and Fisher's exact two-sided test (F). Correlation dependence was assessed using Pearson's correlation coefficient (r). Differences between compared values were considered statistically significant at $p<0.050$. The study protocol complied with the Declaration of Helsinki of 1975, as revised in 2000. The protocol was approved by the Ethics Committee of Azerbaijan Medical University, as reflected in Protocol No.11 dated 29 December 2019.

Results of the study. Among the examined patients, common forms of NL were diagnosed in 24 patients (66.7 %): the classic form in 23 patients (63.9 %) and a granuloma-annulare-like form in 1 patient (2.8 %). Rare forms of NL were diagnosed in 12 patients (33.3 %). In our study, the classical localization of NL lesions was most often on the lower leg, in 30 patients (83.3 %); in descending order of frequency, lesions were also located in the ankle region in 7 patients (19.4 %), on the foot in 6 patients (16.7 %), on the forearm in 3 patients (8.3 %), on the hand in 2 patients (5.6 %), and on the upper limbs in 1 patient (2.8 %).

In the overall population, the mean duration of NL was 3.1±0.5 years (range: 2 months to 12 years). The duration of NL showed a weak positive correlation with age ($r = 0.295$).

Disturbances in carbohydrate metabolism and the close association between NL and DM are considered key factors in the etiopathogenesis of NL. In our study, NL was associated with DM in 27 patients (75.0 %), whereas 9 patients (25.0 %) had NL without concomitant diabetes mellitus ($p <0.001$).

A family history of DM was identified in 24 patients (66.7 %), and was absent in 12 patients (33.3 %) ($p>0.05$). The duration of DM according to age was characterized by a positive correlation ($r=0.42$). The durations of NL and DM showed a weak positive correlation ($r=0.3$).

Concomitant diseases were observed in 24 patients (66.7 %). According to ICD-10, concomitant diseases were distributed as follows: diseases of the circulatory system (I00-I99) in 15 patients (41.7 %), endocrine diseases (E00-E90) in 6 patients (16.7 %) ($p>0.05$).

Histomorphological examination of specimens from three patients revealed an epidermis with a compact stratum corneum and orthokeratosis. At the level of the papillary dermis, scattered predominantly perivascular lymphohistiocytic infiltrates were observed. In some areas, the infiltrate extended into the deep dermis and even subcutaneously into the adipose tissue. At the level of the reticular dermis, centrally located necrotic collagen fibers and circular granuloma-like infiltrates containing histiocytes with mucin deposits were observed; isolated multinucleated Langhans giant cells were also identified. The observed histological changes were characteristic of NL

In the classic form of NL, histology of the epidermis was represented by mild hyperkeratosis with slight desquamation. On the surface of the dermis and deeper layers, necrobiotic collagen was observed together with a considerable cellular infiltrate composed of epithelioid cells (histiocytes, granulomatous structures and isolated Pirogov-Langhans cells) .

The clinical picture of NL in typical cases was represented by one or more plaque-like lesions, the surface of which consisted of two zones: a central scleroderma-like zone and a slightly elevated peripheral zone.

According to morphology, NL lesions were round in 25 patients (69.4 %) and polycyclic in 11 patients (30.6 %) ($p=0.425$, $p>0.05$). The surface of the lesions had a soft consistency in 17 patients (47.2 %) and a dense consistency in 19 patients (52.8 %) ($p=0.303$, $p>0.05$).

Typical disease course in the overall population of patients with NL was observed in 30 patients (83.3 %); ulcerations were observed in 6 patients (16.7 %) ($p<0.001$). In the overall cohort, the mean number of NL lesions was 3.0±0.3 (range: 1-7). With respect to the number of lesions, the following pattern was observed: two lesions (lower leg and ankle, or lower leg and forearm) were most common, in 38.9 % of patients; three lesions were recorded in 19.4 %, four lesions in 11.1 %, five lesions in 13.9 %, and seven lesions in 5.5 % of patients.

Before treatment, the mean lesion diameter in the overall NL population was 3.5±0.3 cm; in Group I, 3.8±0.8 cm; in Group II, 3.3±0.9 cm; and in Group III, 3.0±0.5 cm ($p>0.05$).

