CASE REPORT

International Journal of Occupational Medicine and Environmental Health 2021;34(4):565–573
https://doi.org/10.13075/ijomeh.1896.01670

INNOVATIVE BIODEGRADABLE DIBUTYRYLCHITIN DRESSING FOR THE TREATMENT OF ULCERS OCCURRING DURING CHRONIC VENOUS INSUFFICIENCY IN PATIENTS WITH TYPE 2 DIABETES

EWA BIENIEK[1], KAROLINA SKOŁUCKA-SZARY[2], JAN BRZEZIŃSKI[1], SYLWESTER PIASKOWSKI[2], and ANDRZEJ LEWIŃSKI[1,3]

[1] Polish Mother's Memorial Hospital – Research Institute, Łódź, Poland
Department of Endocrinology and Metabolic Diseases
[2] Celther Polska Sp. z o.o., Konstantynów Łódzki, Poland
[3] Medical University of Lodz, Łódź, Poland
Department of Endocrinology and Metabolic Diseases

Abstract
The aim of this study was to assess the course of the healing process following the use of dibutyrylchitin (DBC) dressing, a fully degradable material used in the treatment of ulcers which occur during chronic venous insufficiency common in patients suffering from type 2 diabetes. These diseases have a significant impact on the patients' standard of living, including the potential employment, and on the declining attendance at the current workplace. The implementation of this innovative therapeutic solution may positively affect the above-mentioned difficulties. An analysis of the healing process, following the application of the DBC dressing, was performed. Once the dressing was positioned on the wound, the analysis indicated that it underwent a process of degradation facilitated by the enzymes occurring naturally in the wound. When fully degraded, a further layer was applied. This process was repeated until the wound was fully healed. The study group consisted of 4 patients previously diagnosed with type 2 diabetes. During the observation period, the ulcers in all 4 cases had healed. The examined wound dressings adhered well to the wound surface and degraded within it. No side effects or adverse effects of the applied innovative therapy were observed. An addition of the biodegradable DBC dressing to the standard therapy procedure of ulcers occurring during chronic venous insufficiency among patients with type 2 diabetes indicate safe and effective treatment, which may have a direct reflection in the patient's professional capacity enhancement. It resulted in the complete healing of all ulcers in each of the observed cases. Int J Occup Med Environ Health. 2021;34(4):565–73

Key words:
type 2 diabetes, chronic venous insufficiency, venous ulcers, biodegradable dressing, dibutyrylchitin, professional capacity

Funding: this grant was supported by the Polish Agency for Enterprise Development (grant No. POIG.01.04.00-10-020/10 entitled "Innovative biodegradable «living» dressing suitable for chronic wounds and ulcers," grant manager: Sylwester Piaskowski and Karolina Skołucka-Szary).
Conflict of interests: During the research period included in this study Dr. Ewa Bieniek was employed as Medical Consultant in Celther Polska Sp. z o.o. During the research period included in this study Dr. Sylwester Piaskowski was employed as Project Coordinator and President of Celther Polska. Dr. Karolina Skołucka-Szary was employed, and still is, as Project Coordinator at Celther Polska. Prof. Jan Brzeziński and Prof. Andrzej Lewiński declare no conflicts of interest.
Received: June 1, 2020. Accepted: November 17, 2020.
Corresponding author: Andrzej Lewiński, Polish Mother's Memorial Hospital – Research Institute, Department of Endocrinology and Metabolic Diseases, Rzgowska 281/289, 93-338 Łódź, Poland (e-mail: andrzej.lewinski@umed.lodz.pl).

INTRODUCTION

The treatment of ulcers occurring during chronic venous insufficiency is both a complex and multidirectional process which requires regular medical visits and repetitive changes of dressings. The therapeutic process is further complicated by the presence of other associated diseases, the risk of which increases with the age of patients. One of the most common diseases is type 2 diabetes affecting 25–30% of the elderly population, i.e., individuals aged ≥65 years [1]. According to the International Diabetes Federation forecast, 7.7% of the world's population (439 million) will suffer from diabetes by 2030. Both diseases, venous insufficiency and diabetes, are linked to common risk factors such as age, a sedentary lifestyle and obesity, which further increase the likelihood of their incidence [2]. Moreover, diabetes itself, especially long-term (i.e., lasting >10 years), alongside microangiopathic and neuropathic lesions which develop throughout the course of the disease, are all factors which promote ulcer formation [3]. According to available literature data, around 15–25% of diabetic patients will develop ulcers during their lifetime.

