

# The Effect of Routine Immunonutrition Support on Nutritional Biomarkers and Wound Size in Hospitalized Diabetic Foot Ulcer Patients: A Prospective Cohort Study

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## ABSTRACT

**Objective:** This study aimed to evaluate the association between routine clinical administration of an oral immunonutrition supplement containing arginine, omega-3 fatty acids, and RNA and short-term changes in nutritional biomarkers and wound size in hospitalized patients with DFU.

**Materials and Methods:** This prospective cohort study included 72 adult patients hospitalized with DFU. Patients were followed for 30 days. Patients with normal renal function received an oral immunonutrition supplement (237 mL providing 18 g protein, 4.3 g arginine, 1.4 g omega-3 fatty acids, and 0.43 g RNA) twice daily for 30 days (intervention group), whereas patients with elevated renal parameters did not receive supplementation (control group). Serum albumin, total protein, and creatinine levels were obtained from the hospital information system. Ulcer size was measured at baseline and on day 30, and ulcers were classified according to the Wagner classification system.

**Results:** Seventy-two patients were included; 36.9% (n = 24) were female and the mean age was 65.1 ± 9.2 years. The mean daily dietary protein intake was 95 ± 5.9 g. Oral immunonutrition supplementation was significantly associated with higher serum albumin and total protein levels on day 30 and with greater increases in these biomarkers during follow-up ( $p < 0.001$  for all comparisons). No significant difference in Wagner ulcer stage was detected between groups ( $p > 0.05$ ). However, ulcer length reduction was significantly greater in the intervention group ( $p = 0.008$ ).

**Conclusion:** Routine administration of an oral immunonutrition supplement containing arginine, omega-3 fatty acids, and RNA was associated with significant improvements in serum albumin and total protein levels in hospitalized patients with DFU.

**Keywords:** Diabetic foot ulcer, albumin, total protein, immunonutrition

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## INTRODUCTION

Diabetic foot ulceration (DFU) is one of the most common and debilitating complications of diabetes mellitus (DM). The lifetime incidence of DFU in individuals with DM has been reported to be as high as 25%. Diabetic foot ulceration represents a major public health concern due to its association with impaired quality of life, high recurrence rates, increased risk of amputation, and elevated mortality (1–3).

The management of DFU is often complex and costly, frequently requiring prolonged hospitalization and multidisciplinary treatment approaches. In the United States, approximately one-third of the direct healthcare costs associated with DM and its complications are attributed to diabetic foot ulcers (4). With the global prevalence of DM increasing rapidly, the incidence of DFU is also expected to increase further in the coming years.

Effective prevention and management of DFU require careful clinical evaluation and comprehensive treatment strategies. Patient education, optimal metabolic control, identification of risk factors, and early intervention are critical components in preventing DFU progression (3). Multidisciplinary management, including medical therapy, surgical intervention, infection control, vascular assessment, and nutritional support, is recommended to improve clinical outcomes (5).

Malnutrition is recognized as an important systemic factor affecting wound healing in chronic wounds such as DFU. Adequate nutritional support may improve immune response, reduce infection risk, and promote tissue repair, particularly in older adults. Monitoring nutritional biomarkers, such as serum albumin and prealbumin, may provide valuable information on the nutritional status of patients with chronic wounds (6,7).

The present study aimed to evaluate the association between routine clinical use of an oral immunonutrition supplement and changes in serum albumin and total protein levels, as well as wound measurements in hospitalized patients with DFU.

## MATERIALS AND METHODS

This study was designed as a prospective cohort study conducted between May 2023 and October 2023 at the Diabetic Foot Service of Hitit University Erol Olçok Training and Research Hospital. Adult patients hospitalized with a diagnosis of DFU who agreed to participate in the study were included. Ethical approval for the study was obtained from the Hitit University Faculty of Medicine Clinical Research Ethics

Committee on March 29, 2023, with decision no. 2023-44.

Within the routine clinical nutritional support protocol of the service, some patients received an oral immunonutrition supplement containing arginine, omega-3 fatty acids, and RNA based on their clinical condition and laboratory findings. Each 237 mL serving of the supplement contained 18 g of protein, 4.3 g arginine, 1.4 g omega-3 fatty acids, and 0.43 g RNA.

Patients with normal renal function parameters (urea and creatinine levels) received the supplement twice daily for 30 days as part of routine clinical care. Patients with elevated renal function parameters did not receive immunonutrition supplementation. Accordingly, patients were categorized into two cohorts: those receiving oral immunonutrition and those not receiving it.

Diabetic foot ulcers were classified according to the Wagner classification system. Daily dietary intake records were collected for 15 days, and average daily protein intake was calculated using the Turkish National Food Composition Database. Clinical data, including serum albumin, total protein, and creatinine levels, were obtained from the hospital information system. Ulcer measurements were performed at baseline and on day 30 using a sterile disposable ruler. No modifications were made to systemic or local treatment protocols routinely applied in the diabetic foot unit during the study period.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. Continuous variables were compared using the independent samples *t* test or the Mann-Whitney *U* test, depending on the distribution. Categorical variables were compared using the Pearson's chi-square test or Fisher's exact test when appropriate. Multivariate linear regression analysis was conducted to evaluate the association between immunonutrition supplementation and changes in serum albumin, total protein levels, and wound size, while accounting for potential confounding variables, including renal function parameters. A *p*-value < 0.05 was considered statistically significant.

## RESULTS

A total of 72 patients hospitalized with diabetic foot ulcers were included in the study and divided into the intervention group (*n* = 36) and the control group (*n* = 36). Among these patients, 36.9% (*n* = 24) were female, and the mean age was 65.1 ± 9.2 years. The mean daily dietary protein intake was 95 ± 5.9 g/day.

