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Effect of Branched-Chain Amino Acids on Wound Healing in Patients with Diabetic Foot Ulcers

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Abstract

Introduction: Branched-Chain Amino Acids (BCAAs), which include leucine, isoleucine, and valine, have been demonstrated to promote wound healing and stimulate insulin production. Diabetic Foot Ulcers (DFUs) are a common complication in patients with poorly controlled diabetes mellitus. Although studies have investigated the associations of arginine, isoleucine, leucine, and threonine with wound healing in limb-threatening DFUs, the direct effects of BCAAs on healing in DFU patients remain underexplored. Therefore, this study evaluated the effects of BCAAs on nutritional status and wound healing outcomes in patients with DFUs.

Materials and Methods: This was a prospective, nonblinded, randomized controlled trial. A total of 16 eligible patients who were treated at the Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, between March 2019 and April 2022 were enrolled. Baseline assessments were performed at week 0, followed by subsequent evaluations at 8 and 14 weeks. All patients received standard wound care for the first 2 weeks, after which they received standard treatment with BCAA supplementation (Licure Suspension) for an additional 12 weeks. Blood tests were performed at 2 time points to determine the benefits of oral supplements. Wound images were captured during each visit.

Results: Upon the completion of the 12-week combined regimen of BCAA supplementation and standard wound care, an obvious reduction in wound size was observed in the study group ($P<0.05$). Although various nutritional laboratory parameters exhibited a tendency toward improvement, statistical significance was not achieved.

Conclusion: Our study findings highlight the beneficial effect of oral BCAA supplementation on wound healing in patients with DFUs, as evidenced by a significant reduction in wound area ($P<0.05$). Although no significant differences were observed in serum albumin, prealbumin, and transferrin values, our results underscore the potential of oral BCAA supplementation in enhancing wound healing. Further investigations involving longer observation periods and larger patient cohorts are required to obtain a more comprehensive understanding of the role of BCAAs in DFU healing.

Keywords: Branched-chain amino acids; Diabetic foot ulcers; DFU

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Introduction

Branched-Chain Amino Acids (BCAAs), including leucine, isoleucine, and valine, are essential nutrients. These amino acids play roles in the regulation of protein synthesis and promotion of anabolic pathways. This function is vital in mitigating cachexia, preventing or treating manifestations of hepatic encephalopathy, attenuating exercise-induced fatigue, promoting wound healing, and stimulating insulin production [1]. Under demanding conditions, such as sepsis, cancer, infections, burns, and trauma, BCAAs are oxidized, which limits their availability in tissues, thereby affecting protein synthesis mechanisms. Thus, BCCA supplementation is emerging as a nutritional strategy for the treatment of many diseases.

BCAAs have been reported to reduce protein loss, promote protein synthesis, and enhance the nutritional status of patients with hepatic illnesses. Thus, BCCAs have become a standard intervention in the treatment of chronic liver diseases, particularly liver cirrhosis and hepatic encephalopathy [2,3]. Additionally, studies have demonstrated that BCAAs yield significant improvements in sarcopenic parameters, including grip strength, 6-meter gait speed, and bioelectrical-impedance-analysis-derived skeletal mass index in patients with presarcopenia and sarcopenia [4-6]. Furthermore, several studies have shown that BCAAs promote nitrogen retention during bed rest [7]; augment the nutritional status of patients with burn injury, sepsis, and traumatic

brain injury [8,9]; and foster anabolic effects on proteins involved in skin wound healing [10].

Diabetic Foot Ulcers (DFUs) are a common complication in patients with Diabetes Mellitus (DM), which typically develop as a result of poor glycemic control, underlying neuropathy, peripheral vascular disease, or poor foot care. Notably, DFUs can lead to lower extremity amputations. A study identified an association between arginine, isoleucine, leucine, and threonine and the healing of limb-threatening DFUs [11]. However, the direct effects of BCAAs on the healing process among DFU patients remain relatively unexplored. This study evaluated the effects of BCAAs on the nutritional status and healing outcomes in patients with DFUs.

