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Post-Covid-19 Diabetic Foot Ulcers: Assessing the Efficacy of Vac Therapy in Advanced Wound Care

Abdurakhmanov F. M.
Department of General and Pediatric Surgery No. 1, Tashkent Medical Academy

Annotation: Diabetic foot syndrome is the most common complication of diabetes mellitus, since both angiopathy and neuropa-thy are a component of this pathology. In patients who have had COVID-19, diabetic foot syndrome proceeds in a more aggressive form, characterized by an increase in necrobiotic processes, even if the patency of the vessels of the lower extremities is restored. In this work, we tried to show the main clinical and laboratory signs of the onset and course of diabetic foot syndrome in patients who have had COVID-19.

Keywords: diabetic foot syndrome, diabetes mellitu, COVID-19.

INTRODUCTION

Currently, the International Diabetes Federa-tion estimates that the prevalence of dia-betes mellitus worldwide is 8.3%. Accord-ing to forecasts, by 2030, the number of affected adults in the population will increase by 69%, and by the end of 2045 it will reach 700.2 million [1].

This problem is of particular relevance among pa-tients who have had COVID-19, since most of them are patients not only with diabetes mellitus, but also with diabetic foot syndrome [2]. It is known that the most common complication of diabetes mellitus is diabetic foot syndrome, which affects from 9.1 to 26.1 million people worldwide [3].

Currently, the frequency of complicated forms of diabetic foot syndrome is recorded in 12–18% of patients with type 2 diabetes mellitus, and in 0.6–2% with type 1 diabetes mellitus, and this value will increase with the aging of the population along with an increase in risk factors for the development of athero-sclerotic occlusion, such as smoking, obesity, etc. Literature data indicate that within three years, this group of patients has a relapse of the disease in 40% of cases, incomplete healing in 12.3%, and within 3 years, approximately 12% of patients with diabetic foot have undergone amputation of the lower extremi-ties [5].

The pathogenesis of diabetic foot syndrome in pa-tients with COVID-19 is characterized by heterogeneity. It is based on the following factors: hyperproduction of reactive oxygen species and free radical oxidation, ac-cumulation of metabolic end products, microangiopathy, and local immunity disorders [6].Relevant in the study of the pathophysiology of dia-betic foot syndrome among patients who have had COVID-19 is the determination of the rate of granulation tissue formation, neovasculogeny, and the participation of growth factors in tissue repair. One of the pathogenet-ic links of diabetic foot syndrome deserves special atten-tion - this is a violation of immune reactions against the background of hyperglycemia. The risk of infection spread increases and the structural and functional proper-ties of proteins are disrupted with the development of complications in the form of microangiopathy [7].

Such diverse metabolic disorders in diabetes mellitus as insulin resistance, accumulation of glycation of pro-teins and fats in the tissues of end products, lipotoxicity, glucose toxicity, in association with the activation of neurohumoral systems (sympathetic, renin-angiotensin-aldosterone) and systems of pro-inflammatory and profi-brotic cytokines, are the basis for the formation and ac-celerated progression of endothelial dysfunction, athero-sclerotic vascular lesions. diabetic cardiomyopathy [8]. Finally, the issues of drug organ-protective therapy in patients with a combination of diabetic foot syndrome with various macro- and microvascular complications of diabetes are also insufficiently studied. Many

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researchers report on the frequent combination of manifestations of diabetic foot with other macro- and microvascular com-plications of diabetes [9].

In this regard, the study of the nature of the relation-ship between the characteristics of the diabetic foot and common macro- and microvascular complications of diabetes mellitus in patients with COVID-19 is very rel-evant, since it will improve the quality of predicting the course of concomitant lesions and improve the tactics of therapeutic measures.The aim of the study was to substantiate the choice of surgical treatment programs for patients with diabetic ulcerative-necrotic lesions of the lower extremities after COVID-19 based on the clarification of information on the pathogenesis of the wound process (the most signifi-cant prognostic predictors of the wound process were identified) and the created mathematical model.

