ORIGINAL ARTICLE

Malnutrition in type 2 diabetic patients does not affect healing of foot ulcers

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Abstract

Aim Protein–energy malnutrition is known to be involved in wound healing. While wound healing in patients with diabetic foot ulcers (DFU) is a complex and multifactorial process, the role of malnutrition in this case has rarely been explored. The objective of this study was to determine whether the nutritional status of diabetic patients influences the healing of DFU.

Methods 48 patients were included in this prospective, single-center study. All patients with comorbidities or factors involving malnutrition or influencing biological measurements were excluded. Patients were followed up for 24 weeks.

Results The malnutrition rate was 29.2% at baseline and 25.6% at the end of the study. The difference was not significant. Of the 35 patients with wound healing, 29% were undernourished at inclusion and 17% at the end of the study. Of the 12 patients without wound healing, 50% were undernourished at inclusion, and 42% at the end of the study. These differences were not significant. Rate and speed of wound healing were not associated with malnutrition at inclusion. 15% of patients without malnutrition at baseline had final malnutrition.

Conclusion We demonstrated that wound healing was not affected by the initial presence of malnutrition. In our study, there is no evidence to support nutritional intervention to improve wound healing in diabetic patients. Nevertheless, malnutrition is responsible for an increase in morbidity and mortality and it is essential to identify malnutrition systematically for all patients with DFU, initially and during follow-up to treat it quickly and efficiently.

Keywords Diabetic foot ulcer · Malnutrition · Type 2 diabetes · Healing

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Introduction

Protein–energy malnutrition is a state of energy and protein deficiency which is mainly responsible for muscle loss and the resulting functional consequences [1]. Protein–energy malnutrition is common in hospitals, with a prevalence of 20–40% in hospitalized patients [2] and 30–50% in the hospitalized or institutionalized elderly population [3].

Malnutrition is responsible for an increase in morbidity and mortality. A study of 455 hospitalized patients found an increased risk of mortality of 72% at 1 year for patients with serum albumin < 35 g/L and 73% for those with a mid-upper arm circumference of less than 28 cm [4]. In another study, the hospital mortality rate of undernourished patients was 7% versus 1.5% in patients who were not undernourished [5].

Malnutrition is accompanied by an increase in infection, which has been reported at 19% of undernourished patients but only 10% of other patients [6].

Malnutrition is also one of the factors involved in the occurrence of bedsores and wounds. It slows the healing rate of wounds and increases severity. It has been shown that more severe malnutrition leads to more wounds and more severe bedsores [7].

Malnutrition increases health costs. Undernourished patients incur a 24% increase in costs, and the risk of re-hospitalization increases by 60% in cases of malnutrition [8].

Diabetic foot ulcer (DFU) is defined as the presence of ulceration, infection or destruction of deep tissue in a diabetic patients with secondary neuropathy or arterial disease [9].

The prevalence of DFU is in the range of 1.8–7.4% [10]. It is estimated that 15–25% of diabetic patients will experience a foot wound during their lifetime [11], with a 50–70% risk of recurrence within 5 years [10]. In France, incidence of DFU is estimated at 2.5% per year, which means 40,000–80,000 new cases [11].

The presence of foot ulcers in diabetic individuals is a marker of poor prognosis in terms of morbidity, mortality and quality of life. Accordingly, patients with diabetic foot ulcers are at higher risk of premature death, fatal myocardial infarction and fatal stroke [12].

Even though malnutrition is more common in the diabetic population, plays a negative role in wound healing and is responsible for increased morbidity and mortality, the link between malnutrition and DFU has rarely been studied. One study showed that the surface of DFU was larger in undernourished patients with arterial disease [13]. It has also been shown that wounds are generally deeper and more severe in undernourished patients [14]. One study evaluating the possible benefits of nutritional supplementation on diabetic foot ulcers was unable to demonstrate an improved rate of wound healing in patients receiving nutritional supplementation [15]. Another study investigated whether supplementation with arginine, glutamine* and β-hydroxy-β-methylbutyrate might improve the healing of foot ulcers in individuals with diabetes: no difference was observed in non-ischaemic patients or those with normal albumin. However, healing times did improve in patients with a risk of poor limb perfusion and/or low albumin levels [16]. Indeed, this study suggests that certain types of nutritional supplementation may be advantageous in a high-risk subgroup of patients with DFU. In any case, research centered on wound healing is so complex that it can pose major methodological problems [15], which is perhaps the reason there are so few studies in this field. As DFU is a major complication of diabetes which is associated with a high level of morbidity and mortality, it is important to clarify the effect that malnutrition may have on wound healing.

