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ABSTRACT



Diabetic foot is a severe complication of diabetes that occurs as a result of poor glycemic control, being associated with significant morbidity and mortality. Mortality associated with this disease is estimated at 5% in the first 12 months, and about 42% in the next 5 years. On average, it affects about 15% of people with diabetes during their lifetime, including as possible manifestations neuropathy, peripheral vascular disease, and subsequent ulceration which, if treated incorrectly, can lead to amputation.

This paper presents a retrospective and descriptive study of patients diagnosed and treated for diabetic foot ulcers in the Proctoven Clinic. The study includes a group of 50 cases diagnosed with diabetic foot over a period of 5 years, from 01.01.2017 to 31.12.2021. In this study, the effectiveness of the modern treatment methods most frequently used in the surgical treatment of the diabetic foot is analyzed based on several parameters.

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Introduction

Diabetic foot is a frequent and very severe complication due to its deforming nature, having an incidence of 3-4% among patients already diagnosed with diabetes. In addition to the poor insulin-related mechanisms, environmental factors such as obesity, sedentary lifestyle or unhealthy diet, as well as genetic factors are involved in altering glucose homeostasis [1]. A strategy that includes prevention, patient and health care education methods, multidisciplinary treatments of the diabetic foot, and close monitoring can reduce the amputation rate by 49-85% [2-4].

At the same time, diabetic foot is one of the most expensive complications of diabetes. The value of medical services is enormous, with the overall cost estimated at around \$ 1.3 trillion in 2015. The latest studies in the UK estimated an annual cost of over \$ 1.3 billion for diabetic foot management alone, which is about 1% of the budget of the National Health Service [5].

Neuropathy and ischemia are the two main pathogens of diabetic foot, which together lead to ulceration and neuro-arthropathy Charcot. In association with infection, the mortality of the diabetic population increases, having both a clinical and economic impact. Ischemia in the form of peripheral arterial disease is an important contributor to the diabetic foot, mainly affecting the lower limb, distal to the knee joint. The risk of developing a diabetic foot ulcer is between 19% and 34%, with recurrence being common after a healed episode. Approximately 40% of patients experience a recurrence of a diabetic ulcer within one year of healing, about 60% within 3 years, and 65% within 5 years [6].

Shortly after diabetic foot ulcers were described in the 19th century, the most common method of treatment was prolonged bed rest. Dr. Frederick Treves (1853-1923) revolutionized the management of diabetic ulcers by establishing three important principles in their treatment, which continue to be the basis of modern care. This

includes debridement, lowering pressure on the lesion, and educating the patient about the peculiarities of the diabetic foot. Added to these essential principles today are local wound care with surgical debridement, dressings that promote a moist wound environment, vascular assessment, treatment of active infection and glycemic control. In addition to these principles, multidisciplinary diabetic foot care is now becoming a standard of therapy [7,8].

Historically, wound dressings were primarily considered to play only a passive, protective role in the healing process. Modern surgical therapy for the diabetic foot was revolutionized by the discovery of observations that wet dressings can help wounds heal more quickly. In addition, a humid environment in the wound is also an important factor in inducing the proliferation and migration of fibroblasts and keratinocytes, as well as in improving the synthesis of collagen, which leads to a reduction in scar formation [9].

This work represents an analysis of modern methods currently used in the treatment of patients with diabetic foot and their impact on the quality of life of patients diagnosed with this disease. The study also reviews the specialized literature presenting the results obtained, related to the long practice of other medical centers and international literature.

The purpose of this paper is therefore to present the results obtained through different modern treatment methods - vacuum therapy and hydro-colloidal-absorbent dressings - and the correlations with risk factors in the patients of the study group, composed of patients from the Proctoven Clinic in Sibiu.

Materials and Methods

This study is an observational, longitudinal (cohort) retrospective study on patients admitted to the Proctoven Clinic in Sibiu, diagnosed with diabetes. The study includes a general group of 50 patients (carried out over a period of 5 years, from 01.01.2017 to 31.12.2021) treated using modern surgical methods (Hydrocolloid Dressings and Vacuum Therapy). The criteria for including patients in the study were represented by the Wagner Classification (Table 1) [10]. Thus, patients with grade I and II ulcers were included in the study, and patients with III-V grade ulcers were excluded, benefiting from classic surgical treatment.