MATERIAL AND METHODS

We studied the results of treatment of 782 patients with diabetic foot syndrome who were on inpatient treatment in the multi-disciplinary clinic of the Tashkent Medical Academy in the period from 2021 to 2024. For bacteriological studies, one of the most important and reliable criteria for assessing the quality of treatment was used - the method of quantitative determination of pathogenic microorganisms in 1 g of tissue. With its help, it is possible to objectively assess the result of treatment, control the timing of wound closure, as well as assess the effectiveness of methods used for the local treatment of diabetic ulcers. The study of the dynamics of microbial contamina-tion of purulent wounds was carried out as follows. After surgical debridement of the wound, pieces of tissue from the bottom and edges of the wound were excised as ma-terial to determine the initial level of bacterial contami-nation. This procedure was repeated on days 3, 5 and 7 in cases where the wound was not completely closed. Excised areas weighing 1 g were placed in a mortar and pounded with saline at a rate of 1:10. To determine the number of each type of bacteria in the studied contents, the method of "sector cultures" was used. It is based on determining the number of microbial cells in 1 ml of material (colony-forming units/ml). A loop with a diameter of 2 mm was inoculated in certain sectors of the Petri dish on each medium. In sector A, the seed was inoculated with a bacteriological loop on a nu-trient medium (30-40 strokes). After that, the loop was burned and 4 line crops were made from sector A to I, similarly from I to II and from II to III, burning the loop after reseeding from each sector. Blood levels of VEGF, PDGF-BB, TGF-1β, INFγ, TNFα, IL-1β, IL-6, IL-10, Apolipoprotein A1, Apolipoprotein B, and lipoprotein (a) were determined using enzyme-linked immunosorbent test systems: VEGF-ELISA-BEST, gamma-interferon-ELISA-BEST, Interleukin 1 beta-ELISA-BEST, alpha-TNF-ELISA-BEST, Interleukin 6-ELISA-BEST, Interleukin 10-ELISA-BEST (Vector-Best JSC, Russia), ELISA Kit "Human PDGF-BB Quantikine ELISA Kit" (R&D Sys-tems; USA), "Human TGF1β" (Cloud-Clone Corp. , USA), Bender MedSystems (Austria), "Human Apo A1 ELISA Kit" (USA), "Human Apo in ELISA Kit" (USA), "Human Lp(a) ELISA Kit" (USA). As a control group, 30 people who could be classified as healthy individuals were studied.

In order to quantify these substances, the principle of two-site enzyme-linked immunosorbent assay (sandwich method) is used in these test systems. The test sample and a conjugate containing anti-specific antibodies la-beled with horseradish peroxidase were introduced into the wells of the plate with the immobilized specific anti-gen.

RESULTS AND DISCUSSION

Diabetes mellitus in the compensation stage was present in 76 patients (9.7 (1.0)%), sub-compensation in 240 patients (30.7 (1.7)%), decompensated diabetes mellitus was present in the ma-jority of patients (466 patients (59.6 (1.7)%).Ischemic form of diabetic foot was detected in 156 patients (19.9 (1.4)%), neuropathic in 290 patients (37.1 (1.7)%), and mixed form in 336 patients (43.0 (1.8)%).Most of the patients were in moderate condition – 368 people (47.1 (1.8)%), 266 patients were admitted in serious condition (29.0 (1.6)%), 148 patients were in relatively satisfactory condition (18.9 (1.4)%).A total of 162 patients (20.7 (1.5)%) of the total num-ber of patients were subjected to pathomorphological examination, who were divided into 4 groups depending on the type of treatment programs. In this sample of pa-tients, immediate closure of the wound defect was not possible due to the geometry and

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depth of the wound. Histological control of the course of the wound process in the first group of patients was studied in 42 (31.3 (2.1)%) patients, in the second group – in 46 (32.4 (2.4)%), in the third group – in 37 (14.5 (5.0)%) and in the fourth – in 37 (14.6 (5.0)%) patients with diabetic foot syndrome after COVID-19.

The study groups were representative. At the time of admission to the hospital on days 1-2 and 8 after treat-ment, all examined patients with diabetic foot underwent morphological examination of areas of the edges and center of wounds obtained after primary surgical de-bridement In patients of group 1, by the 8th day of VAC therapy, leukocyte infiltration of wound margins was significantly 1.27 times higher than with conventional treatment (group 4) (mean 85.4% vs. 62.3%; p=0.010). In the central parts of the bottom of wounds, neutrophils were registered 2.3 times less often in patients after VAC therapy (Me = 19.1%; [12.8:27.7]) than in pre-treatment patients (IU=43.8%, [37.2:52.9]), (p=0.033; Mann-Whitney U-test).

