

QUALITY OF LIFE DYNAMICS IN PATIENTS WITH DIABETIC FOOT SYNDROME WITH COMBINED TREATMENT BY PHYSIOTHERAPY AND AUTOLOGOUS PLASMA*

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According to the International Diabetes Federation in Ukraine, the number of patients with diabetes mellitus (DM) between the ages of 20 and 79 years is about 7 % of the total population [1], with an increasing estimate of approximately 629 million patients worldwide by 2045 [2]. DM is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation [3]. DM related ulcers rank first among lower extremity ulcers, which in most cases result to sensitivity loss [4]. Diabetic neuro- and angiopathy are major factors causing diabetic foot ulcers (DFU) [5], resulting from ischemic reduction of oxygen and nutrients supply to the ulcerous site, thus hindering the optimal wound healing process in such patient cohorts. In oxygen and nutrient deprived states, epithelial cells in the ulcerous site fail to release vital healing factors such

as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) [6]. Some growth factors such as epidermal growth factor (EGF), granulocyte-colony stimulating factor (GCSF), nerve growth factor (NGF) and VEGF have been evaluated in patients with DFU [7, 8]. In recent studies a pool of growth factors from autologous plasma rich growth factors were analyzed [9, 10].

Health Related Quality of life (HRQoL) research has become an integral part of modern medicine. The World Health Organization (WHO) recommends the use of the following basic HRQoL criteria: physical, psychological, level of autonomy, social life and environment [11], thus the EuroQol-5D-5L (Ukrainian Version for Ukraine) questionnaire developed by the European Quality of Life Study (EuroQol Group), which was officially approved,

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was used to assess patients' quality of life in this study. This questionnaire demonstrates both physical and psycho-emotional indicators as well as permits quality of life assessments at different stages of the treatment process.

MATERIALS AND METHODS

The study included 61 outpatients with type 2 DM with Wagner grade II diabetic foot syndrome, who gave informed consent to participate in the study in accordance with the world medical association (WMA) Helsinki Declaration — Ethical Principles for Medical Research Involving Human Subjects, 2013.

The inclusion criteria for the groups were the presence of trophic ulcers with an area $\leq 5 \text{ cm}^2$ (1st group — $4.39 \pm 0.5 \text{ cm}^2$, 2nd group — $4.45 \pm 0.45 \text{ cm}^2$), HbA1c $\leq 7 \%$ (1st group — 6,9 %, 2nd — 6,8 %).

Depending on the regimen of the proposed therapy, patients were divided into two groups comparable in clinical status, age (1st group — $60,53 \pm 9,98$ years, 2nd — $62,23 \pm 8,64$ years), gender (1st group — males = 7, females = 23; 2nd — males = 8, females = 23).

Antihyperglycemic treatment in the both groups (n = 61) included combination therapy: long-acting insulin + metformin — 22.95 % (14 patients), sulfonylurea + metformin — 63.93 % (39 patients), dipeptidyl peptidase 4 inhibitor + metformin — 6.56 % (4 patients), sulfonylurea + sodium — glucose cotransporter 2 inhibitor — 3.28 % (2 patients), and monotherapy with metformin — 3.28 % (2 patients) [12].

Glucose-lowering therapy was supplemented with antibiotics (according to the results of microbiological examination of the discharge), while wound debridement (1st group), in the 2nd group (n = 31) standard therapy (ST) was supplemented by PDT and PRGFT procedures.

Initially patients were prescribed PDT using a laser machine «Lika-Surgeon M» (Photonica-Plus, Ukraine) with a wavelength of 660 nm in a continuous regiment every other day (8 procedures). Methylene blue 1 % aqueous solution as a photosensitizer was used.

After 2 weeks post wound surface cleaning and transitioning to the granulation phase, PRGFT was added to treatment process. The procedures were performed once a week, a total of 4 treatment course procedures.

The **aim** of this study is to evaluate the efficacy of combined photodynamic therapy (PDT) and plasma rich growth factors (PRGFT) therapy on the quality of life improvement in patients with diabetic foot syndrome.