After treatment, the mean lesion diameter in the overall NL population was 2.8±0.7 cm. In Group I, a moderate reduction in lesion size was observed, from 3.8±0.8 cm to 3.3±1.1 cm ($p>0.05$). In Group II, a significant reduction in lesion diameter was observed, from 3.8±0.8 cm to 2.2±0.5 cm ($p<0.010$). In Group III, lesion diameter decreased only slightly, from 3.0±0.5 cm to 2.9±0.4 cm ($p>0.05$). After treatment, a decrease in the intensity of erythema of the lesions and of the peripheral plaque rim was also observed in

the study groups. In Group I before treatment, brick-red lesions were observed in 5 patients (41.7 %), pinkish-red lesions in 1 patient (8.3 %) and yellowish lesions in 6 patients (50.0 %). After treatment in Group I, erythema intensity decreased, with lesion color shifting from brick-red to paler pink and, in some cases, yellowish-brown. The number of patients with brick-red lesions decreased from 5 to 1 (8.3 %); the number with pale-pink lesions increased from 1 to 4 (33.3 %); and the number with yellowish-brown lesions increased from 6 to 7 (58.3 %). Before and after treatment in Group I, no statistically significant differences were observed in the number of brick-red lesions ($p>0.05$, $p=0.060$), nor in the number of pale-pink and yellowish-brown lesions ($p=0.132$ and $p=0.683$, respectively).

After treatment in Group II, lesion color changed from bright erythematous or brick-red to pale yellow or skin-colored. Before treatment, the number of patients with brick-red lesions was 4 (33.3 %), the number with yellowish lesions was 7 (58.3 %), and 1 patient (8.3 %) had reddish-cyanotic lesions. After treatment in Group II, brick-red lesions disappeared; pale-yellow lesions became predominant in 9 patients (75.0 %); and reddish-cyanotic lesions changed to pinkish-red in 3 patients (25.0 %). Before and after treatment in Group II, statistically significant differences were observed in the number of brick-red lesions ($p<0.05$, $p=0.029$), whereas no statistically significant differences were observed in the number of yellow lesions ($p>0.050$, $p=0.387$) or pinkish-red lesions ($p=0.274$).

After treatment in Group III, the intensity of lesion color decreased only slightly and showed weak or moderate positive dynamics. Before treatment in this group, brick-red lesions were present in 4 patients (33.3 %); after treatment, in 2 patients (16.7 %). No statistically significant differences were observed before and after treatment in Group III in the number of patients with brick-red lesions ($p>0.05$, $p=0.346$). Pinkish-red lesions were present in 4 patients (33.3 %) before treatment and in 5 patients (41.7 %) after treatment. Yellowish lesions were present in 4 patients (33.3 %) before treatment and in 5 patients (41.7 %) after treatment. No statistically significant differences were observed before and after treatment in Group III in the number of patients with pinkish-red or yellowish lesions ($p>0.05$, $p=0.674$). Before treatment, the margins of the affected areas were irregular in 17 patients (47.2 %) and regular in 19 patients (52.8 %) ($p>0.05$). In Group I, the appearance of the plaque rim (well-defined margins) indicated an inflammatory process in 7 patients (58.3 %) and absence of inflammation (irregular margins) in 5 patients (41.7 %) ($p>0.05$).

In Group II, the plaque rim indicated the presence of inflammation in 6 patients (50.0 %) and the absence of inflammation in 6 patients (50.0 %). In Group III, signs of plaque-rim inflammation were present in 8 patients (66.7 %) and absent in 4 patients (33.3 %) ($p>0.05$).

After a 6-month treatment course, the intensity of the inflammatory peripheral plaque rim decreased in Group I. The number of patients with rim inflammation decreased to 4 (33.3 %), while the number of patients without rim inflammation increased to 8 (66.7 %) ($p>0.05$, $p=0.103$).

In Group II after treatment, the plaque rim showed almost complete disappearance of inflammation of the peripheral ridge in 9 patients (75.0 %), with residual inflammation present in 3 patients (25.5 %) ($p<0.05$, $p=0.015$).

In Group III, the inflammatory rim persisted in 7 of 8 patients (58.3 %), although its intensity decreased in some cases. The number of patients without inflammation of the peripheral ridge increased from 4 to 5 (41.7 %) ($p>0.05$, $p=0.674$).

In Group I before treatment, scaling of lesions was present in 8 patients (66.7 %). Subjective sensations included pain in 2 patients (16.7 %), mild pruritus in 4 patients (33.3 %), and mild burning and tingling in 1 patient (8.3 %). After treatment in this group, scaling was observed in 6 patients (50.0 %); in most patients subjective sensations decreased or disappeared. Pain persisted in 1 patient (8.3 %), mild pruritus in 3 patients (25.0 %), and mild burning and tingling disappeared in 2 patients (16.7 %). Overall, no marked regression of atrophic skin changes was observed in Group I before and after treatment ($p>0.05$). In Group II before treatment, scaling was observed in 4 patients (33.3 %), and subjective sensations - soreness, mild pruritus and tingling - were reported by 8 patients (66.7 %). After treatment, scaling was noted in 2 patients (16.7 %), while pain, mild pruritus and tingling disappeared ($p<0.001$), i.e., subjective complaints almost completely regressed. In Group III before treatment, scaling was observed in 4 patients (33.3 %) and after treatment in 3 patients (25.0 %). Pain was reported by 2 patients (16.7 %) before treatment and by 1 patient (8.3 %) after treatment. Mild pruritus was observed in 3 patients (25.0 %) both before and after treatment; tingling was absent. Before and after treatment in Group III, subjective sensations decreased moderately or remained at the same level ($p>0.05$). NL is interpreted as a dermatopathological sign of disturbances in carbohydrate metabolism of diabetic origin, even when neither clinical nor laboratory evidence of carbohydrate-metabolism impairment is detected (Table 1).