The objective of this study was, therefore, to determine whether the nutritional status of diabetic patients could influence the healing of DFU.

Materials and methods

This prospective, single-center, routine care study was carried out in the Department of Endocrinology, Diabetes and Metabolic Disorders of the University Hospital of Dijon. Our regional ethics committee approved this monocentric study. Written informed consent was obtained for all patients included in the study.

We included 48 patients between November 2013 and December 2016. They were followed over a period of 24 weeks with a maximum of eight visits if the DFU was not yet healed.

The inclusion criteria were as follows: patient older than 18 years, diabetic type 1 or 2. The wound had to be located on a toe or the plantar or dorsal surfaces of the foot, present for 1–24 months and presenting no clinical signs of infection according to the International Working Group on the Diabetic Foot.

The exclusion criteria were: progressive cancer, severe chronic renal failure (creatinine clearance < 30 mL/min), severe respiratory failure, terminal heart failure, severe liver impairment, immunodeficiency (immunosuppressive therapy, long-term corticosteroid therapy, condition responsible for immunosuppression), nephrotic syndrome (hypoalbuminemia), inflammatory syndrome characterized by CRP > 15 mg/L, alcohol consumption of more than four glasses per day, systemic infection not controlled by antibiotics, ulcer with clinical signs of infection, Charcot foot, wound on amputation, ankle or leg wound, patient participating or planning to participate in another clinical trial, or severe illness with a poor short-term prognosis.

All conditions that could potentially interfere with the determination of biological parameters of malnutrition and wounds resulting from particular situations (Charcot foot, amputation) were among the exclusion criteria to limit confounding factors involved in wound healing.

Malnutrition is defined at baseline and at the end of the study by the 2003 and 2007 Haute Autorité de Santé (HAS) criteria (ESM Appendices 1A and 1B). Weight, height and BMI were collected during the initial visit. Albumin levels, prealbumin levels and CRP were assayed according to standard measures. Patients diagnosed as malnourished met with a nutritionist who dispensed dietary advice systematically. Oral nutritional supplementation was prescribed if necessary. Undernourished patients were managed according to the 2007 Haute Autorité de Santé (HAS) criteria (ESM Appendix 1C).

The initial size of the DFU after debridement was measured with a tracing paper in order to calculate the surface of the ulcer.

The appearance of the lesion, the local care that was used, prescriptions for antibiotic therapy and hospital

discharge were recorded. In case of multiple wounds, the largest wound was chosen for follow-up. Clinical data were also collected, including type of diabetes, duration, complications and cardiovascular risk factors.

Each patient was seen again at 2, 4, 8, 12, 16, 20 and 24 weeks after inclusion in the study, unless wound healing was achieved. In case of healing, biological data were collected (albumin, pre-albumin and CRP levels) to identify whether the patient remained undernourished at the end of follow-up or not.

The data are expressed as an average ± standard deviation. A mixed linear model and a Kruskal–Wallis test were used to analyze statistical data. The univariate and multivariate analyses were done with a logistic regression test. A result is significant when $p < 0.05$.

Results

Characteristics of study population

Patient characteristics are shown in Table 1.

The patients ($n = 48$) were predominantly men (73%) with type 2 diabetes (98%). The average glycated haemoglobin was $8.2 \pm 2.1\%$ and average BMI was 30.6 ± 5.4 kg/m².