In order to assess quality of life dynamics, all patients were interviewed using the EuroQol-5D-5L survey instrument, which consists of a EQ-5D descriptive system followed by the EQ visual analogue scale (EQ VAS) [13, 14]. In the descriptive section, health status is measured in five dimensions (5D); mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores from 1 to 5 were divided into two subgroups, where scores 1, 2, and 3 corresponded to the overall quality of life scores above average; and 4 and 5 were below average.

The S(AD)SAD (Size (Area, Depth), Sepsis, Arteriopathy, Denervation) classification was used to evaluate clinical status dynamics, which included 4 categories of 2 points, with a maximum of 30 points characterizing the most severe condition [15]. The evaluation criteria included: size (0 — skin intact; 2 — $< 1 \text{ cm}^2$; 4 — $1-3 \text{ cm}^2$; 6 — $> 3 \text{ cm}^2$) and depth of wound surface (0 — skin intact; 2 — superficial — involving skin and subcutaneous tissues but not reaching the tendon, periosteum or joint capsule; 4 — penetrating the tendon, periosteum or joint capsule; 6 — involving bone or joint spaces), presence of infectious process (0 — no infection; 2 — superficial infection, indicated by slough or exudate, but without clinical suspicion of cellulitis or osteomyelitis, also tinea pedis; 4 — cellulitis; 6 — osteomyelitis), degree of angiopathy (evaluated by the ankle-brachial index (ABI), where 1 point was for 0.7–0.9, and 2 points — for ≤ 0.6) and neuropathy (assessed using the Neurological Deficit Scale — NDS, where a score of 0 indicated no neuropathy, a score of 1 — moderate neuropathy, and a score of 2 — severe neuropathy).

The survey was performed in both groups at the beginning of treatment (EuroQol — 1 and S (AD) SAD — 1), after 2 weeks (EuroQol — 2 and S (AD) SAD — 2), after 6 weeks of treatment (EuroQol — 3 and S (AD) SAD — 3).

To evaluate trophic ulcer healing dynamics, a Lesion Meter app was used. Measurements were made at each patient visit. Data for each patient were automatically stored in separate folders.

Statistical analysis was performed with Windows 10 — Office Professional Plus software (Agreement ID: V0731528) with the use

of parametric and non-parametric methods of variation statistics. Shapiro–Wilk test was applied to test normality of parameters in the study. Two-sample Student's t-test was used to determine the significantly changed between groups with a probability mean of 0.05. Relative change method was used to compare ulcer healing dynamics in the two groups.

RESULTS AND THEIR DISCUSSION

Clinical status evaluation in the 1st group demonstrated the average total score at baseline to be 13.97 points according to S(AD) SAD classification, after 2 weeks — 13.20 (improvement by 5.51 %), after 6 weeks — 7.83 (improvement by 43.95 %) ($p > 0,05$) (Tab. 1).

Clinical status improvement in patients in the 1st group after PDT was achieved by a 19.89% inflammation reduction. Other S(AD) SAD categories had significant positive dynamics. The results obtained following PRGFT stimulation of the epithelium in the second stage showed a 30.95% decrease of the ulcer defect area, depth — by 5.00 %, improvement of angiopathy indices — by 28.93 % and neuropathy signs — 15.54 % ($p > 0,05$).

In the 2nd group, baseline average total score was 13.91 points, after 2 weeks — 12.29

(improvement by 11.65 %), after 6 weeks — 6.36 points (improvement by 54.27 %) ($p > 0,05$) (Tab. 2).

The same positive clinic dynamics in the 2nd group post PDT were achieved with more obvious improvement of up to 42.52 %, while positive dynamics were observed in other categories. PRGFT performed at the second stage as part of the combined treatment resulted in: 53.05 % decrease of defective ulcer area, depth — by 11.00 %, improvement indices in angiopathy category — by 43.29 %, in the neuropathic category — by 22.10 % ($p < 0,05$).

An estimation of quality of life dynamics in the 1st group showed significant improvement in «mobility» by 14.78 % after 2 weeks, after 6 weeks — by 27.58 %; in the «usual activities» category — by 2.09 % after 2 weeks, and after

Table 1

S(AD)SAD evaluation of ulcers healing dynamics in the 1st group

Group	Area of the wound surface	Depth of the wound surface	Infection process	Angiopathy	Neuropathy
At baseline	4,2	2,0	3,87	1,97	1,93
2 weeks	4,2	2,0	3,10	1,97	1,93
6 weeks	2,9*	1,9	0*	1,4	1,63

* statistically significant difference compared to the baseline ($p < 0.05$).

