

# Diabetic wounds treated with LED and latex and the risk of unstable glycemia

Feridas de diabéticos tratados com LED e látex e o risco de glicemia instável

Heridas diabéticas tratadas con LED y látex y el riesgo de glucemia inestable

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## REVISA

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## RESUMO

**Objetivo:** caracterizar o Risco de Glicemia Instável de pacientes com feridas de membros inferiores em uso látex associado ao LED. **Método:** Estudo de coorte prospectivo com amostra n=15. Divididos em três grupos Grupo 1 curativo com látex e LED; Grupo 2 carvão ativado; e Grupo 3 realizavam autocurativo com látex e LED e identificação do Risco de glicemia instável. Análise de dados realizada pelo software SPSS®. **Resultados:** Os participantes 60% homens, idade 59,93±10,88 anos, fatores de Risco de glicemia instável: atividade física diária menor que o recomendado; conhecimento insuficiente do controle da doença, em todos os grupos; condição de saúde comprometida grupos I e III; controle insuficiente do diabetes grupo I; falta de adesão ao plano de controle do diabetes início ao fim, exceto pelo grupo II. Ocorreu redução das feridas em todos os grupos e melhor cicatrização no grupo III. **Conclusão:** A feridas maiores estavam no grupo I e ocorreu redução das feridas todos os grupos. Os principais fatores de risco de glicemia instável atividade física diária menor que o recomendado no início e final; condição de saúde comprometida grupos I e III; conhecimento insuficiente do controle da doença em todos os grupos.

**Descritores:** Cicatrização de Feridas; Lesões e Feridas; Avaliação; Enfermagem; Diabetes Mellitus.

## ABSTRACT

**Objective:** to characterize the risk of unstable blood glucose in patients with lower limb wounds using latex associated with LED. **Method:** Prospective cohort study with sample n=15. Divided into three groups Group 1 dressing with latex and LED; Group 2 activated charcoal; and Group 3 performed self-healing with latex and LED and identified the risk of unstable blood glucose. Data analysis performed by SPSS® software. **Results:** Participants 60% men, age 59.93±10.88 years, risk factors for unstable blood glucose: daily physical activity less than recommended; insufficient knowledge of disease control, in all groups; compromised health condition groups I and III; insufficient control of group I diabetes; lack of adherence to the diabetes control plan from beginning to end, except for group II. There was a reduction of wounds in all groups and better healing in group III. **Conclusion:** The major wounds were in group I and there was a reduction of wounds in all groups. The main risk factors for unstable glycemia daily physical activity less than recommended at the beginning and at the end, compromised health condition groups I and III, and insufficient knowledge of disease control in all groups.

**Descriptors:** Wound Healing; Injuries and Wounds; Assessment; Nursing; Diabetes Mellitus.

## RESUMEN

**Objetivo:** caracterizar el riesgo de inestabilidad glucémica en pacientes con heridas en miembros inferiores utilizando látex asociado a LED. **Método:** Estudio de cohorte prospectivo con muestra n=15. Dividido en tres grupos Grupo 1 aderezo con látex y LED; carbón activado del grupo 2; y el Grupo 3 realizó autocuración con látex y LED e identificó el riesgo de glucosa en sangre inestable. Análisis de datos realizado por el software SPSS®. **Resultados:** Participantes 60% hombres, edad 59,93±10,88 años, factores de riesgo para glucemia inestable: actividad física diaria inferior a la recomendada; conocimiento insuficiente del control de enfermedades, en todos los grupos; condiciones de salud comprometidas grupos I y III; control insuficiente de la diabetes del grupo I; falta de adherencia al plan de control de la diabetes de principio a fin, excepto en el grupo II. Hubo reducción de heridas en todos los grupos y mejor cicatrización en el grupo III. **Conclusión:** Las heridas mayores estaban en el grupo I y hubo reducción de heridas en todos los grupos. Los principales factores de riesgo para la glucemia inestable actividad física diaria inferior a la recomendada al principio y al final, condiciones de salud comprometidas grupos I y III, y conocimiento insuficiente del control de la enfermedad en todos los grupos.