Table 1. Wagner's classification of diabetic foot ulcers

Grade - 0	Skin intact but bony deformities lead to "foot at risk"
Grade - I	Superficial ulcer
Grade - II	Deeper, full thickness extension
Grade - III	Deep abscess formation or osteomyelitis
Grade - IV	Partial Gangrene of forefoot
Grade - V	Extensive Gangrene

Also, the patients involved in the study had as main criterion for inclusion the presence of lesions in the diabetic foot (ischemia, ulceration, gangrene, neuropathy, callus, arteriopathy). All patients between the ages of 18 and 90, both male and female, were included in the study. In terms of pathology, all patients had type I or type II diabetes with a diabetic foot complication. Patients under the age of 18 and over 90, patients in whom the data collected were incomplete and those without diabetic foot lesions were excluded from the study. Informed consent was obtained for all patients included in the study, after a reasonable disclosure [11].

For statistical analysis, Microsoft Excel Office 365 software was used for statistical calculation. The differences were considered significant if $p < 0.05$. Data collection and integration was done from sources that were extracted from the database of Proctoven Sibiu Clinic. Based on the data collected, the analysis and comparison of the cases that were represented in the form of tables and figures. These results were correlated with current data from the international literature related to complications of diabetes in the form of diabetic foot.

Among the parameters followed in the evaluation of patients belonging to the group are: age, demographic data (sex, environment of origin), type of diabetes, uni or bilateral impairment, comorbidities and risk factors associated with the group.

Results

This study was conducted over a period of 5 years, between 2017 and 2021, which included a number of 50 patients treated at the Proctoven Clinic. We excluded a patient due to death during the study, death due to heart disease, unrelated to our study. The study targets patients diagnosed with diabetes, that is patients who have associated complications in the area of diabetic foot. All patients benefited from modern surgical treatment methods (hydrocolloid dressings and vacuum therapy). For the patients admitted during Covid-19 pandemic, a strict adherence to specific measures to prevent dissemination of Sars-Cov-2 infection in hospital was adopted, included but not necessarily limited to patient testing at admission of when respiratory signs were suspicious for Covid-19 pneumonia, and wearing complete protective personal equipment, including FFP₂ masks [12].

Regarding the general data of the patients included in the study group (Table 2), their distribution by age groups showed a predominance of the number of cases in the age group 51-70 years, with 33 cases representing 66% of the total group. This distribution was followed by the 71 - 90 years age group, represented by 14 patients. The fewest cases in the current study were recorded in younger patients, consisting of 3 patients in the total analyzed group ($p=0.0490$).

Table 2. General data of the patients included in the study group.

Parameter		Total number / Percentage (%)
Age groups	30 -50	3 (6%)
	51- 70	33 (66%)
	71- 90	14 (28%)
Gender	Male	35 (70%)
	Female	15 (30%)
Type of diabetes	Type I	9 (18%)
	Type II	41 (82%)
Type of foot damage	Unilateral	43 (86%)
	Bilateral	7 (14%)
Environment origin	Rural	12 (24%)
	Urban	38 (76%)

The analysis of the study group according to sex, showed the predominance of diabetic foot in males representing 70% of the total group (p=0.0243). Regarding the type of diabetes, a significant number of patients presented type II diabetes as opposed to type I, where only 9 patients were registered (p=0.0441). Following the analysis of the data, a predominantly unilateral impairment was observed in patients with diabetic foot with 43 cases, representing 86% of the total group (p=0.0403). The distribution of patients according to the environment of origin showed a higher incidence among patients in urban areas, which can be explained by a better accessibility to specialized medical services.

In our study, among the modern modalities of surgical therapy, hydro-colloidal dressings and vacuum therapy were analyzed in patients treated in the Proctoven Clinic, diagnosed with diabetic foot.

Due to the distinct characteristics of the different types of lesions and each stage of wound healing, there is no single dressing that can be applied effectively in all situations. A careful policy regarding patient safety and reporting the possible adverse events related to therapy was followed [13]. The types of dressings used in our clinic were hydrocolloid dressing and vacuum therapy.

The hydrocolloid dressing contains hydrogel combined with a type of synthetic rubber, being a very good absorbent and also achieves a hydration of the lesions. It promotes healing by autolysis and promotes the formation of granulation tissue (Figure 1, a-c). This dressing does not cause pain at the time of change, has a hydrophobic outer layer and can be used in the treatment of deep exudative wounds [14-16].

The application of hydrocolloid dressings to over-infected wounds has been questioned due to the possible hypoxic and excessively moist environment that could

potentiate autolysis of necrotic tissue and therefore increase the risk of wound infection. These dressings are usually applied to granular and epithelial wounds and can therefore also be used for necrotic wounds to facilitate wound debridement. On average, these materials can be stored on diabetic foot ulcers for more than a week. However, there is conflicting information on the usefulness of hydrocolloid dressings in diabetic foot wounds, in the case of superficial wounds, if there are no signs of infection or if it is present in small or medium amount of exudate [9,17]. Compared to conventional dressings, hydrocolloid ones are considered superior in the treatment of diabetic foot ulcers, a fact confirmed by the recent data from the literature [18].