Ulcer formation leads to increased morbidity and mortality of patients with diabetes [4]. Chronic venous ulcers result in the decrease of the living standard, including the possible job search, as well as increase the absence rate at work. Based on the available literature data, it is estimated that 40–70% of all amputations of the lower limbs are related to diabetes, which often precludes permanent work. Around 85% of these amputations are preceded by the occurrence of ulcerations within the lower part of the leg [5]. This is because diabetes not only affects the formation of ulcers, but also considerably delays or impairs their healing [6]. As the disease progresses, changes in the rheological properties of blood, the development of endothelial dysfunction, micro- and macroangiopathy, neuropathy, and eventually disorders in lipid metabolism, are likely to occur which, when combined, accelerate the progression of atherosclerosis [7–13]. The outcome of ulcer treatment in patients with type 2 diabetes is affected by a variety of factors.

Hyperglycemia leads to non-enzymatic glycation of proteins including collagen (increased stiffness of blood vessels), fibrin (increased resistance to degradation), cellular plasma membranes (increased cell adhesion) and antithrombin (increased prothrombotic potential). Moreover, it adversely affects the activity and concentration of several cytokines and growth factors, clearly reflected in impaired vascular formation. In addition, it weakens the functioning of the host immune system, resulting in insufficient inflammation in the second stage of the ulcer healing process [14]. It weakens the immune system, the protective barrier of the skin, immunological response in the site where the tissue continuity became interrupted, the epidermis regeneration and the process of wound healing itself. Both the processes of specific and non-specific response to infectious agents are impaired. The disease depresses the functioning of neutrophils in terms of their phagocytosis and antimicrobial properties [15]. Literature data suggests significant reduction of the *Staphylococcus aureus*-killing ability of granulocytes in patients with uncontrolled diabetes [16]. Diabetes is known to be associated with disorders of the ulcer healing process, including impaired collagen cross-linking and matrix metalloproteinase function [17].

The treatment of venous ulcerations in patients with accompanying type 2 diabetes requires the adoption of a multidirectional approach, i.e., a coordinated action of all members of a specialized therapeutic team. Complex multidisciplinary care of the patient should include both casual treatment (compression therapy, physiotherapeutic treatment), local treatment (according to the Tissue, Infection, Moisture and Edge of wound [TIME] framework, and the use of modern active dressings), general treatment, as well as prevention, care and education. Currently, the new tested therapeutic solutions (active dressings)

will lead to the optimization of the wound healing process, thus shortening its duration, as well as the facilitation of professional activity return in a shorter time. The main goal of active dressings is to create an optimum moist environment which favorably promotes the wound healing process. The dibutyrylchitin (DBC) dressing meets the growing demands currently made on active dressing materials, and also improves the patient's living standard. This innovative dressing consists of a material which, in addition to its standard functions, is fully biodegradable, does not require replacement and creates a type of scaffolding for migratory tissue cells, which may positively affect the shortening of the patient's recovery time.

METHODS

The DBC dressing

The above analyzed dibutyrylchitin dressing (trade mark: DibuCell Active dressing) consists of 100% dibutyrylchitin (or chitin dibutyrate – DBC), an ester derivative of chitin. Chitin dibutyrate is a biocompatible compound, i.e., it does not manifest any cytotoxic, irritant or sensitizing effects, as confirmed by in vitro and in vivo studies. It is characterized by a unique, highly porous spatial structure (various pore sizes and depths, open porosity, and a network of intermittent microchannels) obtained by the leaching method [18]. Due to its innovative spatial structure, this dressing provides an optimum moist environment within the wound (by means of removing excessive excretion, on the one hand, and protecting the wound from excessive drying, on the other), appropriate gas exchange, optimum absorption properties and, most importantly, providing scaffolding for migrating cells being part of the granulation and epidermal growth processes. Moreover, the DBC dressing undergoes full degradation within the wound, mediated by enzymes naturally occurring within it. This results in considerable simplification of the method of use, since the dressing does not need to be removed from the affected site. Once the dressing has degraded, the only essential requirement is a further application of the said dressing.