At the bottom of wounds, patients of Group 1 were 2.38 times more likely to register fibroblasts (Me = 15.5%; [7.3:21.8]) than in those before treatment (Me = 6.5%; [2,8:12,6]), (p=0,017; Mann-Whitney U-test). The r a t i o o f s p e c ific a r e a s o f t i s s u e e l e m e n t s o f LI:PKV:OAV:HMCR in the area of the wound margins was 47:14:13:26, and in the area of the bottom of the wound - 13:10:14:63, which confirms a decrease in the inflammatory process and the dominance of granulation tissue with newly formed HMCR vessels.The use of ultrasonic cavitation in Group 2 patients was accompanied by structural changes in wound tissues similar to Group 1, but signs of hydrooptical transforma-tion of the dermis were preserved and separate areas of necrotic detritus were found. A similar pattern of neu-trophil infiltration was characteristic in the margins and wound bottoms, where the dominant population was neutrophils (the number of neutrophils averaged 1.25-1.41 times higher than that before treatment (p<0.05). In the area of wound margins, the number of fibroblasts increased by 1.81 times (Me = 15.7%; [11.7:20.3]) than in patients before treatment (Me = 8.7%; [3,2:14,6]), p = 0.025, Mann-Whitney U-test). However, the formation of granulations occurred against the background of an increase in the specific area of OAB, which may be associated with increased perme-ability of GMCR vessels. This fact is confirmed by the smaller number of vessel microvessels with a larger av-erage diameter.Fibroblasts of the wound floor were observed 1.77 times less often than in patients before treatment (Me = 3.7%, MCR [2.2:4.8]), Me = 6.5%; [2,8:12,6]), p=0,013; Mann-Whitney U-test).In the group of patients who used laser and ozone therapy (group 3), there were still signs of leukocyte in-filtration of the wound edges and its decrease in the di-rection of the wound bottom. However, the degree of granulation tissue development was less pronounced than in Group 1 of patients with VAC therapy. In the area of the bottom of wounds, neutrophils were recorded 2.1 times less often in patients after laser and ozone therapy (Me = 20.8%; [11.4:30.3]) than in pre-treatment patients (IU=43.8%; [37,2:52,9]), p=0,028; Mann-Whitney U-test). Fibroblasts were detected more often in the area of wound margins - 3.81 times (Me = 33.2%; [17.7:49.5]) than before treatment (Me = 8.7%; [3,2:14,6], p = 0,019; Mann-Whitney U-test).The dominance of the lymphocyte population over macrophages at the wound margins and a similarly low number of lymphocytes and macrophages in the wound floor area were characteristic. Signs of epithelialization were the least pronounced in comparison with other types of physical impact (groups 1, 2) and were found in 14% of the drugs.Using traditional treatment, without the use of meth-ods of physical influence on the wound process (group 4), on the 8th day, an accumulation of hemosiderin, local signs of acute inflammation, an increase in the specific area of granulation tissue in the area of wound edges in 41% of specimens were revealed in wound tissue biop-sies. Leukocyte infiltrates in the dermis of the wound margins remained, but the number of neutrophils de-creased by 1.36 times (Me = 48.2%; [37.9:57.9] vs. Me=65.7%; [56.4:70.8] before treatment), plasma cells increased by 1.7 times (p=0.046), and the proportion of macrophages and lymphocytes increased (3.86 and 2.2 times, p<0.001, respectively). A comparative analysis of the number of neutrophils in the area of the wound floor showed a tendency to a slight increase of 1.15 times in patients of Group 4 (Me = 50.4%; [36.5:62.9]) compared with that in patients before treatment (IU = 43.8%, [37.2:52.9], p=0.077).Under bacteriological control, the results of bacterio-logical examination of wound discharge were positive in all patients in this sample. At the same time, in 75