Materials and Methods

Study design

This is a prospective, nonblinded, randomized controlled trial, conducted in accordance with the Declaration of Helsinki. This clinical trial was approved by the Institutional Review Board (IRB) of our institute (IRB number 20200609D). All patients were enrolled after a detailed explanation of the study was provided to them and informed consent was obtained from them.

Inclusion and Exclusion criteria

The inclusion criteria for the study were as follows: Diagnosis of DM, either type 1 or type 2; age >20 years; DM medication use; and chronic leg ulcers (below the knee) since >4 weeks. Furthermore, the size of the wound was required to be between 1 and 36 cm^2, with a classification of grade 2 or lower according to the University of Texas Diabetic Wound Classification system. Additionally, the ulcer wound was required to be identified as a controlled infection wound by the treating physician following an evaluation of the local heat, swelling, erythema, pus, odor, and wound margins. Furthermore, the patient's ankle brachial index was required to be >0.40 or <0.40 if they had been previously treated with percutaneous transluminal angioplasty.

Patients were excluded if they had the following: Ulcers caused by poor arterial perfusion or venous insufficiency; osteomyelitis as the cause of the wound; poor DM control with HbA1c >10% or neutrophil count < 1000/μL; and persistent necrosis, pus, or fistula after debridement. Additionally, patients undergoing treatment with immunosuppressants, chemotherapy, radiation therapy, steroids, or oral protein supplements were not eligible for participation. Similarly, individuals with comorbidities such as connective tissue disease, maple syrup urine disease, isovaleric acidemia, and other disorders of BCAA metabolism were also excluded. Furthermore, those with a history of cerebrovascular accident, coronary artery disease, or myocardial infarction within 6 months before prior to enrollment as well as those simultaneously included in other clinical trials were not considered for this study. Moreover, female patients with positive pregnancy test results, those who were breastfeeding, or those unwilling to adhere to appropriate contraception methods were excluded.

Study procedure

The patients underwent assessments at baseline (week 0), followed by subsequent evaluations every 2 weeks. Additionally, the patients were subjected to laboratory assessments at weeks 0, 8, and 14. All patients received standard wound care during the initial 2 weeks and subsequently received standard treatment with Licure Suspension twice daily for an additional 12 weeks. The Licure Suspension contained vital BCAAs (4.0 g), including l-leucine (1.904 g), l-isoleucine (0.952 g), and l-valine (1.144 g). Blood tests-including tests for albumin, prealbumin, creatinine, BUN, Glu-AC, HbA1c, GOT (AST), GPT (ALT), CBC/DC, and transferrin - were performed for 9 patients at weeks 0 and 8 and for 8 patients at weeks 0 and 14. This approach allowed for a comparative analysis of the effects of oral supplements at different time points. Images of the wounds were captured during each patient visit. The study procedure is detailed in Figure 1. The standard wound treatment encompassed a range of moderate wound dressing strategies, including but not limited to Aquacel Ag, Aquacel Ag plus, and negative pressure wound treatment. No other oral clinical trial medication was included in this treatment regimen.

Statistical analysis

All data analyses were performed using SPSS version 17.0. The laboratory data derived from blood tests (albumin, prealbumin, HbA1c, and transferrin) and wound area measurements were analyzed using analysis of variance, with a P value of <0.05 considered statistically significant.

Results

Demographic characteristics

Between March 2019 and April 2022, a total of 16 eligible patients received treatment at Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan. All data pertaining to these 16 patients were analyzed. The baseline characteristics of these patients are presented in Table 1. Among the 16 patients who successfully completed the study, the mean age was 59.6 (40.6-76.5) years, and 68.8% were male. The mean Hemoglobin A1c (HbA1c) level of the 16 patients was 7.6% (5.6%-10%). Other baseline characteristics are listed in Table 1.