The study group – diabetic patients from the clinical trial ULCERUS 1/2014

The healing process of ulcers occurring during chronic venous insufficiency in patients with type 2 diabetes was analyzed. The study group was composed of 4 patients, 3 female and 1 male.

These patients were selected from a larger group of patients participating in a prospective, multicentre, randomized, single-blinded clinical trial ULCERUS 1/2014. They constituted 100% of people with diabetes in the study group. The results of clinical trials have already been published [19]. The clinical trial ULCERUS 1/2014 was accepted by the Bioethics Committee (approval No. RNN/189/14/KE). The study protocol was conformed to the ethical guidelines of the 1975 Declaration of Helsinki. All patients participating in the clinical trial, prior to the start of the clinical trial, had provided informed consent which also concerned the clinical trial results publication.

Patients' age, date and cause of ulcer formation, together with information on diabetes duration, metabolic control, and the presence of accompanying diseases, are presented in Table 1.

The course of the study

The study was conducted in 4 independent centers, in the absence of inter-centre communication. The patients were treated according to the TIME framework strategy and in line with the current state of the art. The DBC dressing was applied on flat, shallow ulcers with no clinical signs of infection, following surgical and/or enzymatic debridement as the primary dressing. The Biatain Ag dressing (used as the secondary dressing without direct contact with the wound) was applied as the secondary layer on the hereby investigated dressing. The investigat-

Table 1. Characteristics of the study group of diabetic patients from the clinical trial ULCERUS 1/2014, involved in the study on the course of the healing process following the use of the dibutyrylchitin dressing

Variable	Participants (N = 4)			
	No. 1 (H004)*	No. 2 (F003)*	No. 3 (O007)*	No. 4 (J008)*
Sex	female	female	female	male
Age [years]	79	77	64	67
BMI	23	30	35	35
Diabetes duration [years]	13	10	2	1
HbA_{1c} <96.7 mmol/mol (11%)	yes	yes	yes	yes
Previous thrombosis	yes	no	yes	no
Other diseases in anamnesis	chronic venous insufficiency, hypertension, heart failure (NYHA I)	chronic venous insufficiency, hypertension, chronic heart failure, coronary heart disease, hyperthyroidism, discopathy	chronic venous insufficiency, hypertension, prostatic hypertrophy	chronic venous insufficiency
Births	1	2	n.a.	0
Nicotine addiction	no	no	no	no

BMI – body mass index; HbA_{1c} – glycated hemoglobin; NYHA – New York Heart Association classification.
n.a. – not applicable.
* Patient's ID.

ed dressing underwent spontaneous degradation within the wound. Where the structure of the dressing became disintegrated, a further layer of the dressing was applied, observing a maximum margin of 0.5 cm overlapping the previous dressing layer and the edges of the wound. This application scheme was repeated until the wound was healed completely. The Biatain Ag dressing was replaced regularly, at time intervals according to the manufacturer's recommendations. Once the dressings were positioned on the ulcerated limb, a multilayer banding system (JOBST Comprifore® 4-layer) was applied.

During the qualification process of the patients applying for inclusion to the study (based on physical and questionnaire examinations, the ankle-brachial pressure index value and the USG Doppler examinations of the lower limbs), all possible contraindications of the above-mentioned mode of treatment were excluded. On each subsequent visit, a 0.9% NaCl solution and Octenisept (Schülke) were used to cleanse the wound. All the patients were subjected to personal questionnaires and physical examinations. In the study, each patient attended follow up visits over 12 weeks (2 qualification visits, 9 visits during the active stage of the study – 1 visit/week, with the last 12th visit taking place 2 weeks after the ninth visit of the active stage of the study). The surface area of the ulcers was measured using a sterile film, by means of which the wound contours were imaged following its application to the wound. The full squares were then counted and used as a baseline to determine the magnitude of the change in the ulcer surface area.