Among the potential diabetes complications related to the presence of a foot wound, diabetic neuropathy was reported in 96% of patients and peripheral arterial disease (PAD) in 35%. The ulcers were most often neuropathic (31/48, 64.6%), followed by neuroischaemic (15/48, 31.2%) and ischaemic (2/48, 4.2%).

The DFU were predominantly on the soles of the feet (40%) and on the toes (33%).

At inclusion, 40% of patients were already on antibiotic therapy for a DFU.

Mean CRP was 6.3 ± 4.3 mg/L, and eGFR was in average 87.4 ± 33.4 mL/min/1.73m². Serum albumin was 34.8 ± 4.9 g/L, and prealbumin was 0.24 ± 0.06 g/L.

Does nutritional status improve during the study?

The rate of malnutrition at baseline was 29.2% ($n = 14$). Five patients (10.4%) were severely undernourished. At the end of follow-up, 25.6% of patients ($n = 11$) were undernourished and two were severely undernourished. Although the difference is not significant, the rate of malnutrition declined during the study.

Of the 14 initially undernourished patients, six were no longer undernourished at the end of the study (43%), six were still undernourished (43%) and for two patients the final data on malnutrition were not available. Five of the 11 undernourished patients at the end of the study were not initially undernourished, which means 45% of the patients

undernourished at the end of the study were not undernourished at inclusion.

Initial malnutrition does not influence healing rate, healing time or changes in wound size

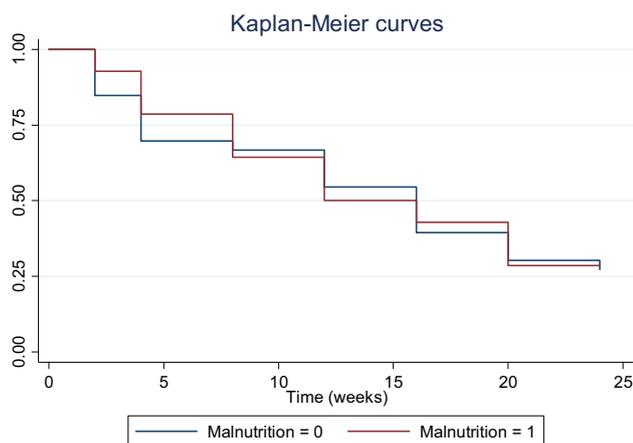The healing rate was not significantly different whether the patients were malnourished (71.5%) or not (73.5%) at

Table 1 Study population characteristics

	$N = 48$
Age	67 ± 10.3
Male sex, n (%)	35 (73)
Diabetes lifespan (years)	16.4 ± 9.4
Weight (kg)	91.7 ± 16.6
BMI (kg/m²)	30.6 ± 5.4
Serum albumin T0 (g/L)	34.8 ± 4.9
Prealbumin T0 (g/L)	0.24 ± 0.06
Creatinine (µmol/L)	92.6 ± 35
eGFR (mL/min/1.73m²)	87.4 ± 33.4
Blood glucose level (g/L)	1.32 ± 0.57
HbA1c (%)	8.2 ± 2.1
CRP T0 (mg/L)	6.3 ± 4.3
Malnutrition at inclusion, n (%)	14/48 (29.2)
Severe malnutrition, n (%)	5/48 (10.4)
Final malnutrition, n (%)	11/43 (25.6)
Severe malnutrition, n (%)	2/43 (4.7)
Retinopathy, n (%)	23 (49)
Heart disease, n (%)	20 (42)
Nephropathy, n (%)	30 (63)
Neuropathy, n (%)	46 (96)
Peripheral arterial disease, n (%)	17 (35)
DFU location	
Sole of the foot (%)	40
Back of the foot (%)	4
Toes (%)	33
Lateral edges of the feet (%)	13
Heel (%)	10
Antibiotic therapy at inclusion, n (%)	19 (40)
Wound area over time (cm²)	
At inclusion	3.5 ± 6.21
2 weeks	2.47 ± 5.34
4 weeks	2.67 ± 5.20
8 weeks	2.14 ± 4.19
12 weeks	1.67 ± 3.06
16 weeks	1.73 ± 3.22
20 weeks	2.73 ± 4.80
24 weeks	2.73 ± 4.27
Wound healing, n (%)	35 (72.9)
Patients with malnutrition at inclusion, n (%)	10 (71.5)
Patients without malnutrition at inclusion, n (%)	25 (73.5)

Fig. 1 Healing time according to the state of malnutrition at baseline (0: no malnutrition, 1: presence of malnutrition)

baseline, even if the rate is slightly higher in patients without malnutrition at baseline.