**Table 1.** Comparison of biochemical parameters between patients receiving and not receiving immunonutrition support.

Parameter, mean $\pm$ SD	Immunonutrition group (n = 36)	Control group (n = 36)	p-value
Mean serum albumin level on day 30 (g/dL)	3.5 $\pm$ 0.4	2.5 $\pm$ 0.5	<0.001
Mean total protein level on day 30 (g/dL)	6.9 $\pm$ 0.6	5.9 $\pm$ 0.7	<0.001
Mean change in serum albumin over 30 days (g/dL)	+0.8 $\pm$ 0.3	-0.4 $\pm$ 0.05	<0.001
Mean change in total protein over 30 days (g/dL)	+0.6 $\pm$ 0.5	-0.2 $\pm$ 0.01	<0.001

**Table 2.** Wagner classification distribution between the groups.

Wagner grade	Immunonutrition group (n = 36), n (%)	Control group (n = 36), n (%)
Grade 1	6 (16.7)	5 (13.9)
Grade 2	14 (38.9)	15 (41.7)
Grade 3	12 (33.3)	11 (30.6)
Grade 4	4 (11.1)	5 (13.9)

A statistically significant association was observed between the use of the oral immunonutrition supplementation and both serum albumin and total protein levels on day 30, as well as changes in these parameters during the 30-day follow-up period ( $p < 0.001$  for all comparisons) (Table 1).

On day 30, the mean serum albumin and total protein levels in the intervention group were 3.5  $\pm$  0.4 g/dL and 6.9  $\pm$  0.6 g/dL, respectively. In contrast, the control group had mean levels of 2.5  $\pm$  0.5 g/dL and 5.9  $\pm$  0.7 g/dL, respectively (Table 1).

During the 30-day follow-up period, serum albumin and total protein levels increased by 0.8  $\pm$  0.3 g/dL and 0.6  $\pm$  0.5 g/dL, respectively, in the intervention group. In the control group, these parameters decreased by 0.4  $\pm$  0.05 g/dL and 0.2  $\pm$  0.01 g/dL, respectively (Table 1).

No statistically significant difference was observed between the Wagner ulcer stages of the two groups ( $p > 0.05$ ) (Table 2). However, a statistically significant difference was found in ulcer length reduction between the groups ( $p = 0.008$ ) (Table 3).

Correlation analysis revealed significant correlations between

changes in serum albumin and total protein levels and dietary protein intake variables (Table 4).

## DISCUSSION

With the global increase in DM cases, inadequate long-term glycemic control in patients with DM causes damage to the distal microvasculature and eventually leads to the development of diabetic foot ulcers (8). Diabetic foot ulcers are one of the most important chronic complications in patients with DM, often requiring surgical intervention and imposing substantial morbidity and economic burden on patients (9).

Systemic factors play an important role in the wound-healing process in the management of chronic wounds. Diabetic foot ulcers generally begin with minor injuries that go unnoticed due to diabetic neuropathy, and the combination of immunological, vascular, nutritional, glycemic, and infectious factors may affect wound healing (9).

In this study, the association between routine immunonutrition support administered as part of routine clinical practice in our hospital and changes in serum albumin and total protein levels, as well as wound measurements, in patients with DFU was evaluated. The findings demonstrated a statistically significant association between changes in serum albumin and total protein levels and the reduction in ulcer length in patients receiving oral immunonutrition support.

Several studies have reported an inverse relationship between serum albumin level, an important indicator of nutritional status, and the risk of amputation in patients with DFU (10–12). It has also been stated that a decrease in albumin level may not only reflect nutritional status but may also be associated with the clinical severity of the disease, including infectious and inflammatory processes (13).

In conclusion, oral immunonutrition supplementation in hospitalized patients with DFU was associated with increased

**Table 3.** Comparison of ulcer size changes between the groups.

Ulcer measurement, mean $\pm$ SD	Immunonutrition group (n = 36)	Control group (n = 36)	p-value
Baseline ulcer length (cm)	4.2 $\pm$ 1.1	4.0 $\pm$ 1.2	0.62
Ulcer length at day 30 (cm)	2.9 $\pm$ 1.0	3.6 $\pm$ 1.1	0.5
Change in ulcer length (cm)	-1.3 $\pm$ 0.6	-0.4 $\pm$ 0.5	0.008

**Table 4.** Correlation analysis between changes in nutritional biomarkers and protein intake (n = 65).

Variable	30-day change in albumin	30-day change in total protein	Mean dietary protein intake, g/day	Mean enteral product protein intake, g/day
30-day change in albumin	1	$r = 0.701; p < 0.001$	$r = 0.392; p = 0.001$	$r = 0.797; p < 0.001$
30-day change in total protein	$r = 0.701; p < 0.001$	1	$r = 0.284; p = 0.022$	$r = 0.479; p < 0.001$
Mean dietary protein intake	$r = 0.392; p = 0.001$	$r = 0.284; p = 0.022$	1	$r = 0.272; p = 0.029$
Mean enteral product protein intake	$r = 0.797; p < 0.001$	$r = 0.479; p < 0.001$	$r = 0.272; p = 0.029$	1

$r$  = Pearson correlation coefficient.

serum albumin and total protein levels. In addition, a significant association was observed between oral immunonutrition supplementation and a reduction in ulcer length during the follow-up period. However, no statistically significant difference was found in ulcer stage between the two groups.

Larger prospective studies with longer follow-up periods are needed to further clarify the potential effects of immunonutrition support on wound healing in patients with DFU.

**Ethical Approval:** Ethical approval for the study was obtained from the Hitit University Faculty of Medicine Clinical Research Ethics Committee on March 29, 2023, with decision no. 2023-44.

**Informed Consent:** Informed consent was obtained from all 72 adult patients who agreed to participate in the study.

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