In Group I, glycated Hb values before treatment did not differ statistically from those after treatment ($pI=0.272$, $p>0.05$). In Groups II and III, no statistically significant differences in glycated Hb values before and after treatment were observed either ($pII=0.088$; $pIII=0.204$).

In Groups I and III, insulin levels before treatment did not differ statistically from those after treatment ($pI=0.083$; $pIII=0.470$; $p>0.05$). In Group II, a statistically significant difference in insulin levels before and after treatment was observed ($pII=0.032$, $p<0.05$).

Table 1

Carbohydrate-metabolism parameters before and after treatment (mean values)

Parameter	Overall mean	Group I	Group II	Group III	Between-group significance
Glycated Hb (%) – before treatment	7.6±0.3	7.7±1.9	7.5±1.7	7.7±1.2	
Glycated Hb (%) – after treatment	6.9±1.5	7.0±1.9	6.5±1.2	7.3±1.1	p>0.05
Glucose (mg/dL) – before treatment	146.2±7.5	141.4±44.6	150.4±60.3	146.9±27.2	
Glucose (mg/dL) – after treatment	132.7±39.8	127.4±43.7	132.0±49.7	138.6±24.6	p>0.05
Insulin (IU/mL) – before treatment	16.2±0.8	14.8±3.7	17.4±3.6	16.0±6.5	
Insulin (IU/mL) – after treatment	13.8±4.2	12.3±2.9	14.2±2.7	14.9±6.0	p>0.05

NL is usually accompanied by hyperlipidemia, hypercholesterolemia, increased plasma-protein levels and disturbances in the profile of higher fatty acids. Lipid-profile parameters before and after treatment are shown in Fig. 1.

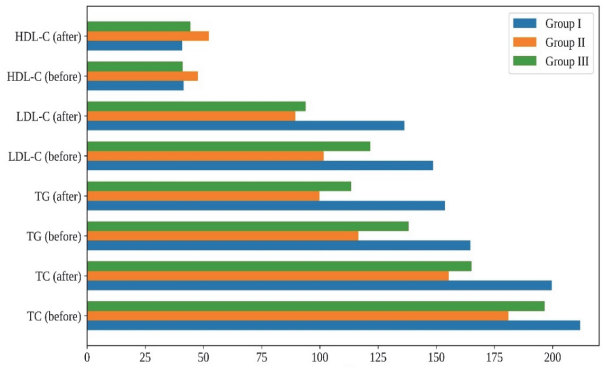

Fig. 1. Lipid-profile parameters in patients with NL before and after treatment (mean values, mg/dL).

As the study results show, in Group I patients receiving Semelil monotherapy, total cholesterol (TC) values before treatment differed statistically from TC values after treatment (pI=0.013). In Groups II and III, TC values before and after treatment showed no statistically significant differences (pII=0.083; pIII=0.175; p>0.050).

In Group I, TG values before treatment differed statistically from those after treatment (p=0.008, p<0.010). In Groups II and III, TG values before and after treatment did not show statistically significant differences (p=0.083 and p=0.133, respectively; p>0.05). LDL-C values in the study groups before treatment did not differ statistically from post-treatment values (pI=0.083, pII=0.094, pIII=0.356; p>0.05). In Group I, HDL-C values before treatment did not differ statistically from those after treatment (p=0.356, p>0.05), as was also the case in Groups II and III (pII=0.100; pIII=0.729).

Disturbances of metabolic processes (carbohydrate and lipid metabolism) observed in NL often lead to microcirculatory disorders. Coagulation-profile parameters before and after treatment are presented in Table 2.