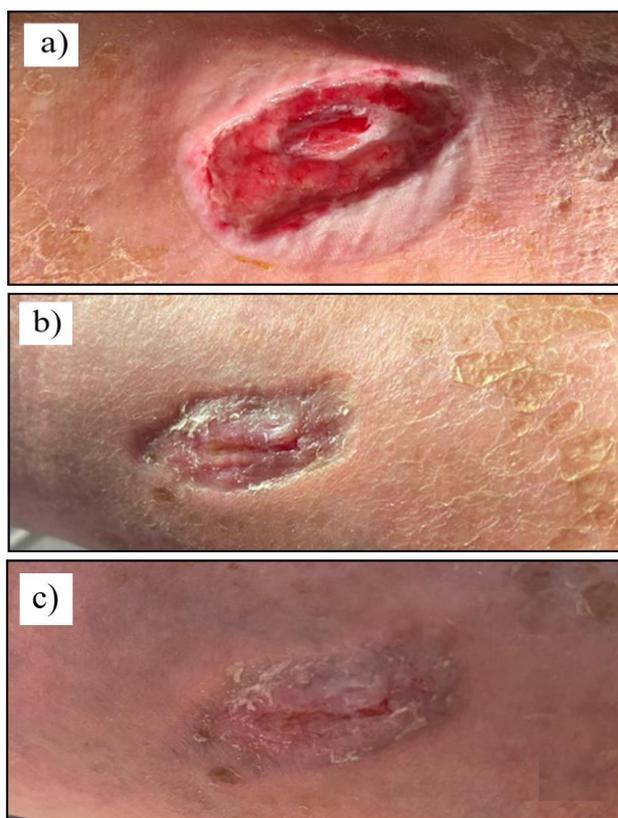


Figure 1. Leg ulcer treated by hydro-colloidal dressings. a) first week; b) week 4; c) week 6. (personal collection)

In general, the hydrogel hydrates and removes necrotic tissue. Absorbent capacity is moderate but favors autolysis, being used in dry, necrotic wounds or with minimal exudate. The gel can be applied directly to wounds and does not cause pain at the time of change and can be used in the treatment of deep wounds.

Foam-type dressings have been developed as alternatives to hydrocolloid dressings for application to wounds with moderate/ high secretion, having good antimicrobial activity and thermal insulation properties. Film dressings are impermeable to liquids and bacteria, have an autolytic role and cause reepithelialization of wounds with limited exudate [15,16,19].

Another modern method used in our clinic for the treatment of diabetic foot is vacuum therapy (Figure 2, a-b). Negative pressure therapy has dramatically changed the care of complex diabetic foot wounds.



Figure 2. Use of vacuum therapy. a) Radial amputation with debridement and disinfection before applying vacuum therapy; b) Sponge application on diabetic foot (personal collection).

Compared to the standard wound care, patients with diabetic foot injuries treated with this method were 5.9 times more likely to recover and 4.4 times less likely to require therapy by amputation. Negative pressure therapy was performed by providing sub atmospheric pressure through a vacuum pump that was connected to a specialized dressing able to maintain a clear closed environment. It increases wound perfusion, as well as accelerates the formation of granulation tissue, reduces edema and reduces the biological load [20]. All these mechanisms accelerate the wound healing by increasing the local blood flow and decreasing the bacterial colonization. Removing the excess fluid also removes inflammatory cytokines, which could worsen the healing process. At the same time, by removing the exudate from the wound, the needs to change the dressings were reduced. This method prevents repeated exposure to the environment through repeated dressing changes [21,22].

During the 5 years included in the study, 39 patients (representing 78% of the study group) benefited from hydro-colloidal dressings. The remaining 11 patients received vacuum therapy, representing 22% of the study group ($p = 0.01360$) as presented in the Table 3.

Table 3. Distribution of patients according to the type of modern surgical treatment

Treatment		Number of cases	Percentage (%)
Modern	H-C Dressings	39	78%
	Vacuum therapy	11	22%
Total		50	100%

Although the number of patients who received modern surgical treatment was initially small, there is a steady annual increase in those who opted for modern therapeutic methods, peaking in 2021 (Figure 3).



Figure 3. Annual distribution of patients with modern treatment

Out of the total number of patients who received hydrocolloid dressings, 31 cases had a favorable evolution, and 8 patients showed a deterioration of the local wound translated by superinfection and the spread of ulceration.