Nutritional status

Blood tests were conducted in 9 patients at weeks 0 and 8. We specifically compared the levels of albumin, prealbumin, transferrin, and HbA1c between the nutritional status and DM control groups. The results of this comparison are presented in Table 2. A trend toward an increase in laboratory parameters, including albumin, prealbumin, and transferrin levels, was observed. However, a downward trend in HbA1c levels was observed. However, none of these differences were statistically significant ($P>0.05$).

Blood tests were administered to 8 patients underwent at weeks 0 and 14. This facilitated a direct comparison of their albumin, prealbumin, transferrin, and HbA1c levels. The results of this comparison are summarized in Table 3. Notably, all variables exhibited an upward trend, including HbA1c. However, none of these associations were statistically significant.

Wound healing

The wounds of all patients were photographed during all visits for comparison. We the area of the wounds was measured, with an area of 0 cm^2 indicating complete wound healing. Notably, only one patient exhibited an increase in wound size at week 14 compared with weeks 0 and 8, from 3.75 to 5 cm^2. This outcome may be attributed to suboptimal pressure-relief management. Unrelieved pressure on the diabetic foot can cause tissue damage, leading to ulcerations, thereby contributing to the increase in the wound size.

A significantly reduction in wound area was observed among the patients ($P<0.05$), indicating an improved overall wound condition.

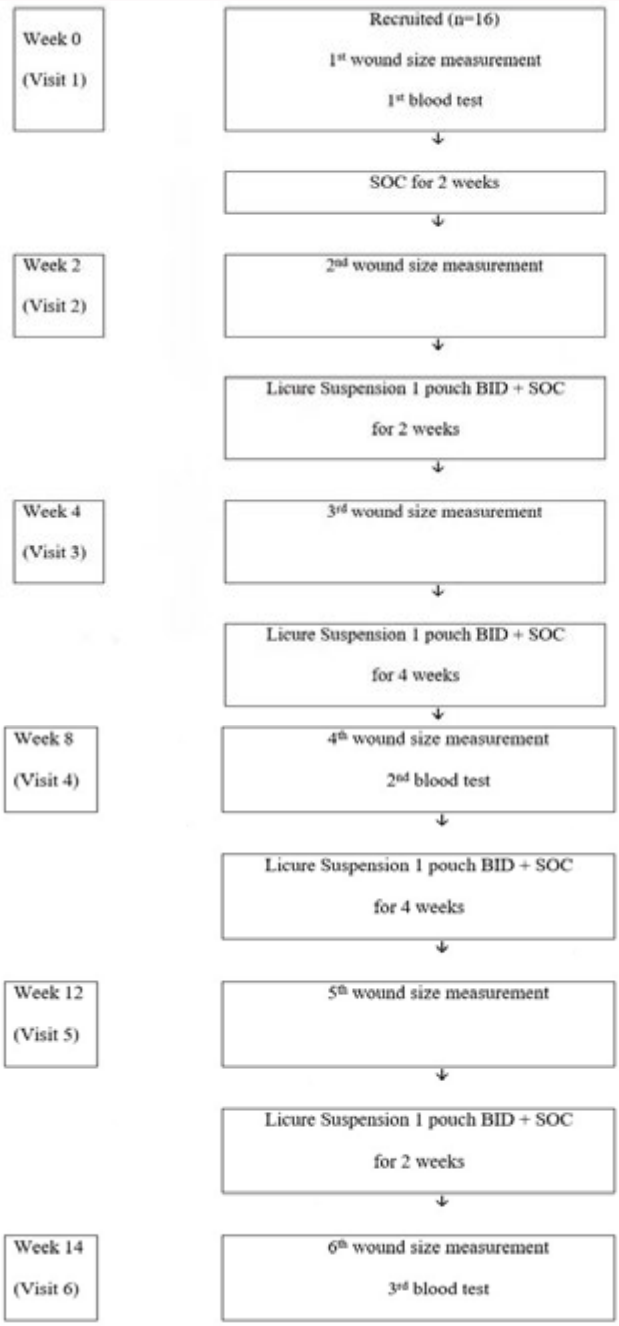

Figure 1: Flowchart of study procedure.