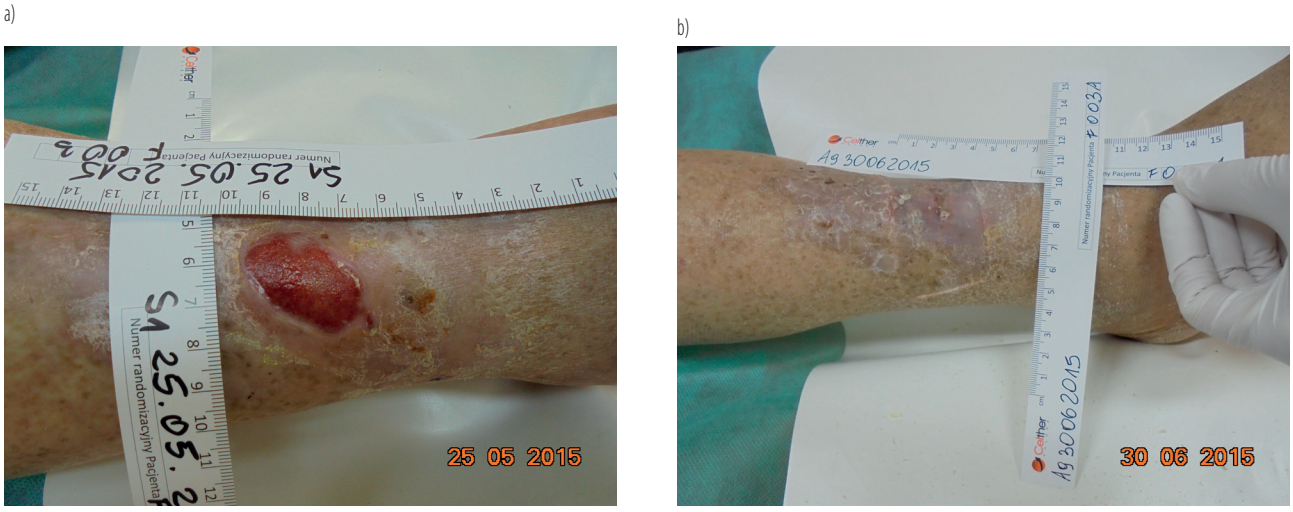

Figure 1. Patient No. 2 (F003): a) the initial qualification visit, b) after 8 weeks of treatment with the dibutyrylchitin dressing

The body mass index (BMI) was calculated according to the following formula:

$$BMI = \text{body weight [kg]/square of height [m]} \quad (1)$$

All the patients participating in the study had given their prior consent to the publication of the results.

RESULTS

In all 4 cases under analysis, the wounds healed completely during the study. This occurred after 8 weeks of treatment in 2 cases (Figure 1) and after 10 weeks of treatment in the remaining 2 patients (Table 2). No adverse effects were observed throughout the study. The DBC dressing adhered well to the wound surface and degraded within it (Figure 2).

DISCUSSION

The process involved in the treatment of ulcerations occurring during chronic venous insufficiency in patients with type 2 diabetes is lengthy, costly and laborious. It is generally associated with pain and requires considerable personal sacrifice by the patient, a close cooperation with the physician and a systematic replacement of wound dressings. Bearing in mind that the majority of patients are typically rather elderly, often with mobility and perhaps memory limitations, complex and complicated therapeutic schemes are inappropriate. In the case of individuals with foot ulcerations, the physical, psychological and social quality of life depreciates dramatically [20,21]. Consequently, the availability of less invasive therapies potentially reduces pain levels and improves the physician-patient relationship. The DBC dressing uniqueness rests on its ability to degrade within the wound. It is imperative that once the previous layer of dressing has degraded within the wound, all that is required is a further layer of the same dressing. This innovative and unique dressing feature originates from the properties of the material (chitin dibutyrate) of which it is made. Dibutyrylchitin is a chitin derivative obtained by the esterification of its hydroxyl groups with short chains of fatty acids [18].