Table 2

S(AD)SAD evaluation of ulcers healing dynamics in the 2nd group

Group	Wound Surface Area	Wound Surface Depth	Infection process	Angiopathy	Neuropathy
At baseline	4,26	2,0	3,81	1,94	1,9
2 weeks	4,26	2,0	2,19*	1,94	1,9
6 weeks	2,0*	1,78*	0*	1,1*	1,48*

* statistically significant difference compared to the baseline ($p < 0.05$).

Table 3

EuroQol-5D-5L evaluation dynamics in the 1st group

1st group	At baseline	After 2 weeks	Δ (2 weeks and baseline)	After 6 weeks	Δ (6 and 2 weeks)
Morbidity	2,03	1,73	- 15	1,47*	- 28
Self-care	2,53	2,53	0	1,90*	- 25
Usual activities	1,43	1,4	-2	1,37	- 5
Pain / discomfort	3,03	2,73	- 10	2,27*	- 25
Anxiety/depression	3,9	3,9	0	3,23*	- 17
VAS	41,73	58,33*	40	62,37*	49

* statistically significant difference compared to the baseline ($p < 0.05$).

Table 4

EuroQol-5D-5L evaluation dynamics in the 2nd group

2nd group	At baseline	After 2 weeks	Δ (2 weeks and baseline)	After 6 weeks	Δ (6 and 2 weeks)
Morbidity	2,0	1,65*	- 18	1,13*	- 44
Self-care	2,42	2,23	- 8	1,74*	- 28
Usual activities	1,42	1,29	- 9	1,1*	- 23
Pain / discomfort	2,97	2,52	- 15	1,97*	- 34
Anxiety/depression	3,9	3,13*	- 20	1,23*	- 69
VAS	41	58,55*	43	71,55*	75

* statistically significant difference compared to the baseline ($p < 0.05$).

6 weeks — by 4.19 %; in «pain/discomfort» — by 9.9 % after 2 weeks, after 6 weeks — by 25.08 % ($p > 0,05$). In the «self-care» and «anxiety/depression» categories, significant improvement in the quality of life was achieved only after 6 weeks — by 24.9 % and 17.18 % ($p > 0,05$), respectively (Tab. 3).

In the 2nd group, quality of life dynamics after PDT demonstrated a 17.5 % improved average score in «mobility», 9.15 % in «usual activities» and by 15.15 % in the «pain/discomfort» categories. Following PRGFT, improvement was achieved by 43.5 % in the «physical activity» category, 22.54 % in the «household activity» and by 33.67 % in the «pain/discomfort» categories ($p < 0,05$) (Tab. 4).

Unlike patients in the 1st group, earlier positive quality of life dynamics in the 2nd group was obtained after PDT in the «anxiety/depression» and «self-care» categories by 19.74 % and 7.85 % respectively, with further improvement

after PRGFT by 68.46 %, and in the «self-care» after 6 weeks — by 28.09 % ($p > 0.05$).

Further quality of life evaluation with Visual Analog Scale VAS in the 1st group revealed a baseline total score of 41.73 points, after 2 weeks' — 58.33 score points and after 6 weeks — 62.37 score points, with appropriate improvement by 28.46 % and 33.09 % after standard treatment ($p < 0,05$). In the 2nd group, 29.97 % post PDT and 42.69 % post PRGFT improvements were obtained ($p < 0,05$).

Discussion. Non-healing trophic ulcers in patients with diabetes mellitus significantly impairs quality of life and inhibits both physical and psychological status. Using PDT as combined therapy for chronic ulcers in DM patients resulted in complete purification of the wound surfaces in shorter time periods compared to ST. This thus influenced all quality of life indicators according to EuroQol scale, including the category of «mobility» (2.72 % im-

provement), «self-care» (7.85 %), «usual activities» (7.06 %), «pain/discomfort» (5.25 %) and «anxiety/depression» category (9.74%) improvements ($p < 0,05$).