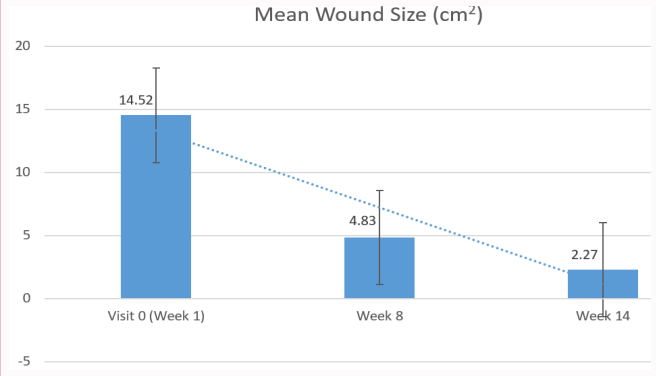

Figure 2: The trend toward a decrease in the mean wound size is illustrated.

Table 1: Baseline characteristics of study participants.

Characteristic	BCAA (n=16)
Age (year)	59.6 (40.6-76.5)
Male gender (%)	68.80%
Height (cm)	165.9 (155-176)
Weight (kg)	70.7 (49.3-100)
BMI (kg/cm²)	25.7 (18.3-40.4)
HTN (%)	25.00%
CAD (%)	18.80%
CKD (%)	25.00%
HLD (%)	31.30%
Type 2 DM (%)	100.00%
Hemoglobin A1C (%)	7.6 (5.6-10)
AST, IU/L	18.2 (11-39)
ALT, IU/L	19.3 (7-55)

Table 2: Levels of albumin, prealbumin, transferrin, and HbA1c at weeks 0 and 8.

N=9	Week 0	Week 8	*P* value
Prealbumin	24.244	27.756	0.08
Transferrin	4.146	4.214	0.668
Albumin	212.778	239.967	0.122
HbA1C	8.022	7.622	0.668

Table 3: Levels of albumin, prealbumin, transferrin, and HbA1c at weeks 0 and 14.

N=8	Week 0	Week 14	*P* value
Prealbumin	22.813	27.038	0.205
Transferrin	201.613	216.013	0.514
Albumin	3.871	4.071	0.305
HbA1C	7.85	7.838	0.989

The trend toward a decrease in the mean wound size is illustrated in Figure 2. The results revealed significant differences in wound size across the entire study period. We report the wound progression of 2 patients who were given BCAA supplements. The first case is that of a 63-year-old man with type II DM, who presented with a left fifth toe ulcer that had progressed from a rupture blister over the dorsal site. The patient underwent 3 debridement procedures and was regular at his outpatient clinic follow-ups. The images in Figure 3 illustrate the progressive improvement of his wound during the study period. The second case is that of a 57-year-old woman with a history of uncontrolled type II DM; a left diabetic foot opens wound s/p debridement, sequestrectomy, and a split-thickness skin graft; and a left tibial fracture s/p open reduction internal fixation. The patient also reported a chronic pressure ulcer wound at the left calcaneus region, accompanied by tendon rupture stemming from a previous splint insertion due to a tibial fracture, for which she received tendon repair and local flap reconstruction. She was consistently followed up at the outpatient thereafter. The images in Figure 4 illustrate the improvement of her wound during the study period.

Discussion

The present study demonstrated that patients with DM and

Figure 3: Progress of a 63-year-old man with type II DM and left fifth toe ulcer. The ulcer originated from a rupture blister located on the dorsal site of the foot. The patient underwent 3 debridement procedures as part of his treatment regimen and was regular in his outpatient clinic follow-ups. The images illustrate the wound healing progression during the study period.