The DBC dressing not only ensures the optimum healing environment for the ulcer (proper thermoregulation, appropriate humidity and proper gas exchange), but also absorbs the exudate and binds secretions. Moreover, it creates a barrier to deter dirt, irritant agents or infections. In addition, being left in the wound, it provides a type

Table 2. The surface area of ulcers, blood pressure readings and the plasma level of glycated hemoglobin (HbA_{1c}) for individual patients, obtained during the initial qualification visit and then followed by 8 and 10 weeks of treatment with dibutyrylchitin dressing

Variable	Participants (N = 4)			
	No. 1 (H004)*	No. 2 (F003)*	No. 3 (O007)*	No. 4 (J008)*
During the qualification visit				
surface area of the ulcer [cm^2]	14.125	6.25	18.125	9.375
blood pressure [mm Hg]	140/90	143/75	140/100	140/90
plasma level of HbA_{1c} [mmol/mol (%)]	31.1 (5.88)	85.8 (10.5)	31.1 (5.4)	42.1 (6.1)
After 8 weeks of treatment				
surface area of the ulcer [cm^2]	0.25	0	4.75	0
blood pressure [mm Hg]	150/75	130/70	147/102	130/80
plasma level of HbA_{1c} [mmol/mol (%)]	42.1 (6.11)	96.7 (11.6)	20.2 (4.7)	42.1 (6.2)
After 10 weeks of treatment				
surface area of the ulcer [cm^2]	0	0	0	0
blood pressure [mm Hg]	125/60	128/68	145/95	120/90

* Patient's ID.

of scaffolding or framework for newly incoming cells of the connective tissue. The latter considerably accelerates and facilitates the healing process with a positive effect on the granulation and epithelialisation process. It does not cause any sensitization. The degradation of the DBC dressing is mediated by enzymes naturally occurring within the wound. Due to the fact that the dressing undergoes a spontaneous degradation within the wound, any discomfort and traumatisation of newly formed tissues related to dressing replacement are alleviated.

The ease associated with the use of the dressing (during the study, the DBC dressing was added to the wound once a week) results in the simplification of the therapeutic regime, thanks to which the professional work during the therapy is possible. This could positively translate into enhanced patient-physician relationships. In addition, the previously mentioned frequency of application seems to be the ideal therapeutic approach especially in the case of elderly patients who are often looked after by third parties.

The effect of application of the DBC dressing (in combination with standard treatments), in terms of ulcer closure, was clearly visible as early as 8 weeks after the start of treatment (in the case of 2 patients – No. 2 [F003] and No. 4 [J008]) (Table 2). At this point in time, the surface area of the 2 remaining ulcers was reduced by 98% (patient No. 1 [H004]) and 74% (patient No. 3 [O007]). After 10 weeks of the same treatment, ulcer closure also occurred in these 2 patients (patient No. 1 [H004] and patient No. 3 [O007]). It is worth emphasizing that 1 of these 2 patients in whom the ulcers healed after 8 weeks was found to have very poorly controlled diabetes. This was indicated by the plasma level of glycated hemoglobin (HbA1c) reaching 85.8 mmol/mol (10.5%) at the beginning of the study, which then increased to 96.7 mmol/mol (11.6%) by the end of the study, corresponding to the mean glycemic values of >13.4 and 14.9 mmol/l (240 and 269 mg/dl), respectively [1]. The rapid closure of the ulcer in this case may indicate high therapeutic and welfare potential resulting from the addition of the tested dressing to the standard therapy.

It is also worth stressing that, except for diabetes mellitus and chronic venous insufficiency, 3 of the 4 study group participants also suffered from obesity, known to cause a series of health problems and to impair mobility, further hindering the healing process. This, alongside the suboptimal blood pressure values obtained at the beginning of the study (Table 2), indicates the coexistence of many pathologies for which the treatment was unsatisfactory. This may have been a direct consequence of aversion or the lack of ability to cooperate, or even failure to comply with the therapeutic recommendations for these patients. Indeed, 3 out of 4 cases were elderly people. In this context, the use of this new innovative dressing that does not require regular replacements, with a simplified application scheme, seems to be crucial to achieve the desired therapeutic effect.