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pa-tients (46.3 (2.9)%) the flora was represented by mono-culture. In 87 patients (53.7 (3.9)%), the microbial land-scape was represented by associations of microorgan-isms. When studying the flora represented by monocul-ture, it was revealed that most of the identified microor-ganisms were gram-positive microorganisms – 52 pa-tients (69.3 (5.3)%), among whom Staphylococcus au-reus was most often detected – 39 people (75.0 (6.0)%). In addition to Staphylococcus aureus, green streptococ-cus was also observed in 8 patients (15.4 (5.0)%) and epidermal staphylococcus in 5 patients (9.6 (4.1)%). Gram-negative monoculture was isolated in 23 patients (30.7 (5.3)%). In the number of gram-negative bacteria, Escherichia coli prevailed – 11 cases (47.8 (10.4)%) and Proteus – 12 cases (52.2 (10.4)%). The microbial land-scape of the mixed flora was mainly represented by asso-ciations of microorganisms: Staphylococcus aureus and Escherichia coli – 21 cases (24.1 (4.6)%), Staphylococ-cus aureus and Pseudomonas aeruginosa – 32 cases (36.8 (5.2)%), Proteus and Pseudomonas aeruginosa – 12 cases (13.8 (3.7)%), Staphylococcus aureus, Proteus and Pseudomonas aeruginosa – 22 cases (25.3 (4.7)%).Prior to treatment, the wounds in all cases were char-acterized by high bacterial contamination (107-8 CFU/1 g of tissue). A decrease in the level of bacterial contami-nation of wound tissues below the critical level (105 CFU/g) with laser therapy was achieved on average by the 3rd day compared to 7 days with traditional methods of local wound treatment ($p<0.001$); with ultrasound cavitation and VAC therapy – by 5 days. On the 7th day of treatment after a course of laser and ozone therapy (group 3), patients with microbial colonization were not encountered, the degree of bacterial contamination of wounds in patients of groups 1, 2, and 4 averaged 102–103 microbial cells per 1 g of tissue. When studying the dynamics of microbial contamination of the purulent focus during treatment, it was revealed that under the influence of physical methods of exposure (laser therapy, ultrasonic cavitation and VAC therapy), its microbial contamination decreases faster in comparison with tradi-tional methods of treatment ($p<0.001$).The observed bactericidal effect turned out to be more pronounced when using laser therapy.The development and scientific substantiation of modern approaches to the treatment of diabetic foot syn-drome are primarily associated with advances in the field of medicine. They provide for compliance with the prin-ciples of primary surgical debridement of the wound with its closure by one of the plastic methods that are performed during reconstructive surgery [10]. Diabetic foot syndrome in patients with COVID-19, in accordance with the concept adopted by the Diabetic Foot Consensus, is characterized by the presence of an ulcer defect or destruction of deep tissues, is associated with neurological disorders, a decrease in the main blood flow in the arterial basin of the lower extremities of vary-ing severity, with a violation of all phases of wound heal-ing in a more severe version of the course of the patho-logical process [11].The healing process consists of four successive and at the same time partially overlapping phases: 1) coagula-tion, 2) inflammation, 3) proliferation, and 4) remodeling with the formation of scar tissue [12].Modern treatment of diabetic foot syndrome in pa-tients with COVID-19 is carried out with the active use of endogenous growth factors as platelet-rich plasma, as well as the use of tissue engineering [13].Platelet growth factors include vasculoendothelial growth factor (VEGF), platelet growth factor (PDGF), transforming growth factor beta (TGF-β), epidermal growth factor (EGF), and insulin-like growth factor-1 (IGF-β) [14]. The problem of treating diabetic foot syndrome in patients with COVID-19 has received a new develop-ment in recent years due to progress in the creation of modern wound coverings, the use of ultrasonic cavitation and the use of negative pressure therapy [2]. The literature presents reports on the benefits of using modern approaches in the treatment of diabetic foot syn-drome [4].Despite the positive results achieved in solving this problem, the question of the choice of method and tim-ing of treatment remains open and requires further study. At the same time, the treatment of diabetic foot syn-drome is a significant not only medical, but also social problem. Recent studies of biochemical, molecular and gene processes in the process of wound healing provide scientifically grounded prerequisites for testing new methods of exposure to local peptide regulators in order to correct the wound process. Such regulators include growth factors used for wound healing [6].In the light of modern approaches to the treatment of patients with diabetes mellitus, it is especially important to study the state of the cytokine system both in the for-mation of diabetic foot syndrome in conditions of imbal-ance of metabolic disorders, and in various options for surgical treatment with the active use of physical meth-ods [8].Thus, the study of the role of growth factors and cy-tokines in the

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pathophysiological processes of repair of ulcerative defects in diabetic foot syndrome in patients with COVID-19 is relevant in the use of various treat-ment programs. However, the lack of evidence and expe-rience in applying these approaches in health care set-tings prompted the study.

CONCLUSION

In the study groups, moderate and severe diabetes mellitus prevailed in patients who had COVID-19. Diabetes mellitus in the compensa-tion stage was detected in 9.7% of patients, in the sub-compensation stage in 30.7%, and decompensated dia-betes mellitus in 59.6%. Ischemic diabetic foot was de-tected in 156 patients (19.9%), neuropathic in 290 pa-tients (37.1%), and mixed in 336 patients (43.0%). Ac-cording to the morphological study, it was found that after VAC therapy, granulation tissue reached its maxi-mum development in the area of the bottom of wounds (p=0.001), and in the margins of woundsit was found 1.75 times more often than before treatment (27.1%). Leukocyte infiltration of wound margins in Group 1 was 1.27 times higher than that of conventional treatment. Reparative processes using VAC therapy were the most effective compared to other methods of treating patients with diabetic foot syndrome after COVID-19. A decrease in the level of bacterial contamination of wound tissues below the critical level with laser therapy was achieved by an average of 3 days compared to 7 days with tradi-tional methods of local wound treatment; with ultrasonic cavitation and VAC therapy – by 5 days.

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