**Descritores:** Curación de Heridas; Lesiones y Heridas; Enfermería; Diabetes Mellitus.

## Introduction

Diabetes Mellitus (DM) is a public health problem, the most common being type 2 DM that affects adults related to insulin resistance or sufficient insulin production.<sup>1</sup> In recent decades and in the future the prevalence of DM increases in all countries in the age group between 20 and 79 years, in 2021 there are about 537 million people with DM and by 2045 about 783 million. In the Americas 32 million in 2021 to 49 million in 2045, estimated by the International Diabetes Federation and the Brazilian Diabetes Society.<sup>2-3</sup>

Among the complications of DM, diabetic foot ulcer (UPD) stands out, which affects more than 50% of patients.<sup>4</sup> Upd is defined when there is infection, ulceration or destruction of tissues of the foot, in addition it is a change that may be associated with neurological abnormalities and/or the various degrees of peripheral arterial disease in people with DM that may result in amputations.<sup>5</sup>

The studies by Serra<sup>6</sup>, Lacerda<sup>7</sup> and Muñoz<sup>8</sup> showed that a considerable percentage of the patients with DM interviewed had similar nursing diagnoses, such as risk of unstable glycemia, impaired skin integrity and liver disease and reduced mobility, diagnoses directly related to diabetic foot ulcers. Another important point is the adoption of coverage for treatment for UPD that can potentiate healing in patients with DM.<sup>4-5,8</sup>

In view of the above, we emphasize the importance of studies that relate the control of glycemia and the adoption of technological innovation of dressings in the healing of UPD, with a view to the better quality of life of patients living with PUD and its complications. Thus, this study aims to characterize the Risk of Unstable Blood Glucose of patients with lower limbs wounds using latex associated with LED.

## Method

This is a prospective cohort study of quantitative approach. Data were collected between March 2016 and August 2017. The place of performance was in the premises of the Wound Outpatient Clinic of a Public Hospital of Brasília and in the residence of the research participants. The study population was composed of individuals with ischemic and neuropathic UPD in the lower limbs. The final sample consisted of 15 participants, divided into three groups: Group 1 (GI) Case - (n=5) dressings performed in their homes by nurses using natural latex (*Hevea brasiliensis*) associated with the use light-emitting circuit of Light-emitting Diode/LED; Group 2 (GII) Control - (n=5) dressings performed in the public outpatient clinic by nurses using activated charcoal and Group 3 (GIII) (n=5) Self-realization - dressings performed by patients in their homes using adhesive derived from the associated natural latex LED for 35 minutes direct to the latex application area. The whole team was trained by nurses and standardized the dressing techniques to perform both dressings in THE AND II and guide the patients of the group self-realization GIII.

The inclusion criteria were to be attended at the outpatient clinic of the Hospital of the Federal District; have ulcer in the lower limb of neuropathic and/or vascular origin; and not be in treatment for some kind of cancer. Those who did not complete the days of treatment were excluded; pregnant, under age or over 75 years of age; being a drug user; have osteomyelitis or gangrene; having

performed topical application at the wound site, after the beginning of the study, that were not adopted in this protocol between groups; missing the treatment program three times in a row.

The instruments adopted were a questionnaire to characterize the sociodemographic and clinical profile of patients and the nursing diagnosis (ND) Risk of Unstable Glycemia was characterized by the use of the International Nursing Diagnoses: Definitions and Classification-NANDA 2018/2020. The ED Risk of unstable glycemia is defined as vulnerability to the variation of glucose/blood sugar levels in relation to normal variation, which may compromise health. It is built by identifying its risk factors. Peripheral capillary blood glucose was assessed once a week.

The dressings were standardized and evaluated by direct observation of the lesions of the Groups (GI, GII and GIII), evaluated for the aspect of the wound, closure of the lesion and were also photographed once a week and compared at the beginning and end of treatment. The images were standardized and analyzed by the ImageJ® software, for the quantification of the total area of the UPD.

Data analysis was conducted in a database in the Package for the Social Sciences (SPSS®) version 20.0 software. Descriptive analysis was performed by calculating absolute frequencies, relative frequencies and dispersion measures.