Although used in only 11 patients in the study group, negative pressure lesion therapy has a number of important benefits, such as reducing the size of the wound in the diabetic foot by increasing the mechanical traction exerted by the subatmospheric pressure on the edges of the wound, promoting healing in a much shorter time (Figure 4). In addition, it reduces the number of septic complications by healing chronic lesions, reduces the number of amputations and decreases the number of days of hospitalization and, therefore, the costs of hospitalization [23,24].



Figure 4. Negative pressure therapy for ulceration in the lower-lateral third of the leg (personal collection).

We analyzed the risk factors in the patients included in the study group and evaluated their impact in correlation with the modern methods of surgical treatment applied in our clinic. These include smoking, obesity, dyslipidemia, age of diabetes (diabetic patients older than 5 years), hepatic steatosis, various pre-existing cardiac pathologies and unbalanced diabetes with HbA1C values over 7.5%. Following the analysis of risk factors associated with diabetic foot, the predominance of pre-existing cardiac pathologies is observed with 36 cases, followed by obesity with 22 cases and dyslipidemia with 10 cases. Patients with diabetes diagnosed for over 5 years represent 18% of the total group and those with unbalanced diabetes 16%. The lowest cases presented as risk factors hepatic steatosis and smoking having a share of 10%, respectively 14% of the studied group ($p = 0.0139$). Out of the total number of patients included in the group, 9 had unfavorable evolutions following the applied treatment. An important aspect to mention is the influence of risk factors in these patients. All the cases that had an unfavorable evolution, presented 5 or more associated risk factors, regardless of the type of treatment followed ($p=0.006$).

In the current study, comorbidities that could accelerate the progression to the diabetic foot and other complications have been identified and analyzed, all of which have a significant role in increasing patient mortality [24]. The comorbidities encountered in the patients included in the study group are: high blood pressure (HBP), chronic ischemic heart disease (CIHD), heart failure (HF), chronic kidney failure (CKD), chronic venous insufficiency (CVI) and macroangiopathy in chronic obliterative arteriopathy (COA). The analysis of the cases included in the study highlighted the predominance of high blood pressure in 80% of patients (40 cases), followed by arteriopathy (27 cases) and ischemic heart disease (21 cases), each with a percentage of 54% and 42%, respectively. Heart failure and chronic venous insufficiency were present in a smaller number of patients with a percentage of 30% and 20% of the total group, respectively. The lowest cases were recorded among patients with chronic renal failure (9 cases), representing only 18% of the group.

Discussion

The management of the diabetic foot aims to avoid amputation, which is a mutilating method and difficult for the patient to accept. It has been observed in various studies that factors such as age, gender, duration of diabetes, peripheral vascular disease or neuropathy, poor glycemic control and renal complications may play an important role in patients' progression to amputation [26]. The treatment applied in the early stages of the infection can reduce the need to perform this procedure. However, in the case of ulcers that do not show significant signs of healing, despite

all the methods used, amputation remains the only method of treatment [27].

An important aspect to mention is that of the 11 patients who received vacuum therapy, only one showed an unfavorable evolution, requiring amputation. The rest of the patients had favorable evolutions, requiring no additional classical surgery.

Therefore, the superiority of Vacuum therapy over modern dressings in the treatment of diabetic foot ulcers can be noted. We considered it necessary to correlate these results with specialized studies to compare the effectiveness of these two modern methods of treating diabetic foot. In a randomized multi-center study with 342 patients, Blume et al. compared the therapy of negative pressure lesions with lesions treated by applying Hydrogel or Alignat dressings to diabetic foot ulcers. They found a higher rate of closure of ulcers that were treated using negative pressure therapy and concluded that this therapeutic strategy is a safe and effective way to improve the healing potential of diabetic foot ulcers. In the same study, a significantly lower incidence of secondary amputations was found in patients receiving negative pressure therapy [28].

In a study conducted by Bagul et al., the effectiveness of negative pressure therapy and that of conventional dressings in the treatment of diabetic foot injuries were compared [29]. The results showed that the patients who received Vacuum therapy developed the granulation tissue much faster (90.9%) at the end of the first week of treatment, compared to the classic dressing where 76% of the patients had a granulation tissue present at the end of the first week. Finally, all patients developed granulation tissue in the 2-nd week [29]. Hasaballah et al. evaluated rates of complete healing of lesions in negative pressure therapy compared to conventional dressings in anatomically difficult areas (heel and ankle regions). The study concluded that at the end of the 120-day period, complete healing of diabetic foot injury was achieved for 72.3% of patients using Vacuum therapy, while only 30.8% fully recovered in patients with conventional therapy [30].

The present study has some limitations: the limited number of patients included in the study, and the lack of a comparative group. Further prospective studies are needed to document the outcomes of this novel therapeutic approach in patients with diabetic foot ulcers.

