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Case Report

# Complex diabetic foot ulcer in patient with Diabetic Nephropathy

## *Úlcera de pie diabético compleja en paciente con Nefropatía Diabética*

## *Ulcère complexe du pied diabétique chez un patient attendu de Néphropathie Diabétique*

## *Úlcera complexa de pé diabético em paciente com Nefropatia Diabética*

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**ABSTRACT**

Diabetes Mellitus represents a global health problem. It constitutes a risk factor for the appearance of diseases of vascular origin that are among the leading causes of death, including diabetic nephropathy. A clinical case of a female patient is presented who, according to the results of the findings, the diagnosis is an infested ischemic diabetic foot, with Wagner Grade V and according to Mac Cook's Cuban classification of diabetic foot. Heberprot-p® treatment was started at 75 mg, and complete granulation of the lesion was achieved after 6 weeks.

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**Keywords**: Diabetic Foot; Mellitus diabetes; Heberprot-p®; Chronic Arterial Insufficiency; Sore; Bacteria; Amputation; Peripheral Pulse; Renal insufficiency; Necrosis; Growth factor; Epidermal Growth; Diabetic Nephropathy.

***RESUMEN***

*La Diabetes Mellitus representa un problema de salud a escala mundial; constituye un factor de riesgo para la aparición de enfermedades de origen vascular que están entre las primeras causas de muerte, entre ellas la Nefropatía diabética. Se presenta un caso clínico de una paciente femenina que según los resultados de los hallazgos, el diagnóstico es un pie diabético isquémico infestado, con Wagner Grado V y según la clasificación cubana de pie diabético de Mac Cook. Se inicia tratamiento Heberprot-p®, 75 mg y se logra la granulación total de su lesión a las 6 semanas.*

***Palabras clave**: Pie Diabético; Diabetes Mellitus; Heberprot-p®; Insuficiencia Arterial Crónica; Úlcera; Bacterias; Amputación; Pulso Periférico; Insuficiencia Renal; Necrosis; Factor de Crecimiento; Crecimiento Epidérmico; Nefropatía Diabética.*

***RÉSUMÉ***

*Le diabète sucré représente un problème de santé mundial. Elle constitue un facteur de risque d'apparition de maladies d'origine vasculaire qui comptent parmi les principales causes de décès, dont la néphropathie diabétique. On présente le cas clinique d'une patiente qui, selon les résultats des constatations, le diagnostic est un pied diabétique ischémique infesté, de gradé V de Wagner et selon la classification cubaine du pied diabétique de Mac Cook. Un traitement par Heberprot-p® a été débuté, 75 mg, et une granulation complète de la lésion a été obtenue au bout de 6 semaines.*

***Mots clés:** Pied diabétique; Diabète mellitus; Heberprot-p®; Insuffisance artérielle chronique; Douloureux; Bactéries; Amputation; Pouls périphérique; Insuffisance rénale; Nécrose; Facteur de croissance; Croissance épidermique; Néphropathie diabétique.*

***RESUMO***

*A Diabetes Mellitus representa um problema de saúde em escala mundial; constitui um fator de risco para o surgimento de doenças de origem vascular que estão entre as principais causas de morte, entre elas a Nefropatia Diabética. Relado de um caso clínico de uma paciente feminina que, segundo os resultados obtidos, o diagnóstico é um pé diabético isquêmico infestado, com Wagner Grau V e segundo a classificação cubana de pé diabético de Mac Cook. Inicia-se tratamento com Heberprot-p®, 75 mg, se observa a granulação total de sua lesão em 6 semanas.*

***Palavras-chave**: Pé Diabético; Diabetes Mellitus; Heberprot-p®; Insuficiência Arterial Crônica; Úlcera; Bactérias; Amputação; Pulso Periférico; Insuficiência Renal; Necrose; Fator de Crescimento; Crescimento Epidérmico; Nefropatia Diabética.*

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## INTRODUCTION

It is known that Diabetic Nephropathy is conditioned by a set of vascular and glomerular degenerative changes in close relationship with the patient's metabolic control and the time of evolution of Diabetes Mellitus. This is what Murphree and their collaborators say. (1)

Diabetic foot is a complication that is related to high morbidity, mortality, high costs, and a reduction in quality of life. It can cause significant disabilities and, if the patient is not properly monitored and managed incorrectly, can lead to a negative outcome that could include amputation of the foot or leg. (2)

The Pan American Health Organization (PAHO) and the World Health Organization (WHO) aim to stimulate and support the adoption of effective measures for the surveillance, prevention, and control of Diabetes Mellitus and its complications, particularly in low- and medium-income countries. (3)

In Cuba, the Center for Genetic Engineering and Biotechnology (CIGB), part of the scientific hub in the country's capital, has created the Recombinant Human Epidermal Growth Factor through the medicine Heberprot-P®. This innovative product, the only one of its kind in the world, has transformed surgical approaches to treating diabetic foot ulcers and offers a variety of therapeutic options for these patients, significantly improving their quality of life. (4)

For this reason, this clinical case shows the effectiveness of using Heberprot-p® in treating diabetic foot.