The closure of ulcers occurring during chronic venous insufficiency in patients with type 2 diabetes is not only a localized effect. It affects the functioning of the whole person, the entire body and the course of the diabetes itself. Once the lesion is healed, the control of diabetes should improve. One direct consequence of this is that the prognosis of these patients should improve whilst their morbidity and mortality should decrease. Apart from measurable somatic effects, the improved general functioning of these patients also has a great impact. It leads to an elimination of the factor/s responsible for their social disengagement and inequality resulting, among others, from the shame related to the presence of ulcers, often associated with an unpleasant odor. Eliminating the social isolation for these patients and restoring social functioning could positively benefit and affect their well-being, spirit and mood, and the healing process itself. Moreover, if it is associated with a simplified therapeutic pattern of application without the need to interfere with the wound, or to remove and replace used dressings, it offers an added, and even key, value. The best therapy, if rejected by the patient, will not provide the desired, expected outcome for either the doctor or the patient.

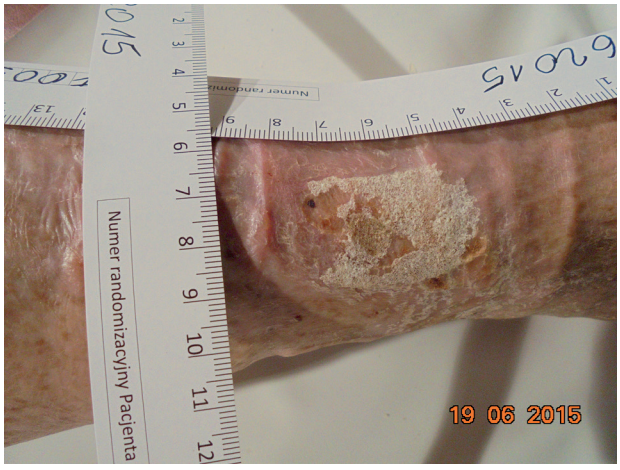

Figure 2. Degradation of the dibutyrylchitin dressing in the wound environment (patient No. 2 [F003])

CONCLUSIONS

Many pathological processes which contribute to ulcer formation and decelerate the healing process occur during the course of diabetes. This is associated with the duration of the disease, metabolic control, the presence of endothelial dysfunction, neuropathy or ischemia caused by accelerated atherosclerosis, as well as micro- and macroangiopathy [3]. The coincidence of diabetes and chronic venous insufficiency, the 2 diseases affecting the quality of the skin, both of which, although independently by means of distinct mechanisms, lead to the development of ulcers, implies major therapeutic problems.

Adding the DBC dressing to standard therapy resulted in good therapeutic outcomes in this group of patients. The use of the innovative dressing that is degraded within the wound and that does not require regular replacements considerably simplified the treatment regime, which is of utmost importance in the population of elderly and sick people. This, indeed, is associated with a reduced number of visits at physicians, and has a direct impact on improving the physician-patient cooperation, as well as improves the patient's professional capacity. In addition to this, the degradation of the DBC dressing eliminates the traumatisation of newly formed tissues and reduces the dis-

comfort associated with the therapy. Due to the small size of the group, this method, certainly, cannot be clearly indicated as dedicated to patients with ulceration and diabetes. However, due to its high safety and good efficacy, this innovative method seems to be applicable to this type of patients, but it requires constant monitoring by a specialist.