The treatment of diabetic foot ulcers can be difficult to manage without a basic understanding of the available treatment options and a thorough assessment of the characteristics of the ulcer. The current literature suggests that if the initial treatment plan does not reduce the size of the ulcer by 50% in four weeks, it should be re-evaluated. The essential components of any initial or re-evaluated treatment plan should include debridement, wet wound

healing, decompression and control of infection. Conservative options are usually used first, but if progress stagnates, the surgical components of the treatment plan can help reduce healing time or even promote healing. The characteristics of a diabetic foot ulcer are important to consider because they directly influence the choice of treatment methods. Assessing the location, size, and depth of the diabetic foot ulcer, the type of tissue, the presence or absence of drainage, the duration of the ulcer, and the vascular intake are important variables to consider when formulating the surgical treatment plan [31-33]. Recently, a large array of biomarkers, such as neutrophil-to-lymphocyte ratio (NLR), thrombocyte-to lymphocyte ratio (TLR), IL-6 and procalcitonin were studied for the predictive value in patients with DFU [34-36].

Diabetes is rarely presented as a unique pathology. Most often the diabetic patient associates a series of comorbidities, complications of diabetes, but also numerous risk factors for the appearance of diabetic foot lesions, which translate over time into an inappropriate lifestyle [37-40]. Recent studies showed the importance of inflammation mechanisms that underlie the pathophysiology of cardiometabolic syndrome, including diabetes mellitus (hyperglycemia and insulin resistance), dyslipidemia, obesity along with visceral adiposity, and cardiac impairment [41-43]. There are significant dysfunctions in immune responses and metabolic regulation, that could impact wound healing. The analysis of the data shows that all patients included in the study had at least 2 associated risk factors, while the patients that had unfavorable outcomes had 5 or more risk factors. This result coincides with the study conducted by Martín-Timón et al., which shows that obesity, heart disease and dyslipidemia are the most common risk factors associated with diabetes complications [44].

An important aspect to mention is that most of the patients included in the study group presented one or more associated comorbidities, a fact confirmed by the study conducted by Iglay et al. They showed that most adults diagnosed with diabetes have at least one comorbidity, and up to 40% of them have at least three comorbidities [45]. In addition, after batch analysis, it was observed that patients who showed unfavorable evolution, regardless of the type of surgical treatment followed, had at least 4 associated comorbidities, mainly due to high blood pressure, lower limb arteriopathy, chronic ischemic heart disease and cardiac insufficiency. Studies conducted by Piette and Huang showed that comorbidities associated with diabetes increase the demand for medical care, the cost of hospitalization and the frequency of medical follow-up [46,47].

Therefore, the management of diabetic foot should be approached in a multidisciplinary team that requires, in addition to medical and surgical treatment, the education

of the patient in all aspects. Following a study by Sharma et al., it was concluded that the only way to minimize the morbidity of diabetic foot is to educate patients about the modifiable risk factors and effective prevention, reducing the chances of developing primary ulcers [48].

Conclusions

Modern surgical treatments have significantly improved in patients with complications of diabetes by lowering the rate of amputations. In our study, there is an annual increase in patients who have received modern treatment, peaking in 2021. Following the analysis, it was observed that vacuum therapy is much more effective compared to hydro-colloidal dressings by increasing the number of wounds healed, reducing healing time and reducing the risk of amputation.

Even if the vacuum therapy is more difficult to accept by the patient (due to the fact that it relatively immobilizes the patient through the attached technology), its benefits make us recommend it comparing to the therapy with hydro-colloidal absorbent dressings.

Risk factors play an important role in the occurrence of diabetic foot lesions, but also in the healing period of lesions, regardless of the type of modern therapy applied.

Highlights

- ✓ Modern surgical treatments have improved significantly in patients with diabetes complications resulting in decreased amputation rates.
- ✓ Management of associated risk factors, such as dyslipidemia, hypertension, high HbA1C, is extremely important in patients with diabetic foot to ensure favorable outcomes.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

The study followed the international regulations in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Proctoven Clinic in Sibiu. Patient informed consent for publication of the data/ images associated with the manuscript was obtained.