## PATIENT OR CASE STUDY INFORMATION

A clinical case is presented of a 69-year-old black female patient with a history of hypertension, type I diabetes mellitus, and renal failure on dialysis. He has a residual lesion on his right foot as a result of several debridements during the 6 years since his injury, measuring 20 $cm^2$ that affected the plantar region and the dorsum of his foot, abundant chocolatey purulent discharge characteristic of an enterobacterium, accompanied by stench with necrosis.

The inflammatory signs reached up to the middle third of the leg, with peripheral pulses present in both extremities, which indicates that tissue necrosis is due to the pathogenicity of the bacteria and not due to a vascular cause. At the time of the evaluation, the patient was admitted to intensive care at the Salvador Allende Hospital.

## CLINICAL FINDINGS OF THE CASE STUDY

The complementary examinations offered the following results:

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**Table 1.** Results of the complementary examinations.

| Complementary exams | Results |
|---|---|
| Electrocardiogram (ECG) | Sinus tachycardia |
| Chest X-ray | Normal |
| AP right foot X-ray | Signs of osteomyelitis in all fingers |
| Ionogram and Gasometry | Na 12mmol/l, Cl 102 mmol/l, K 6 mmol/l, Ca 1.10 mmol/L. PO 291 mmhg, PCO2 32 mmhg, PH 7.30, HCO-3 26 mmol/l, EB -2.5 |
| Leukogram | 23 x 109 $mm^3$, polymorphic |
| Hemoglobin | 7.5 g/dl |
| Lymphocytes | Lymphocytes 15% |
| Polymorphs | 95% |
| Gasometry | PO 291 mmhg , PCO2 32 mmhg, PH 7.47, HCO-3 26 mmol/l, EB -2.5 mmol/l |
| Erythrocyte sedimentation rate | 100mm/h |
| Blood glucose | 15.5 mmol/l |
| Creatinine | 500 mmol/l |
| Transaminase glutamic oxalacetic (TGO) | 60U/L |
| Glutamic pyruvic transaminase (GPT) | 45U/L |
| C Reactive Protein | 0.3 mg/ dL |
| Lactic acid | 3[mmol/l |
| Procalcitonin | 10ng/ml |
| Abdominal Ultrasound | Increased hepatic echogenicity, a slight increase in size, kidneys with good cortico-medullary relationship, rest normal. |
| Culture of purulent secretions from the foot | Staphylococcus is sensitive only to Piperacillin with Tazobactan. |
| Creatinine clearance | 133.97ml/min |
| Right foot X-ray | Signs of osteomyelitis in all fingers |

## CALENDAR

| Events | Dates |
|---|---|
| Comprehensive evaluation of the patient in intensive care | 10/05/2022 |
| Amputation transmetatarsal | 10/7/2022 |
| Surgical Debridement | 10/11/2022 |
| Surgical Debridement | 10/17/2022 |

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| | |
|---|---|
| Initiation of treatment with Heberprot P | 10/24/2022 |
| 10 doses of Heberprot P | 01/02/2023 |
| 16 doses of Heberprot P | 02/13/2023 |

## DIAGNOSTIC EVALUATION

The patient presents a mucous skin paleness characteristic of anemia caused by renal failure due to Erythropoietin deficiency. Characteristic scratching lesions were also due to the accumulation of urate, bilateral edema that was more pronounced in the right leg, residual injury and other signs already explained previously, and tissue damage that occupied nearly 80% of the foot. The severe infection caused shortness of breath because it had spread throughout his body, the inflammatory signs reaching up to the middle third of his leg.

During the vascular physical examination, peripheral pulses were present in both extremities, which indicates that tissue necrosis is due to the pathogenicity of the bacteria and not due to a vascular cause. With all these conditions, she was evaluated in hospital services in three countries, where they indicated limb amputation as the only therapeutic option. Urgent studies are indicated to evaluate the condition and act depending on the findings.