This study was approved by the FEPECS Research Ethics Committee (1,458,781/2016) and followed all ethical precepts according to the ethical standards of CNS resolution 466/2012.

## Results

In the evaluation of the 15 participants, the mean age was 59.93±10.88 years (Min.=42 and Max.=75), 60% were men, 46.7% were between 60 and 69 years old, 53.3% were obese, 93.3% did not smoke or drink and had DM. The majority (86.7%) had systemic arterial hypertension (SAH). The profile remained similar in the Self-Realization, Control and Case groups, classified by the dressing covers (Table 1).

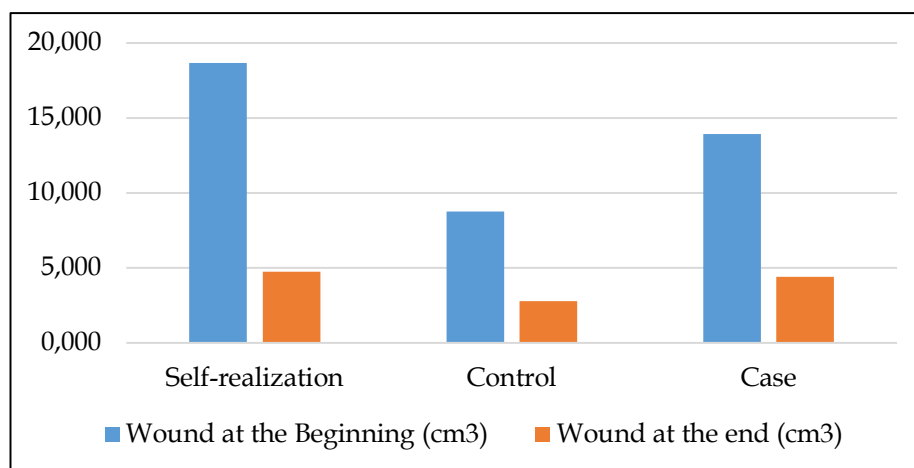
**Table 1-** Sociodemographic and clinical profile of patients with lower-lower limbs wounds, Brasília, 2022.

	Groups							
	Total		Group I Case		Group II Control		Group III Self-realization	
	n	%	n	%	n	%	n	%
<b>Sex</b>								
Male	9	60,00	3	60,00	3	60,00	3	60,00
Female	6	40,00	2	40,00	2	40,00	2	40,00
<b>Age (years)</b>								
40 to 49	4	26,70	1	20,00	1	20,00	2	40,00
50 to 59	2	13,30	1	20,00	0	0,00	1	20,00
60 to 69	7	46,70	1	20,00	4	80,00	2	40,00
Over 70	2	13,30	2	40,00	0	0,00	0	0,00
<b>BMI</b>								

Normal	3	20,00	1	20,00	1	20,00	1	20,00
Overweight	4	26,70	2	40,00	1	20,00	1	20,00
Obesity	8	53,30	2	40,00	3	60,00	3	60,00
<b>Smoking</b>								
Yes	1	6,70	1	20,00	0	0,00	0	0,00
No	14	93,30	4	80,00	5	100,00	5	100,00
<b>Alcoholism</b>								
Yes	1	6,70%	1	20,00	0	0,00	0	0,00
No	14	93,30	4	80,00	5	100,00	5	100,00
<b>SAH</b>								
Yes	13	86,70	4	80,00	5	100,00	4	80,00
No	2	13,30	1	20,00	0	0,00%	1	20,00
<b>Diabetes mellitus</b>								
Yes	14	93,30	5	100,00	4	80,00	5	100,00
No	1	6,33	0	0,00	1	20,00	0	0,00

**Legend:** Body mass index (BMI) - Normal (18.5 To 24.9); Overweight (25 and 29.9); Obesity ( $\geq 30$ ); Systemic Arterial Hypertension (SAH).