References

1. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, Hu FB, Kahn CR, Raz I, Shulman GI, Simonson DC, Testa MA, Weiss R. Type 2 diabetes mellitus. *Nat Rev Dis Primers*. 2015 Jul 23;1:15019. doi: 10.1038/nrdp.2015.19

2. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. *Ann N Y Acad Sci.* 2018 Jan; 1411(1):153-165. doi: 10.1111/nyas.13569
3. Brocco E, Ninkovic S, Marin M, Whisstock C, Bruseghin M, Boschetti G, Viti R, Forlini W, Volpe A. Diabetic foot management: multidisciplinary approach for advanced lesion rescue. *J Cardiovasc Surg (Torino).* 2018 Oct;59(5):670-684. doi: 10.23736/S0021-9509.18.10606-9
4. Bakker K, Apelqvist J, Schaper NC; International Working Group on Diabetic Foot Editorial Board. Practical guidelines on the management and prevention of the diabetic foot 2011. *Diabetes Metab Res Rev.* 2012 Feb;28 Suppl 1:225-31. doi: 10.1002/dmrr.2253
5. Jeffcoate WJ, Vileikyte L, Boyko EJ, Armstrong DG, Boulton AJM. Current Challenges and Opportunities in the Prevention and Management of Diabetic Foot Ulcers. *Diabetes Care.* 2018 Apr;41(4):645-652. doi: 10.2337/dc17-1836
6. Edmonds M, Manu C, Vas P. The current burden of diabetic foot disease. *J Clin Orthop Trauma.* 2021 Feb 8;17:88-93. doi: 10.1016/j.jcot.2021.01.017
7. Lavery LA, Davis KE, Berriman SJ, Braun L, Nichols A, Kim PJ, Margolis D, Peters EJ, Attinger C. WHS guidelines update: Diabetic foot ulcer treatment guidelines. *Wound Repair Regen.* 2016 Jan-Feb;24(1): 112-26. doi: 10.1111/wrr.12391
8. Bakker K, Apelqvist J, Lipsky BA, Van Netten JJ; International Working Group on the Diabetic Foot. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. *Diabetes Metab Res Rev.* 2016 Jan;32 Suppl 1:2-6. doi: 10.1002/dmrr.2694
9. Moura LI, Dias AM, Carvalho E, de Sousa HC. Recent advances on the development of wound dressings for diabetic foot ulcer treatment--a review. *Acta Biomater.* 2013 Jul;9(7):7093-114. doi: 10.1016/j.actbio.2013.03.033
10. Shah P, Inturi R, Anne D, Jadhav D, Viswambharan V, Khadilkar R, Dnyanmote A, Shahi S. Wagner's Classification as a Tool for Treating Diabetic Foot Ulcers: Our Observations at a Suburban Teaching Hospital. *Cureus.* 2022 Jan 22;14(1):e21501. doi: 10.7759/cureus.21501
11. Serban D, Spataru RI, Vancea G, Balasescu SA, Socea B, Tudor C, Dascalu AM. Informed consent in all surgical specialties: from legal obligation to patient satisfaction. *Rom J Leg Med.* 2020;28(3):317-321. doi: 10.4323/rjlm.2020.317
12. Serban D, Socea B, Badiu CD, Tudor C, Balasescu SA, Dumitrescu D, Trotea AM, Spataru RI, Vancea G, Dascalu AM, Tanasescu C. Acute surgical abdomen during the COVID-19 pandemic: Clinical and therapeutic challenges. *Exp Ther Med.* 2021 May; 21(5):519. doi: 10.3892/etm.2021.9950
13. Serban D, Smarandache AM, Cristian D, Tudor C, Duta L, Dascalu AM. Medical errors and patient safety culture - shifting the healthcare paradigm in Romanian hospitals. *Rom J Leg Med.* 2020;28(2):195-201. doi: 10.4323/rjlm.2020.195
14. Shi C, Wang C, Liu H, Li Q, Li R, Zhang Y, Liu Y, Shao Y, Wang J. Selection of Appropriate Wound Dressing for Various Wounds. *Front Bioeng Biotechnol.* 2020 Mar 19;8:182. doi: 10.3389/fbioe.2020.00182
15. Saco M, Howe N, Nathoo R, Cherpelis B. Comparing the efficacies of alginate, foam, hydrocolloid, hydrofiber, and hydrogel dressings in the management of diabetic foot ulcers and venous leg ulcers: a systematic review and meta-analysis examining how to dress for success. *Dermatol Online J.* 2016 Aug 15;22(8):13030/qt7ph5v17z
16. Lim JZ, Ng NS, Thomas C. Prevention and treatment of diabetic foot ulcers. *J R Soc Med.* 2017 Mar; 110(3):104-109. doi: 10.1177/0141076816688346
17. Jin Y, Li J, Wu S, Zhou F. Comparison of polyurethane foam dressing and hydrocolloid dressing in patients with pressure ulcers: A randomized controlled trial protocol. *Medicine (Baltimore).* 2021 Jan;100(2): e24165. doi: 10.1097/MD.00000000000024165
18. Kavitha KV, Tiwari S, Purandare VB, Khedkar S, Bhosale SS, Unnikrishnan AG. Choice of wound care in diabetic foot ulcer: A practical approach. *World J Diabetes.* 2014 Aug 15;5(4):546-56. doi: 10.4239/wjd.v5.i4.546
19. Gökçe S, Türeyen A, Gökçimen A. Effects of hypericum perforatum, clinoptilolite and hydrocolloid dressing on wound healing in diabetic rats. *Wound Medicine.* 2018; 22:14–22. doi: 10.1016/J.WNDM.2018.05.002
20. Mallow PJ, Tepsick J, Davis KE, Lavery LA. Cost-minimization analysis of negative pressure wound therapy technologies for the treatment of moderate-to-severe foot infections. *J Comp Eff Res.* 2020 Oct; 9(14):1027-1033. doi: 10.2217/cer-2020-0127
21. Liu Z, Dumville JC, Hinchliffe RJ, Cullum N, Game F, Stubbs N, Sweeting M, Peinemann F. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst Rev.* 2018 Oct 17;10(10):CD010318. doi: 10.1002/14651858.CD010318.pub3
22. Agarwal P, Kukrele R, Sharma D. Vacuum assisted closure (VAC)/negative pressure wound therapy (NPWT) for difficult wounds: A review. *J Clin Orthop Trauma.* 2019 Sep-Oct;10(5):845-848. doi: 10.1016/j.jcot.2019.06.015
23. de Oliveira Leite TF, Ribeiro da Silva E, Joviliano EE. Effect of negative pressure wound therapy for legs in