The average duration of healing was 10.5 weeks and was not significantly different in patients with or without malnutrition at baseline (Fig. 1).

The surface area of the wound was independently and negatively associated with healing time. Antibiotic therapy at baseline and malnutrition were not associated with changes in the wound surface (data not shown). Other models which accounted for infection, hospital discharge or creatinine clearance did not show any significant association with changes in the wound surface.

Does evolution of nutritional status during follow-up influence wound healing?

Of the 35 patients whose ulcer healed during the study period, 29% were initially undernourished and 17% were still undernourished at the end of the study.

Of the 12 patients whose ulcer did not heal, 50% were initially undernourished and 42% were still undernourished at the end of the study.

The malnutrition rates at the beginning and the end of the study were not significantly different for healed and unhealed patients, even if nutritional status during follow-up was better in healed patients (Fig. 2).

Discussion

In this study, we found that the presence of malnutrition at baseline of DFU management had no influence on wound healing, and, therefore, there is no evidence to support the claim that nutritional intervention improves wound healing in diabetic patients.
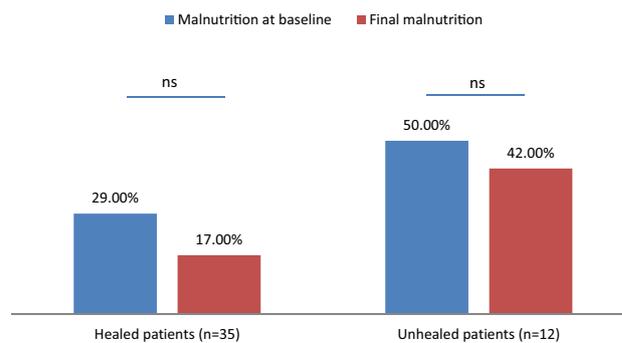
Fig. 2 Malnutrition at beginning and end of study in healed and unhealed patients

Nutrition in DFU is a challenging topic seeing as the existing general recommendations are not based on robust data. A Cochrane review has underlined the lack of evidence available to support nutritional intervention for DFU [17]. As wound healing is a complex process, studies evaluating the impact of malnutrition on the healing of DFU encounter major issues with methodology, which may explain why there are so few studies in this domain. We show in this study, for the first time, that malnutrition at baseline has no negative effect on wound healing.

The prevalence of malnutrition was high in our study (29.2% at baseline). A previous French study reported a prevalence of 15.2% in 33 diabetic inpatients without DFU, other major comorbidities or uncontrolled infection [18]. Malnutrition was significantly less prevalent in inpatients that did not have DFU than in inpatients that did.

In a 2004 study of 53 patients older than 60 years with DFU, the malnutrition rate was 32% [15]. The authors used inclusion criteria and parameters to define malnutrition which were comparable to ours, which may explain the similar rates. A French study from 2010 found a malnutrition rate of 45% in 54 patients with DFU, averaging 64.7 years old and hospitalized for ulcer management [13]. The malnutrition criteria were the same as ours, but all the patients were hospitalized and the exclusion criteria were not similar to ours. Behague et al. [14] found a malnutrition rate of 65% among 65 diabetic patients with DFU. However, there were no exclusion criteria and infected DFU were included, which likely explains the higher rate of malnutrition. The rate of malnutrition observed in our study (29.2%) is consistent with the literature.