Based on contemporary data [9, 10], PRGFT was included in the combined treatment scheme post PDT-course to stimulate epithelialization of the wound defects in patients of the 2nd group. The effectiveness of the proposed algorithm was confirmed by the improvement of all categories of the EuroQol scale: «mobility» — by 18 %, «self-care» — by 9 %, «usual activities» — by 9 %, «pain/discomfort» 15 % and «anxiety/depression» categories by 20 % ($p < 0.05$).

Advantages of using PDT and PRGFT in sequential stages of wound healing reveals new therapeutic perspectives in regenerative medicine. This treatment scheme has obvious advantages compared to the traditional debridement. Both components have demonstrated properties for active stimulation of cell proliferation, differentiation and angiogenic potential. This approach permits healing time reduction, thus improving quality of life of DM patients.

As limitations, only local wound status dynamic effects on quality of life were evaluated, while other general conditions were not considered in the current study, aspects envisaged in future studies.

CONCLUSIONS

Photodynamic and autologous plasma rich growth factors combined therapy is preferable vis-a-vis standard care in the treatment and

improvement of quality of life in outpatients with diabetic foot syndrome.

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QUALITY OF LIFE DYNAMICS IN PATIENTS
WITH DIABETIC FOOT SYNDROME WITH COMBINED TREATMENT
BY PHYSIOTHERAPY AND AUTOLOGOUS PLASMA

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Introduction. Diabetic neuro- and angiopathy are major factors causing diabetic foot ulcers. Ischemia reduces oxygen and nutrients supply to wounds. In oxygen and nutrients deprived conditions, epithelial cells in wounds fail to sufficiently release important wound healing factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). In recent studies a pool of growth factors from autologous plasma rich growth factors were analyzed. The **aim** of the study is to evaluate the efficacy of combined photodynamic (PDT) and autologous plasma rich growth factor therapy (PRGFT) on quality of life improvements in patients with diabetic foot syndrome.

Materials and methods. 61 outpatients with type 2 diabetes mellitus and Wagner grade II diabetic foot syndrome were included in this study. Patients of the 1st group (n = 30) received standard therapy (ST), in the 2nd group (n = 31) ST was supplemented by PDT and PRGFT.

Results. Using PDT in combined therapeutic management of chronic ulcer in patients with DM resulted in complete purification of the wound surfaces during shorter time durations vis-a-vis standard therapy, thus influencing all quality of life indicators according to EuroQol scale, including the category of «mobility» (improvement by 2.72 %), «self-care» (by 7.85 %), «usual activities» (by 7.06 %), «pain/discomfort» (by 5.25 %) and «anxiety/depression» categories (by 19.74 %). PRGFT was included in the combined treatment scheme post PDT-course to stimulate epithelialization of wound defects in patients of the 2nd group. Efficacy of this combined algorithm was confirmed by overall EuroQol scale category improvements: «mobility» — by 18 %, «self-care» — by 9 %, «usual activities» — by 9 %, «pain/discomfort» 15 % and «anxiety/depression» categories by 20 %.

Conclusions. Combined photodynamic and autologous plasma rich growth factor therapy is preferable to standard therapy in the therapeutic management and improvement of quality of life in outpatients with diabetic foot syndrome.

Key words: Diabetes mellitus, diabetic foot, photodynamic therapy, autologous plasma.

ДИНАМІКА ЯКОСТІ ЖИТТЯ
У ХВОРИХ З СИНДРОМОМ ДІАБЕТИЧНОЇ СТОПИ
ПРИ КОМБІНОВАНОМУ ЛІКУВАННІ З ВИКОРИСТАННЯМ ФІЗІОТЕРАПІЇ
ТА АУТОЛОГІЧНОЇ ПЛАЗМИ

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Вступ. Діабетична нейропатія та ангіопатія – це основні патогенетичні фактори, що призводять до утворення трофічних виразок у хворих на цукровий діабет. Ішемія призводить до гіпоксії та недостатнього вивільнення факторів росту ендотелію судин (VEGF) та тромбоцитарного фактору (PDGF) епітеліальними клітинами. Згідно сучасних досліджень, для загоєння трофічних виразок актуальним є використання аутологічної плазми, збагаченої факторами росту.

Мета дослідження — оцінити ефективність комбінованої фотодинамічної терапії (ФДТ) та плазмотерапії, збагаченої факторами росту (PRGFT) для покращення якості життя пацієнтів із синдромом діабетичної стопи.