- complex wound diabetic patients: Therapeutic challenge and review. *SAGE Open Med Case Rep.* 2021; 9:2050313X211025920. doi: 10.1177/2050313X211025920
24. Pouget C, Dunyach-Remy C, Pantel A, Boutet-Dubois A, Schuldiner S, Sotto A, Lavigne JP, Loubet P. Alternative Approaches for the Management of Diabetic Foot Ulcers. *Front Microbiol.* 2021 Oct 5;12:747618. doi: 10.3389/fmicb.2021.747618
 25. Savlovski C, Serban D, Trotea T, Borcan R, Dumitrescu D. Post-surgery morbidity and mortality in colorectal cancer in elderly subjects. *Chirurgia (Bucur).* 2013 Mar-Apr;108(2):177-9.
 26. Sun JH, Tsai JS, Huang CH, Lin CH, Yang HM, Chan YS, Hsieh SH, Hsu BR, Huang YY. Risk factors for lower extremity amputation in diabetic foot disease categorized by Wagner classification. *Diabetes Res Clin Pract.* 2012 Mar;95(3):358-63. doi: 10.1016/j.diabres.2011.10.034
 27. Bekele F, Chelkeba L. Amputation rate of diabetic foot ulcer and associated factors in diabetes mellitus patients admitted to Nekemte referral hospital, western Ethiopia: prospective observational study. *J Foot Ankle Res.* 2020 Nov 4;13(1):65. doi: 10.1186/s13047-020-00433-9
 28. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care.* 2008 Apr;31(4):631-6. doi: 10.2337/dc07-2196
 29. Bagul A, Narwade N, Bhupatkar A, Murali S, Shah Y. Is vacuum assisted closure dressing better than conventional management of diabetic wounds?. *Int Surg J.* 2018;5(6):2199-2204. doi: 10.18203/2349-2902.isj20182222
 30. Hasaballah A, Aboloyoun H, Elbadawy A, Ezeldeen M. Impact of negative pressure wound therapy in complete healing rates following surgical debridement in heel and ankle regions in diabetic foot infections. *Egypt J Surg.* 2019 Jan-Mar;38(1):165-9. doi: 10.4103/ejs.ejs_180_18
 31. Răcățăianu N, Leach NV, Bolboacă SD, Soran ML, Flonta M, Valea A, Lazăr AL, Ghervan C. The crosstalk between insulin resistance, systemic inflammation, redox imbalance and the thyroid in subjects with obesity. *J Mind Med Sci.* 2021;8(1):139-148. doi: 10.22543/7674.81.P139148
 32. Serban D, Papanas N, Dascalu AM, Stana D, Nicolae VA, Vancea G, Badiu CD, Tanasescu D, Tudor C, Balasescu SA, Pantea-Stoian A. Diabetic Retinopathy in Patients With Diabetic Foot Ulcer: A Systematic Review. *Int J Low Extrem Wounds.* 2021 Jun;20(2):98-103. doi: 10.1177/1534734620982237
 33. Snyder RJ, Cardinal M, Dauphinée DM, Stavosky J. A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing by 12 weeks. *Ostomy Wound Manage.* 2010 Mar 1;56(3):44-50.
 34. Serban D, Papanas N, Dascalu AM, Kempler P, et al. Significance of Neutrophil to Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) in Diabetic Foot Ulcer and Potential New Therapeutic Targets. *Int J Low Extrem Wounds.* 2021 Nov 18;15347346211057742. doi: 10.1177/15347346211057742
 35. Brănescu C, Serban D, Dascălu AM, Oprescu SM, Savlovski C. Interleukin 6 and lipopolysaccharide binding protein - markers of inflammation in acute appendicitis. *Chirurgia (Bucur).* 2013 Mar-Apr; 108(2):206-14.
 36. Korkmaz P, Koçak H, Onbaşı K, Biçici P, Özmen A, Uyar C, Özatağ DM. The Role of Serum Procalcitonin, Interleukin-6, and Fibrinogen Levels in Differential Diagnosis of Diabetic Foot Ulcer Infection. *J Diabetes Res.* 2018;2018:7104352. doi: 10.1155/2018/7104352
 37. Ardeleanu V, Toma A, Pafili K, Papanas N, Motofei I, Diaconu CC, Rizzo M, Stoian AP. Current Pharmacological Treatment of Painful Diabetic Neuropathy: A Narrative Review. *Medicina (Kaunas).* 2020 Jan 9;56(1):25. doi: 10.3390/medicina56010025
 38. Bondar A, Popa AR, Papanas N, Popoviciu M, Vesa CM, Sabau M, Daina C, Stoica RA, Katsiki N, Stoian AP. Diabetic neuropathy: A narrative review of risk factors, classification, screening and current pathogenic treatment options (Review). *Exp Ther Med.* 2021 Jul; 22(1):690. doi: 10.3892/etm.2021.10122
 39. Dascalu AM, Stoian AP, Cherecheanu AP, Serban D, Costea DO, Tudose MS, Stana D, Tanasescu D, Sabau AD, Gangura GA, Costea AC, Nicolae VA, Smarandache CG. Outcomes of Diabetic Retinopathy Post-Bariatric Surgery in Patients with Type 2 Diabetes Mellitus. *J Clin Med.* 2021 Aug 22;10(16):3736. doi: 10.3390/jcm10163736
 40. Constantin VD, Socea B, Popa F, Carâp AC, Popescu G, Vlădescu T, Ceaușu Z, Berteșteanu ȘV, Ceaușu MC. A histopathological and immunohistochemical approach of surgical emergencies of GIST. An interdisciplinary study. *Rom J Morphol Embryol.* 2014;55(2 Suppl):619-27.
 41. Busnatu SS, Salmen T, Pana MA, Rizzo M, Stallone T, Papanas N, Popovic D, Tanasescu D, Serban D, Stoian AP. The Role of Fructose as a Cardiovascular Risk Factor: An Update. *Metabolites.* 2022 Jan 12;12(1):67. doi: 10.3390/metabo12010067
 42. Dănciulescu Miulescu RE, Guja L, Socea B, Dumitriu A, Paunica S, Ștefănescu E. Oral pathology induced by excess or deficiency of glucocorticoids in adults. *J Mind Med Sci.* 2020;7(2):141-147. doi: 10.22543/7674.72.P141147