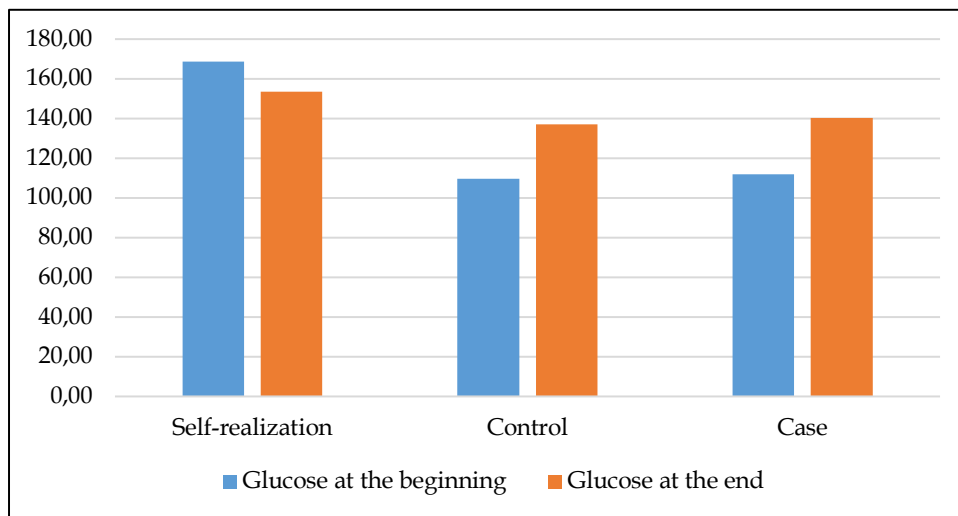
According to Figure 1, the size of the lesions was observed at the beginning and end of the study. The self-realization group presented the highest wounds  $M=18.66\pm 19.26\text{cm}^3$  (Min.=5.22 and Max.=52.39) and was also the group with the best final results, reaching a final average of  $4.75\pm 6.64\text{cm}^3$  (Min.=0.00 and Max.=15.59). The Case and Control groups were followed by initial averages of  $13.920\pm 15.88$  (Min.=1.769 and Max.=40.8) and  $8.78\pm 12.3\text{cm}^3$  (Min.=0.166 and Max.=29.8) respectively (Figure 1). The final means of the Case and Control groups were both  $4.42\pm 3.32$  (Min.=1.20 and Max.=10.0). The duration of the dressings was on average between 5.0 and 7.2 weeks between the groups..



**Figure 1-** Characterization of lower limbs wounds, patients with lower limbs wounds. Brasilia, 2022.

The best glycemetic control at the beginning and in the end was observed in the groups Control and Case, with initial averages of  $109.60\pm 85.27\text{mg/dL}$  (Min.=60.0 and Max.=261.0) and  $111.8\pm 28.38\text{mg/dL}$  (Min.= 80.0 and Max.= 156.0) and averages final of  $137.2\pm 48.98\text{mg/dL}$  (Min.= 78.0 and Max.= 198) and  $140.4\pm 28.92\text{mg/dL}$  (Min.=119.0 and Max.=191.0), respectively. The worst values were from the Self-realization group, with means of  $168.8\pm 99.0\text{mg/dL}$  (Min.=86.0

and Max.=339.0) at the beginning and 153.60±48.09mg/dL(Min.=98.0 and Max.=221.0) at the end (Figure 2).



**Figure 2-** Glycemic control of capillary glycemia of patients with wounds in the lower limbs. Brasilia, 2022.

The ED Risk of Unstable Glycemia was characterized by the identification of the main risk factors. Physical activity lower than recommended was identified in all groups and there was a reduction from 100.0% to 0.0% in the Self-Realization group, 20.0% in the Control group and 40.0% in the Case group. The Impaired Physical Health Condition remained stable from beginning to end among all groups (40.0%). The risk factor of Insufficient Knowledge of Disease Control decreased in the Case and Control group from 60% to 40.0%. As for the Risk Factor Insufficient Control of Diabetes, Self-Realization and Control did not demonstrate the risk, from beginning to end, while the Caso group has the risk in less than half of the patients. On the Risk of Lack of Access to the diabetes control plan, it remained similar from beginning to end, except for the Control group (Table 2).

**Table 2-** Characterization of the nursing diagnosis Risk of unstable glycemia, beginning and end of treatment of patients with wounds in the lower limbs. Brasilia, 2022.