Table 2

Coagulation-profile parameters before and after treatment (mean values)

Parameter	Overall mean	Group I	Group II	Group III	Between-group significance
APTT (s) – before treatment	25.1±1.1	25.2±8.4	24.6±7.1	25.5±3.2	
APTT (s) – after treatment	24.1±5.5	24.9±6.9	23.1±6.2	24.2±3.1	p>0.05
Significance	p>0.05	p>0.05	p>0.05	p>0.05	
INR – before treatment	1.03±0.03	1.0±0.11	1.0±0.12	1.07±0.27	
INR – after treatment	1.02±0.13	1.0±0.09	1.0±0.07	1.05±0.19	p>0.05
Significance	p>0.05	p>0.05	p>0.05	p>0.05	
PT (s) – before treatment	10.6±0.5	8.6±1.9	10.1±2.2	13.2±2.0	
PT (s) – after treatment	10.4±2.4	9.2±1.9	9.5±1.8	12.7±1.8	pI/pII>0.05; pI/pIII<0.001; pII/pIII<0.001
Significance	p>0.05	p>0.05	p>0.05	p>0.05	
PTI (%) – before treatment	106.9±2.5	104.2±13.4	105.1±17.3	111.3±14.3	
PTI (%) – after treatment	107.4±12.5	104.1±12.5	108.0±11.4	110.0±13.8	p>0.05
Significance	p>0.05	p>0.05	p>0.05	p>0.05	
Fibrinogen (mg/dL) – before treatment	269.8±9.1	254.3±60.5	284.7±55.9	270.5±47.6	
Fibrinogen (mg/dL) – after treatment	267.9±49.6	258.5±53.7	277.7±51.7	267.5±45.4	p>0.05
Significance	p>0.05	p>0.05	p>0.05	p>0.05	
TT (s) – before treatment	16.3±0.9	16.8±6.6	15.8±6.3	16.4±1.9	
TT (s) – after treatment	15.9±4.9	16.8±6.0	15.1±5.8	15.9±1.9	p>0.05
Significance	p>0.05	p>0.05	p>0.05	p>0.05	

In the study groups, APTT values before treatment did not differ statistically from APTT values after treatment (p>0.050): pI=0.840 in Group I, pII=0.488 in Group II, and pIII=0.298 in Group III.

In the study groups, INR values before treatment did not differ statistically from INR values after treatment (pI=0.583, pII=0.817, pIII=0.931; p>0.05). In the study groups, PT values before treatment did not differ statistically from PT values after treatment (pI=0.272, pII=0.436, pIII=0.436; p>0.05). PT values after treatment were within the normal range (5.6-15.2 s).

No statistically significant differences were observed between PTI values before and after treatment (pI=0.772, pII=0.908, pIII=0.623).

In the study groups, fibrinogen values before treatment did not differ statistically from those after treatment (pI=0.285, pII=0.525, pIII=0.773; p>0.05). After treatment, fibrinogen values were within the normal range.

In the study groups, TT values before treatment did not differ statistically from those after treatment (pI=1.000, pII=0.751, pIII=0.402; p>0.05). After treatment, TT values (15.9±4.9 s) were within the normal range.

Discussion. As in our study, the predominance of lesions localized on the lower extremities has also been consistently reported by other authors [12, 14].

The high prevalence of NL among patients with type 1 DM (T1DM) observed in our study is consistent with the findings of other investigators [5,14]. However, previous studies have also confirmed that NL may occur in the absence of DM [6]. In our study, endocrine disorders represented the second most common category of comorbidities, which is consistent with the findings reported by other authors [4]. The histopathological changes observed in our study were characteristic of NL and were consistent with previous descriptions reported in the literature, including detailed histological features and staining characteristics of the affected tissues [13, 15].

Conclusions

1. The most significant improvements in the condition of patients with NL were observed after the use of Semelil in combination with conventional treatment (Group II).

2. Combination therapy with Semelil contributed to a significant reduction in lesion diameter ($p<0.010$), a change in lesion color from bright erythematous or brick-red to pale yellow or skin-colored ($p<0.050$), almost complete disappearance of inflammation of the peripheral rim ($p<0.050$), and complete regression of subjective complaints ($p<0.001$).

3. Semelil contributed to favorable changes in carbohydrate-metabolism, lipid-metabolism and coagulation-profile parameters: HbA1c decreased 1.15-fold, glucose 1.14-fold and insulin 1.22-fold; TC decreased 1.17-fold, TG 1.17-fold and LDL-C 1.14-fold, while HDL-C increased 1.1-fold; APTT decreased 1.1-fold, INR did not change, PT decreased 1.1-fold, PTI increased 1.03-fold, fibrinogen decreased 1.03-fold, and TT decreased slightly.

Prospects for further research. The findings of the present study suggest that medicinal products based on Melilotus granulomatous skin disorders and other dermatoses associated with microangiopathy, chronic inflammation, and impaired tissue perfusion.

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Conflict of interest. The authors have no conflicts of interest to declare.

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