REFERENCES

1. Araszkiewicz A, Bandurska-Stankiewicz E, Budzyński A, Cypryk K, Czech A, Czupryniak L, et al. 2019 Guidelines on the management of diabetic patients. A position of Diabetes. Clin Diabetol. 2019;8(1):1–95, https://doi.org/10.5603/DK.2019.0001.
2. Jawień A, Szewczyk M, Kaszuba A, Gaciong Z, Krasiński Z, Wroński J, et al. [Guidelines of the Group of Experts on the healing of venous leg ulcers]. Leczenie Ran. 2011;8:59–80. Polish.
3. Hingorani A, LaMuraglia GM, Henke P, Meissner MH, Loretz L, Zinszer KM, et al. The management of diabetic foot: a clinical practice guideline by the Society for Vascular Surgery in collaboration with the American Podiatric Medical Association and the Society for Vascular Medicine. J Vasc Surg. 2016;63:3–21, https://doi.org/10.1016/j.jvs.2015.10.003.
4. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293:217–28, https://doi.org/10.1001/jama.293.2.217.
5. Apelqvist J, Bakker K, van Houtum WH, Nabuurs-Franssen MH, Schaper NC. International consensus and practical guidelines on the management and the prevention of the diabetic foot. International Working Group on the Diabetic Foot. Diabetes Metab Res Rev. 2000;16:84–92, https://doi.org/10.1002/1520-7560(200009/10)16:1+<::aid-dmrr113>3.0.co;2-s.
6. Potempa M, Jonczyk P, Janerka M, Kucharzewski M, Krawczyk-Krupka A. Rany przewlekłe – epidemiologia i czynniki wpływające na proces gojenia. Leczenie Ran. 2014;11:43–50, https://doi.org/10.15374/LR2014007. Polish.
7. Papanus N, Ziegler D. Prediabetic neuropathy: does it exist? Curr Diabetes Rep. 2012;12:376–82, https://doi.org/10.1007/s11892-012-0278-3.
8. Sytze Van Dam P, Cotter MA, Bravenboer B, Cameron NE. Pathogenesis of diabetic neuropathy: focus on neurovascular mechanisms. Eur J Pharmacol. 2013;5:180–6, https://doi.org/10.1016/j.ejphar.2013.07.017.
9. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837–53, https://doi.org/10.1016/S0140-6736(98)07019-6.
10. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854–65, https://doi.org/10.1016/S0140-6736(98)07037-8.
11. Holman RR, Paul SK, Bethel MA, Neil AW, Matthews DR. Longterm follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008;359:1565–76, https://doi.org/10.1056/NEJMoa0806359.
12. Holman RR, Paul SK, Bethel MA, Mathews DR, Neil AW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–89, https://doi.org/10.1056/NEJMoa0806470.
13. Gaede P, Lund Andersen H, Parving HH, Pedersen O. Effect of multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580–91, https://doi.org/10.1056/NEJMoa0706245.
14. Guo S, Dipietro LA. Factors affecting wound healing. J Dent Res. 2010;89:219–29, https://doi.org/10.1177/0022034509359125.
15. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol. 1999;26:259–65, https://doi.org/10.1111/j.1574-695X.1999.tb01397.x.
16. Marhoffer W, Siein M, Maeser E, Federlin K. Impairment of polymorphonuclear leukocyte function and metabolic control of diabetes. Diabetes Care. 1992;15:256–60, https://doi.org/10.2337/diacare.15.2.256.

17. Lobmann R, Ambrosch A, Schultz G, Naldmann K, Schiweck S, Lehnert H. Expression of matrix metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia. 2002;45:1011–6, https://doi.org/10.1007/s00125-002-0868-8.
18. Skołucka-Szary K, Ramięga A, Piaskowska W, Janicki B, Grala M, Rieske P, et al. Synthesis and physicochemical characterization of chitin dihexanoate – a new biocompatible chitin derivative – in comparison to chitin dibutyrate. Mater Sci Eng C Mater Biol Appl. 2016;60:489–502, https://doi.org/10.1016/j.msec.2015.11.078.
19. Bieniek E, Skołucka-Szary K, Lewiński A, Piaskowski S. Leg ulcer treatment using an innovative biodegradable dressing not requiring replacements. Clinics Surg. 2018;3:1–6.
20. Vileikyte L. Diabetic foot ulcers: a quality of life issue. Diabet Metab Res Rev. 2001;17:246–9, https://doi.org/10.1002/dmrr.216.
21. Meijer JW, Trip J, Jaegers SM, Links TP, Smits AJ, Groothoff JW, et al. Quality of life in patients with diabetic foot ulcers. Disabil Rehabil. 2001;23(336):40, https://doi.org/10.1080/09638280010005585.