Risk Factors		Groups					
		Self-realization		Control		Case	
		n	%	n	%	n	%
Daily physical activity less than recommended onset	Yes	5	100,0	3	60,0	4	80,0
	No	0	0,0	2	40,0	1	20,0
Daily physical activity less than the recommended end	Yes	5	100,0	3	60,0	4	80,0
	No	0	0,0	2	40,0	1	20,0
Physical health condition compromised beginning	Yes	2	40,0	0	0,0	2	40,0
	No	3	60,0	5	100,0	3	60,0
Final compromised physical health condition	Yes	2	40,0	0	0,0	2	40,0
	No	3	60,0	5	100	3	60,0
Insufficient knowledge of disease onset control	Yes	3	60,0	2	40,0	2	40,0
	No	2	40,0	3	60,0	3	60,0
Insufficient knowledge of final disease control	Yes	3	60,0	3	60,0	3	60,0
	No	2	40,0	2	40,0	2	40,0
	Yes	0	0,0	0	0,0	2	40,0

Insufficient control of diabetes onset	No	5	100,0	5	100,0	3	60,0
Insufficient control of final diabetes	Yes	0	0,0	0	0,0	2	40,0
	No	5	100,0	5	100,0	3	60,0
Lack of access to early diabetes control plan	Yes	2	40,0	0	0,0	2	40,0
	No	3	60,0,0	5	100,0	3	60,0
Lack of access to the final diabetes control plan	Yes	2	40,0	1	20,0	2	40,0
	No	3	60,0	4	80,0	3	60,0

## Discussion

The participants were elderly, overweight and had DM and SAH. Similar results were found in the Study by Tonetto<sup>9</sup> in which 52.6% of the patients attending primary care for the treatment of UPD were obese elderly men with SAH. In Sergipe, another study showed that more than half of the sample studied were of men with a mean age of 67 years and 80% also had SAH.<sup>10</sup>

DM induces changes in microvasculature, affecting the capillary basement membrane, including lesions in arterioles, glomeruli, retina, myocardium, skin and muscle, increasing its thickness, leading to the development of diabetic microangiopathy. This thickening develops abnormalities in vessel function, inducing multiple clinical problems, such as hypertension, hypoperfusion, delay in wound healing and tissue hypoxia.<sup>11</sup> Thus, it is essential to emphasize the importance of glycemic control through dietary interventions, physical exercises and medication treatment adhering, in order to ensure the management of the pathology and the success of treatment.

Regarding the lesions and their size, the self-realization group presented greater wounds and better healing followed by the Case and Control groups, respectively. Wound healing is a complex and dynamic event, which can be divided into three phases, which are inflammatory, proliferative and remodeling phase. In the inflammatory phase, neutrophils and macrophages migrate to the injured area; Pro-inflammatory cytokines TGF- $\beta$ , IL-1, IL-8, TNF- $\alpha$  and IFN- $\gamma$  act as aiding in cellular chemotaxis and differentiation of monocytes in macrophages; in the proliferative phase, fibroplasia occurs, responsible for collagen deposition, and angiogenesis begins by giving the appearance of "granulation tissue" to the wound, then reepithelialization occurs, characterized by the migration of undamaged keratinocytes from the wound margins to the center. In the last phase, remodeling occurs the deposition of type I collagen by fibroblasts and increased contraction force of the edges, reestablishing the homeostasis of the body.<sup>12</sup>

In the present study, the Case and Self-realization groups used LED circuits in their therapy associated with natural latex (*Hevea brasiliensis*), which when used along with phototherapy, has healing properties.<sup>13</sup> Lethal Diodes (LeDs) are photobiomodulatory devices formed by solid semiconductors united with each other, which generate a reliable and high-power light source that has been gaining prominence in the context of health and aesthetics.<sup>14</sup>

