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Prompt Improvement of Venous Leg Ulcers by Oral Administration of Fish Compound Peptides in a Man with Liver Cirrhosis and Diabetes: A Case Report

Chao Xing Wang[1] and Yule Yue Wang[2*]

[1]*WCX Private Clinic of Changtai County, China*

[2]*Marine Biomedicine Center, Tekwon Genetic Technologies Ltd., Xiamen Biopharmaceutical Industrial Park, China*

***Correspondence to:** Yule Yue Wang, Marine Biomedicine Center, Tekwon Genetic Technologies Ltd., Xiamen Biopharmaceutical Industrial Park, China,E-mail: yuleyuewang@tekwon.com

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Abstract

We report a case of a 47-year-old man with venous leg ulcers coexisting with liver cirrhosis and diabetes. The patient had received standard wound care for 12 weeks, but the leg ulcers were still worsening. Oral administration of fish compound peptides was used to reduce local protein catabolism and promote granulation tissue formation. The healthy granulation tissue was observed in the second week of nutritional intervention. The ulcers were constricted at the end of the third week. After eight weeks, the ulcers were completely healed. The case study demonstrated the positive impact of nutritional intervention with fish compound peptides in venous leg ulcers healing.

Keywords: Chronic ulcer; Cirrhosis; Diabetes; Fish compound peptides; Nutrition intervention;Venous leg ulcer.

Introduction

Leg ulceration is a chronic condition affecting about 1-3% of the adult population. Venous leg ulcers (VLU) account for approximately 70% of all leg ulcers [1]. The main causes of VLU are venous hypertension, arterial insufficiency, diabetes, or a combination of these causes. Treatment modalities of VLU are either conservative or surgical. Conservative treatment involves local treatment and compression therapy. Surgical treatment of venous ulcers is based on correcting venous hypertension by vascular reconstruction and skin replacement [2]. In spite of the application of these evidence-based therapies, healing rates for venous leg ulcers still remain at ca. 50-60% after 12 weeks of treatment. Thus, a large number of ulcers are unhealed by this time, many patients suffer from leg ulceration for years, and those that heal often recur. Chronic VLU is hard to heal and requires a multipronged and interprofessional approach to care [3]. There is an obvious need to develop new treatments to improve healing rates.

Case Report

A 47-year-old gentleman presented to us with two venous ulcers on his left foot: 54 cm^2 (9 cm x 6 cm) and 15 cm^2 (5 cm x 3 cm) (Figure 1). He had long suffering with the associated pain and reduced mobility and had received standard wound care in a hospital for 12 weeks, but the VLU was still worsening. He became very distressed at the lack of improvement in his ulceration and has been repeatedly proposed amputation in that hospital, but he refused to do so. The ulcers were well defined with regular swollen borders and covered by a yellowish slough, with moderate exudation and malodor. Perilesional tenderness and pitting edema were observed. The patient was also diagnosed with type II diabetes, liver cirrhosis, ascites, hypertension, hypoalbuminemia, and proteinuria. Notably, his serum bilirubin was increased to 57.84 μmol/L (normal: 1.7~17.1 μmol/L), while his serum albumin was only 19.6 g/L (normal: 35~55 g/L). (Table 1), indicating the occurrence of severe malnutrition due to cirrhosis [4]. Therefore, it was proposed that besides conservative wound debridement and local wound care, the treatment plan should be mainly based on nutritional support. As we known, wound healing phase is extremely energy demanding and dependent on the nutritional substrates available [5]. Proteins play the most important role throughout the entire wound-healing process. A lack of protein decreases the synthesis of collagen, the proliferation of fibroblasts, and the

formation of new capillaries. Most of the wound-healing of VLU could be stuck in the inflammatory phase due to insufficient supply of protein nutrient (Figure 1 and Table 1).

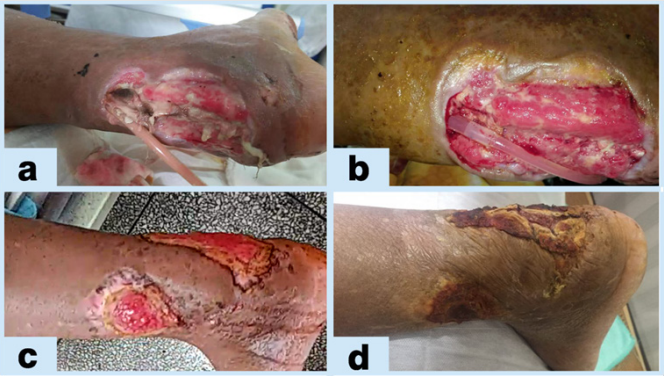

Figure 1. Stagewise pictures of the wound during intervention with orally administered FCP

- The malleolar ulcer at admission
- The malleolar ulcer after debridement and disinfection treatment with iodine solution
- Granulation tissue in wound bed after six weeks' nutrition intervention with FCP
- The ulcers were healed and epithelized in the eighth week.