Figure 4: Case of a 57-year-old woman with a history of uncontrolled type II DM; left diabetic foot open wound s/p debridement, sequestrectomy, a split-thickness skin graft; and left tibial fracture s/p open reduction internal fixation. The patient also had a chronic pressure ulcer wound at the left calcaneus region with tendon rupture, which originated from a previous splint insertion due to tibial fracture. The patient had undergone interventions such as tendon repair and local flap reconstruction. She remained committed to regular outpatient clinic follow-ups. The images illustrate the wound healing progression during the study period.

chronic foot ulcers exhibited increased levels of serum albumin, prealbumin, and transferrin after a 6- and 12-week BCAA supplementation regimen. These results suggest the potential efficacy of BCAA supplementation in the treatment of chronic foot ulcers in patients with DM. Notably, these 3 outcome measures are commonly believed to play vital roles in accelerating the wound healing process. Despite these encouraging trends, a comprehensive data analysis did not indicate significant differences in the measured laboratory parameters (albumin, prealbumin, and transferrin levels). One possible explanation for this lack of statistical significance is that the study period was relatively short, which may not have allowed sufficient time for substantial changes to manifest in these outcome measures. To observe significant increases in serum albumin, prealbumin, and transferrin levels, a longer period of BCAA supplementation may be required. Our results are consistent with those obtained in another study [12], which also reported a significant rise in mean plasma albumin concentration after a prolonged supplementation period of 6 months.

Regarding HbA1c levels, slight decreases were observed following 6 and 12 weeks of BCAA supplementation, although these reductions were not significant (P=0.668 and 0.989 for the 2 groups, respectively). This result implies that the HbA1c level remains unaffected by BCAA intake within a specific period. A similar conclusion was reached in another study [4], in which neither the HbA1c nor NH_3 levels were significantly altered after a 3-month BCAA supplementation regimen.

Our results demonstrated the beneficial effect of treatment with BCAAs for 6 and 12 weeks on wound healing. Among the 16 patients who completed the study, 5 achieved wound healing by week 8, and the other 6 achieved wound healing by week 14. In total, 11 of the 16 patients achieved complete wound healing by the end of the study. Most patients demonstrated a consistent reduction in wound areas throughout the study period, except for one patient, who experienced an increase in wound size at week 14, which was attributable to inadequate pressure-relief management. Because pressure equals the force divided by area, foot injury can arise due to a high force being concentrated in a small area, sustained pressure from wearing tight shoes over prolonged periods, or the intermittent and repetitive moderate stress that neuropathic patients experience with elevated foot pressure. To mitigate these risks, the use of pressure-relieving mattresses, footwear overlays, and foam leg troughs or wedges for heel elevation is crucial. The identification of at-risk patients and provision of adequate pressure relief can help prevent the increase

in the size of pressure ulcers. A study in 2022 reported that 18 of 24 wounds (75%) achieved complete closure after a 12-week treatment regimen. The average reduction in the wound surface area over 12 weeks was 96% ± 10%. The average time for wounds to fully close was reported to be 6.4 ± 2.5 weeks [13]. Another study highlighted that after 20 weeks of effective wound care, approximately 30.9% (95% CI 26.6-35.1) of diabetic neuropathic ulcers were completely healed. Similarly, after 12 weeks of effective care, approximately 24.2% (19.5-28.8) of neuropathic ulcers achieved complete healing.

Limitations

The present study has several limitations that must be addressed. First, the sample size was relatively small, with only 16 patients enrolled. This small sample size may have limited the statistical power of the study, potentially rendering it inadequate to detect differences in the endpoints between the groups. Moreover, despite observing an upward trend in serum levels of albumin, prealbumin, and transferrin with BCAA supplementation, we did not observe a significant superior response in these parameters. Furthermore, the study duration might also have influenced the outcomes. A longer period of BCAA supplementation might be necessary to observe significant differences in the measured values.

Conclusion

Although the levels of serum albumin, prealbumin, and transferrin did not significantly differ, oral supplementation with BCAAs was demonstrated to be beneficial in wound healing among patients with DFUs, as indicated by a significant decrease in wound area (P=0.046).

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