Photobiomodulation, using different types of light source, has proven to be a possible alternative for the activation of enzyme action and cell cycle progression during the healing process, in addition to possibly increasing the production and release of cytokine, circulation of growth factors, production of

mitochondrial ATP of the cells involved, vasodilation and nerve regeneration. A study conducted in Fortaleza in which 10 LED applications were performed demonstrated the reduction of the healing time of UPD. On the first day of application, the wounds presented an average size of 1.52cm<sup>2</sup>, evolving on the fifth day to 1.22cm<sup>2</sup> and on the tenth day, 0.812cm<sup>2</sup>. As a percentage, these values translate to 47.60% between the first and fifth sessions and 62.26% between the first and tenth sessions.<sup>15</sup>

Nunes's study<sup>16</sup> demonstrated the evolution of wounds treated with LED and latex circuit, divided into two groups: experimental (dressing performed with LED light and latex) and control (dressing performed with debridement and conventional dressings). The experimental group showed a reduction in wound size by 51.80% in the second week of treatment and 78.40% in the fourth week while the control group obtained a reduction of 22.70% in the first week and 78.40% in the fourth week, so it is possible to affirm that the experimental group presented better results when compared to the control group.

Attention is drawn by the adoption of combined coverings can help in the healing process in patients with UPD. They have properties that aid in the process of cell development.<sup>4,11</sup>

In this study, it was observed that the DE Risk of Unstable Glycemia contributed to the healing process, which can be observed when comparing the initial and final blood glucose values and the size of the wounds of the the groups Control and Case, for example. Repair of injured tissue in diabetic patients occurs more slowly compared to individuals who do not present the pathology, and this difference in healing time is explained by the impairment of leukocyte chemotaxis, reduced function of macrophages that facilitates the development of severe infections, besides also reducing collagen synthesis and growth factors, which means saying a delay in the contraction and closure of the open wound, so it is necessary an approach focused on glycemic control and wound care.<sup>17</sup>

The control of DM can be performed by several strategies, one of which is to recognize the problem, such as in the adoption of the Nursing Taxonomy NANDA-I, which describes one of the health problems in diabetics. The risk of unstable blood glucose is recognized as vulnerability to the variation of blood glucose levels in relation to normal variation, which may compromise health.<sup>18</sup> This problem can be identified through ED, and be related to DM and its complications, such as impairment of renal, cardiac and epithelial functions, besides directly and negatively influencing the quality of life of patients with DM and living with PU.<sup>19</sup>

In the present study, it was found that more than half of the patients who received follow-up from nurses at home presented the risk of unstable glycemia. This ED presents many risk factors, such as lower than recommended physical activity, insufficient knowledge of disease control, insufficient diabetes control and lack of disease control plan, demonstrating similarity between our findings of the present study, which also found these risk factors.<sup>20</sup>

The analysis of the ED Risk of unstable glycemia indicated that the lower than recommended risk factor for physical activity is related to other diagnoses, such as impaired skin integrity, chronic and acute pain in patients living with this type of wound. A study conducted in Ribeirão Preto showed that 42.9% of the 50 patients interviewed had impaired physical mobility and more than half also had chronic pain, resulting in a higher incidence for the lower risk of

physical activity than recommended in the patients evaluated.<sup>20</sup>

Another study conducted in Campina Grande with 75 elderly diabetic patients, it was found that although physical exercise is an ally in the reduction of glycated hemoglobin, weight loss and shorter duration of DM, patients were instructed in the health service to keep rest, due to the fact that the impacts caused by physical exercises could slow the healing process of ulcerative wounds.<sup>21</sup>

Several other studies show in their results that many patients have reduced mobility, impaired health condition and pain as a result of the development of ulcers, causing a negative impact on well-being, quality of life and especially on the actions and care plans proposed for the treatment of diabetes itself.<sup>6-7, 22-24</sup>

A research developed in Itajaí with people with DM and assisted by the family health strategy brought statements through interviews, in which patients justified the difficulty in performing physical activity. Among the reports, we highlight the non-indication of physical exercise by other professionals who accompany the patient outside of primary care, pain when trying to exercise and vision problems caused by diabetes that prevented the practice. Some patients stated that they knew the importance and benefits of physical activity.<sup>24</sup>