## THERAPEUTIC INTERVENTION

The patient is taken to the emergency operating room, where post-metatarsal amputation is performed with a wedge towards the dorsum of the foot and plantar region. Then he went to the operating room two more times, giving local anesthesia where the objective was to eliminate the entire focus of infection and area of necrosis, control his infection, and stabilize his metabolic state.

**Figure 1**. Start of Treatment

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**Applied Treatment.**

Antimicrobial treatment was started with Piperacillin + Tazobactam at a renal dose that lasted 14 days. After the injury was prepared, his general condition was much better, reaching a hemoglobin level of 10.8 g. Treatment is started with Heberprot-p® 75 mg (Recombinant Human Epidermal Growth Factor) three times a week, 2 hours before hemodialysis, to minimize adverse events and achieve better use of the product.
In a patient with Wagner Grade V and according to Mac Cook's Cuban classification of diabetic foot, an infested ischemic diabetic foot, total granulation of her lesion was achieved after 6 weeks.

**Figure 2**. Ten application doses of Heberprot

## MONITORING AND RESULTS

The patient improved in her general condition when she began treatment with Heberprot-P®, whose active ingredient is EFG. Recombinant human growth factor does not negatively influence the kidney function of type 2 diabetic patients with diabetic foot ulcers. After eight weeks of treatment with said product, the patient's kidney function improved.

Monitoring is the most appropriate method to prevent and/or slow the disease's progressive evolution and achieve adequate metabolic control. This can be achieved by acting on other factors that influence the progression, such as high blood pressure and albuminuria, smoking, and being overweight. [5]

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## DISCUSSION

It is known that Diabetic Nephropathy affects 25-40% of diabetic patients and is a marker of morbidity and mortality. Complications related to renal failure present in these patients become more relevant as glomerular filtration decreases. [6]

Epidermal Growth Factor is a peptide that promotes cell growth, proliferation, differentiation, and survival through the ligand with its receptor (EGFR) on the cell surface. [7]

As far as the authors could review, few published studies were found related to the effect of Heberprot-P® on kidney function, but the works refer to the solution that growth factors have on the kidney. The findings obtained in the present case study coincide with those reported by Flaquer and collaborators [8], who discussed the relationship between growth factors and renal regeneration, suggesting that tubular epithelial cells that survive damage secrete EGF that interact with resident cells and with renal and extrarenal stem cells, accelerating tubular repair mechanisms.

Heberprot-P® is a new medication prescribed for diabetic foot ulcers based on recombinant human growth factor through intralesional infiltration directly into the wound site. It is a product that accelerates the healing of deep, neuropathic, or neuro-ischemic ulcers. It is very useful in advanced stages with a high risk of amputation. Its proven preclinical safety, active pharmaceutical ingredient, and therapeutic benefits for this complex disease justify its clinical application. [9]

There is a contradiction about the role that recombinant human epidermal growth factor plays in the development of ERD. According to Flaquer et al., recombinant human epidermal growth factor is involved in the progression of kidney damage. [8-11]

In the patient in the present study, HbA1c values decreased, which is considered a positive result since it has been shown that optimal glycemic control is associated with partial remission of hyperfiltration and initial glomerular hypertrophy.

This study coincides with those carried out by the authors Yanes Quesada M. et al. [12], Campos Acosta et al. [12], Alcázar R., and Albalate M. [13], who report that after the patients were treated with Heberprot P, renal function improved due to its cytoprotective nature, as happened in this patient, who also achieved 100% granulation of his injury.

## PATIENT PERSPECTIVE

The patient declares a noticeable improvement. At the end of the study, a comprehensive assessment with the endocrinologist and the angiologist demonstrated no dependency relationship between the duration of diabetes and the degree of renal function, nor was the relationship between initial metabolic control and the degree of function significant.

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**CONFLICTS OF INTEREST**

No conflicts of interest are declared.

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# LETTER OF AUTHORIZATION FOR PUBLICATION AND DISTRIBUTION

To the editorial committee of the Medical and Life Sciences Journal

Article Title: COMPLEX DIABETIC FOOT ULCER IN PATIENT WITH DIABETIC NEPHROPATHY. CASE REPORT

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The authors of this work undertake to comply with the following standards:

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2. All authors reviewed the final version of the work and approved the publication in the **Journal of Medical and Life Sciences**.

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7. The authors declare that the protocols have been followed to protect the informants' data, prior informed consent, and compliance with the other ethical principles of scientific research and bioethics approved by their institution's ethics committee.

8. There is no conflict of interest.

9. I have limited all references to the Vancouver style and have not committed plagiarism.

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**Author contribution**: All authors participated in all stages.

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