Матеріали і методи. У дослідження включено 61 пацієнт з цукровим діабетом 2 типу з синдромом діабетичної стопи II ступеня за Wagner. Пацієнти 1-ї групи (n = 30) отримували стандартну терапію (СТ), у 2-й групі (n = 31) СТ була доповнена ФДТ та PRGFT.

Результати. Використання ФДТ у комбінованому лікуванні хронічних виразок у хворих на ЦДД покращує очищення ранової поверхні у більш короткі терміни порівняно із СТ, що впливає на показники якості життя за шкалою EuroQol, категорію «фізична активність» поліпшило на 2,72 %, «самообслуговування» — на 7,85 %, «побутова активність» — на 7,06 %, «біль/дискомфорт» — на 5,25 % та категорії «тривожність/депресія» — на 19,74 %. PRGFT було включено в комбіновану схему лікування після ФДТ для стимулювання епітеліалізації ранового дефекту у пацієнтів 2-ї групи. Ефективність заданого алгоритму підтверджено покращенням показників категорій шкали EuroQol: «фізична активність» — на 18 %, «самообслуговування» — на 9 %, «побутова активність» — на 9 %, «біль/дискомфорт» на 15 % та «тривожність/депресія» на 20 %.

Висновки. Комбінована фотодинамічна терапія та плазмотерапія, збагачена факторами росту, є ефективнішою, у порівнянні з стандартною терапією, у лікуванні та покращенні якості життя хворих із синдромом діабетичної стопи.

Ключові слова: цукровий діабет, діабетична стопа, фотодинамічна терапія, аутологічна плазма.

**ДИНАМИКА КАЧЕСТВА ЖИЗНИ
У БОЛЬНЫХ С СИНДРОМОМ ДИАБЕТИЧЕСКОЙ СТОПЫ
ПРИ КОМБИНИРОВАННОМ ЛЕЧЕНИИ С ИСПОЛЬЗОВАНИЕМ ФИЗИОТЕРАПИИ
И АУТОЛОГИЧЕСКОЙ ПЛАЗМЫ**

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Введение. Диабетическая нейропатия и ангиопатия – это основные патогенетические факторы, которые приводят к образованию трофических язв у больных сахарным диабетом. Ишемия приводит к гипоксии и недостаточному высвобождению факторов роста эндотелия сосудов (VEGF) и тромбоцитарного фактора (PDGF) эпителиальными клетками. Согласно современным исследованиям, с целью заживления трофических язв, является актуальным использование аутологической плазмы, обогащенной факторами роста.

Цель исследования — оценить эффективность комбинированной фотодинамической терапии (ФДТ) и плазмотерапии, обогащенной факторами роста (PRGF) для улучшения качества жизни пациентов с синдромом диабетической стопы.

Материалы и методы. В исследование включено 61 пациент с сахарным диабетом 2 типа с синдромом диабетической стопы II степени по Wagner. Пациенты 1-й группы (n = 30) получали стандартную терапию (СТ), во 2-й группе (n = 31) СТ была дополнена ФДТ и PRGF.

Результаты. Применение ФДТ в комбинированном лечении хронических язв у больных СД улучшает очищение раневой поверхности в более короткие сроки, по сравнению с СТ, улучшает показатели качества жизни по шкале EuroQol, категорию «физическая активность» улучшило на 2,72 %, «самообслуживания» — на 7,85 %, «бытовая активность» — на 7,06 %, «боль/дискомфорт» — на 5,25 % и категории «тревожность/депрессия» — на 19,74 %. PRGF была включена в комбинированную схему лечения после ФДТ для стимуляции эпителиализации раневого дефекта у пациентов 2-й группы. Эффективность данного алгоритма была подтверждена улучшением показателей категорий шкалы EuroQol: «физическая активность» — на 18 %, «самообслуживания» — на 9 %, «бытовая активность» — на 9 %, «боль/дискомфорт» на 15% и «тревожность/депрессия» на 20 %.

Выводы. Комбинированная фотодинамическая терапия и плазмотерапия, обогащённая факторами роста является более эффективной, по сравнению со стандартной терапией, в лечении и улучшении качества жизни амбулаторных больных с синдромом диабетической стопы.

Ключевые слова: сахарный диабет, диабетическая стопа, фотодинамическая терапия, аутологическая плазма.