The Brazilian Diabetes Society recommends that a diabetic adult practice at least 150 hours of physical exercise per week, and these hours can be divided between days of the week, not exceeding two days without physical activity.<sup>3,25</sup> Patients with diabetic neuropathy or installed wounds should avoid exercises with repeated impact, such as prolonged walking, running, or stair. Preference should be given to water aerobics, swimming, brachyma ergometry (exercises involving only the arms) and bodybuilding exercises in a sitting position to avoid direct gravity on the lower limbs.<sup>3-4</sup>

Nutritional therapy, based on guidance and the establishment of an individualized dietary plan, associated with the practice of physical exercise, is considered a therapy of choice for the control of DM and its benefits have been evidenced in the literature. Nutritional therapy can lead to a 2% reduction in glycated hemoglobin (HbA1c) in people recently diagnosed with DM2, as well as a 1% reduction among people with an average of four years of disease progression. On the other hand, the regular practice of physical exercises by diabetic individuals, within the recommended intensities, can result in a reduction of 10% to 20% in glycated hemoglobin and also in better transport of oxygen through the bloodstream.<sup>26</sup>

Therefore, it is possible to conclude that full access to the diet and the practice of appropriate physical exercises and in the correct proportion is an indispensable factor for and prevention of wounds and also of their healing, since it provides the healing mechanisms with the necessary conditions to happen.<sup>3</sup> Nursing needs to develop a care plan for the patient together with the family, taking into account the limitations so that there is motivation in self-care and to make it aware that the earlier it becomes involved in the adoption of physical activity, it may have the healing process improved due to the contribution of physical activity in this process, together with nutritional control.

In the present study, the Case and Control groups showed an increase in the Risk of Insufficient Knowledge in disease control, since blood glucose values were increased at the end of the study. One study identified that insufficient



knowledge risk is one of the main factors related to unstable glycemia. The same study showed that of 35 diabetic elderly, 29 received an ND named Insufficient knowledge about diabetes, since 27 did not attend any meeting of the diabetic group and 2 attended only one or two.<sup>8</sup>

Non-adhering or ineffective management of medications can lead to variation in blood glucose levels and may lead to short-term complications such as diabetic ketoacidosis and the state of osmolar hyperglycemia and also to long-term complications such as neuropathies, nephropathies and retinopathies, as well as cardiovascular damage.<sup>28</sup> Among the reasons for non-treatment treatment may include psychological and financial factors.<sup>27-29</sup>

In Mexico, a study with 35 diabetic elderly showed that 29 of them had the ND risk for unstable glycemia, since they had insufficient knowledge about the disease and its complications, 19 had ineffective maintenance of drug therapy and 14 did not adhere to the therapeutic plan, mainly to the proposed food plan.<sup>8</sup>

The lack of ad treatment is a public health problem and it is necessary to know the situation in real way, so that the occurrence of events, such as the emergence of PUD, is preventable. A study conducted in a primary care unit demonstrated the main factors that lead to non-treatment compliance, which are related to care or the proposed treatment plan. Among them are insufficient coverage of care and inadequate access to care, financial barriers and complex treatment regime.<sup>28</sup>

The following limitations of this study indicate replication since study in a larger sample, time of nonsimilar wounds between groups and the possibility of memory bias for the self-reported variables studied.

The findings of this study may contribute to the analysis of glycemic control in the face of the use of wound treatment therapies of patients with DM. It can help in planning actions for patients who live with UPD and are in the community.

## Conclusion

This study showed that individuals with PUD are men, obese and most also had sah diagnosis. The ED Risk of unstable glycemia was characterized by identifying the main risk factors, of which: reduction of the risk of physical activity lower than recommended for all groups, impaired physical health condition remained stable at the beginning and end of the study, in all groups. The risk factor of insufficient knowledge of disease control occurred as a reduction in the Control and Case groups. On the risk of lack of access to the diabetes control plan, the percentages remained similar from beginning to end, except for the Control group. There was a reduction in wounds in the lower limbs of all patients analyzed, with better results in group III self-realization.

Thus, it is possible to conclude that the control of glycemia added to the use of natural latex associated with LED light proved to be an effective and economical alternative, which can result in the improvement of the quality of life of individuals with UPD by reducing healing time, since both have properties capable of increasing angiogenesis and collagen production.

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