43. Shah H, Shah R, Sanghani H, Lakhani N. Health related quality of life (HRQoL) and its associated surgical factors in diabetes foot ulcer patients. *J Clin Invest Surg.* 2020;5(2):83-90. doi: 10.25083/2559.5555/5.2/83.90
44. Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, Del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? *World J Diabetes.* 2014 Aug 15;5(4):444-70. doi: 10.4239/wjd.v5.i4.444
45. Iglay K, Hannachi H, Joseph Howie P, Xu J, Li X, Engel SS, Moore LM, Rajpathak S. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. *Curr Med Res Opin.* 2016 Jul;32(7):1243-52. doi: 10.1185/03007995.2016.1168291
46. Piette JD, Kerr EA. The impact of comorbid chronic conditions on diabetes care. *Diabetes Care.* 2006;29(3):725-31. doi: 10.2337/diacare.29.03.06.dc05-2078
47. Huang ES. Management of diabetes mellitus in older people with comorbidities. *BMJ.* 2016 Jun 15;353:i2200. doi: 10.1136/bmj.i2200
48. Sharma R, Kapila R, Sharma AK, Mann J. Diabetic Foot Disease—Incidence and Risk Factors: A Clinical Study. *J Foot Ankle Surg Asia-Pacific.* 2016;3(1):41-46. doi: 10.5005/jp-journals-10040-1046