Items	Result	Reference range
ALB ↓	19.62 g/L	35-55 g/L
HGB↓	108 g/L	120-160 g/L
PLT ↓	90 * 10^9/L	100-300 * 10^9/L
HDL-C ↓	0.42 mmol/L	1.14-1.91 mmol/L
LDL-C ↓	1.3 mmol/L	2.0-3.5 mmol/L
GLU ↑	7.78mmol/L	3.61-6.11 mmol/L
BUN↑	8.17 mmol/L	2.5-7.0 mmol/L
TBIL ↑	57.84 μmol/L	1.7-17.1 μmol/L
DBIL ↑	30.60 μmol/L	0-6 μmol/L
IBIL ↑	27.24 μmol/L	1.7-10.2 μmol/L
TBA ↑	38.10 μmol/L	0-10 μmol/L
PT ↑	14.10 s	10-14 s
INR↑	1.23	0.8-1.2
FIB ↑	4.53 g/L	2-4 g/L
FDP ↑	19.80 mg/L	0-5 mg/L
AT-III ↓	48.50 %	80-120 %
Urine test		
RBC ↑	55/μL	-
WBC ↑	32/μL	-

Table 1. Results of the biochemical examination upon admission

ALB: Albumin; HGB: Hemoglobin; PLT: Platelet; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; GLU: glucose; BUN: Blood urea nitrogen; TBIL: Total bilirubin; DBIL: Direct bilirubin; IBIL:Indirect bilirubin; TBA: Total bile acid; PT: Pro-thrombin time; INR: International normalized ratio; FIB: Fibrinogen; FDP: Fibrin degradation products; AT-III: Anti-thrombin-III; RBC: Red blood cell; WBC: White blood cell.

Hence, the aims of nutritional support in this case were to reduce the local protein catabolism, reduce the amount of slough and promote granulation tissue formation. Although high-protein oral nutritional supplement is essential for accelerating wound healing in this case, the question of the type of supplementation remains open. After assessing the patient's systemic condition, the nutrition intervention team suggested that supplementation with high levels of intact protein nutrient such as whey protein isolate (WPI) was not appropriate for the individual due to the coexistence of liver cirrhosis and renal impairment. Therefore, we used fish compound peptides (FCP) with an average molecular weight under 500 Dalton for enteral nutritional support. The FCP, Beaulab®, provided by Tekwon Genetic Technologies Ltd is a patent-pending blend of purified fish short compound peptides with some collagen characteristics, but has a more balanced amino acid composition than collagen peptides [6,7].We believe that when patients are decompensate or acutely ill, it may be better to start with a low level of FCP. As the patient begin to recover and able to regain lean body mass, relatively high levels of FCP can be applied gradually [8]. Thus, the nutrition intervention with oral supplementation of FCP was designed and conducted as follows: FCP, 0.15g/kg/d p.o. for D1 to D3, FCP, 0.30g/kg/d p.o. for D4 to D7, FCP, 0.50g/kg/d p.o. for D8 to D42. One week later, we did a second assessment. There was no reduction in ulcer size, but new granulation tissue formation was observed. The ulcer constriction was obvious at the end of the third week. Figure 1c shows the granulation tissue in wound bed after six weeks nutrition intervention. Finally, the venous leg ulcers were completely healed in the eighth week (Figure 1d). The gentleman was able to back to working and living a normal life. He was delighted with the significant improvement to the ulcers that help him avoid limb amputation.

Discussion

Nutrition is an important factor in chronic wound prevention and treatment. Patients with venous leg ulcers tend to be nutritionally deficient [9]. Some previous studies showed that nutritional status deteriorated as the severity of the wound increased, and malnutrition could delay the wound healing process [10]. It has been reported that micronutrients, including vitamin A, C, D, zinc, carotenes, and folic acid may improve wound healing in patients with venous leg ulcers [11,12]. However, there is lack of agreement of when and how to conduct nutrition intervention in VLU patients and the effect of nutritional intervention is less clear [13,14].In this case, we emphasize that the risk of protein malnutrition is particularly high in the chronic wound patients coexisting liver cirrhosis and diabetes, and lack of adequate nitrogen source impairs the wound collagen accumulation. Therefore, appropriate protein nutrition supplementation is pivotal in the cure of this kind of leg ulcers. Plasma levels of albumin and bilirubin are key biochemical indicators correlated with the healing of pressure ulcers in liver cirrhosis patients [15]. They can also be applied as useful independent predictors of prognosis in VLU patients.

FCPs have a wide range of applications in clinical nutritional support and treatment because they are reliable nitrogen sources which can directly participate in protein metabolism, and correct patients' malnutrition. Many of FCPs also have specific biological functions such as anti-oxidation, blood pressure control, cardiovascular protection, and immuno-modulation [16,17].In this case, we demonstrated that orally administered Beaulab® FCP (MW ≤ 500 Da.)was effective to reverse protein-energy malnutrition in VLU patient that coexisted with liver cirrhosis and diabetes, and hence could be applied to improve the healing rate [6,7]. Due to the compact molecular weight, FCP can be absorbed directly via peptide transporter 1 (pepT1), or endocytosis in the intestines. Some of them can be used fornourishing intestinal epithelial cells; some of them can enter the liver via hepatic portal vein to reinforce the synthesis of albumin; others can be systemically distributed and further utilized in the body, e.g. for enhancing the endogenous collagen synthesis [18]. Although FCP contain lots of small oligo-peptides with collagen characteristics, FCP also possess a wider range of small compound peptides with other bioactive functions that collagen peptides do not contain. Recently, anti-inflammatory properties of FCP were reported [7]. We speculate that another possible beneficial effect of the FCP on the healing of VLU is helping with down-regulation of local inflammation responses, but more efforts should subsequently be implemented for further exploitation and confirmation.

Conclusion

This case reinforces the importance of protein nutrition support in the healing of venous leg ulcers in patient coexisting with liver cirrhosis and diabetes. Supplementation with (0.15~0.5g/kg/d) fish compound peptides (FCP) is an ideal strategy to promote wound healing and decrease wound severity in home care patients with chronic wounds and metabolic diseases.

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Author's Contribution

CX, Wang: Acquisition and analysis of data; YY,Wang: Conception and design of study, and drafting of the manuscript. All Authors: Approval of the final version of the manuscript to be published.

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