Though we observed a decrease in malnutrition from 29.2 to 25.6% over the course of the study, the difference is not statistically significant. It should be noted that 43% ($n = 6$) of patients undernourished at inclusion were not malnourished at the end of the study, and 15% ($n = 5$) of patients who were not malnourished at baseline were malnourished at the end of the study. The management of malnutrition

was, therefore, effective in nearly half of the initially undernourished patients. The persistence of malnutrition in 43% ($n=6$) of cases may be the result of non-adherence to nutritional recommendations and oral nutritional supplementation or by worsening of wound during the study. This result highlights the difficulty of correcting malnutrition for our study population.

The onset of malnutrition may be explained by a worsening of the wound during the study, particularly if the wound became infected. Among the 11 patients with final malnutrition, 5 (14%) were not undernourished at inclusion. While this particular result may partially explain the lack of association between baseline malnutrition and wound healing, it points to the importance of screening for malnutrition during patient follow-up and not only at the beginning of wound management.

The rate of malnutrition dropped from 29 to 17% in patients whose wound healed during follow-up. The difference is not significant, but it is a little more pronounced than in patients who did not heal during follow-up (50–42%). The difference between malnutrition at baseline in patient with or without healing (29 vs 50%), even it is not significant, underlines the fact that nutritional status may play a role in the healing process.

Undernourished diabetic patients have been shown to suffer from deeper, more severe [19] and more extensive [13] DFU than patients without malnutrition. One study showed that systematic arginine, glutamine and β-hydroxy-β-methylbutyrate supplementation had no benefit on wound healing in diabetic patients with DFU [16]. In contrast, supplementation was found to improve healing in patients with serum albumin < 40 g/L. Our data can be considered in line with this study because patients were screened for malnutrition and provided with dietary follow-up and oral nutritional supplementation if necessary. However, Armstrong et al. [16] did not assess nutritional status at the beginning and at the end of the study and did not investigate the impact of initial nutritional status on wound healing.

We also demonstrated that the healing rate was on average 72.9% after 24 weeks of follow-up.

Armstrong et al. [16] found a healing rate of 50.8% in 61 undernourished diabetic patients who received oral supplementation with arginine, glutamine and β-hydroxy-β-methylbutyrate. This study, however, used a definition of malnutrition different from ours, since patients with albumin < 40 g/L were considered undernourished. In another study [15], healing rate at 6 months was 50% in patients without malnutrition and 23.5% in patients with malnutrition at baseline, but this difference was not significant. The wound healing rate in patients with malnutrition in our study was higher than in these studies.

The number of patients included in our study ($n=48$) is low, negatively affecting statistical power. Still, it should be noted that we were careful to exclude all patients with comorbidities, inflammatory syndrome or any clinical sign of infection that may have affected nutritional status. However, we chose to retain patients taking antibiotic treatment if there was no sign of infection. Antibiotic treatment may be a confusion bias, but it was not associated with wound healing in multivariate analysis. In subgroup analysis, the healing rate and the average duration of healing were not significantly different in patients taking antibiotics at inclusion. As infection is a frequent complication of DFU and patients with DFU are usually prescribed antibiotic treatment, we consider that our study reflects a "real life" situation.

These elements reflect the challenges of studying diabetic patients with DFU. Our study's lack of statistical significance may also be explained by the heterogeneity of diabetic patients and the various factors involved in healing (hospital discharge, tissue perfusion and glycaemia levels).

In addition, it is not possible to establish a control group who receives no treatment for malnutrition for ethical reasons, which limits the ability to make comparisons.

In the current study, we demonstrate that malnutrition at the initial consultation for DFU treatment was not associated with wound healing. In addition, we found no evidence that nutritional intervention improves wound healing in diabetic patients.

Nevertheless, we have shown that the prevalence of malnutrition is high in patients with DFU and is difficult to improve. We have also shown that 15% of patients went from being not malnourished at baseline to being malnourished at the end of the study. Because malnutrition is responsible for an increase in morbidity and mortality, it is essential to screen for malnutrition in a systematic way for all patients with DFU both at the beginning of wound management and during follow-up. Doing so would allow the care team to treat malnutrition more quickly and effectively.

Compliance with ethical standards

Conflict of interest All authors have nothing to disclose.

Research involving human and/or animal rights All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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