

# Evaluating the efficacy of protein-based nutritional supplements in patients with chronic wounds: a pilot study



### Authors:

Harikrishna KR Nair,  
Sylvia SY Chong

The concept of preparing the wound bed was updated in 2007 to consider the whole patient before treating the wound (Sibbald et al, 2007). A full and detailed patient assessment will highlight the underlying aetiology of the wound and other factors that may impede wound healing, such as pain and poor nutrition (Dealey, 2000). In hospitals, malnourished patients face increased complications, such as infections — particularly a higher risk of infection at surgical sites, slower recovery and an overall higher risk of death (Schneider et al, 2004; Agarwal et al, 2013).

Nutrition plays a vital role throughout all stages of wound healing. Leigh et al (2012) observed that well-nourished patients displayed greater improvement in healing rates, than malnourished patients. NHS improvement (2014) highlighted the fact that nutritional status plays a critical role in the wound healing process. The study highlighted protein, energy fluid, vitamin A, C, B complex, zinc, iron and copper as being nutritional components, essential for wound healing. Various studies have concluded that micronutrients, such as arginine, glutamine and branched-chain amino acid leucine, isoleucine and valine are important components of wound healing.

A pilot study of six patients with chronic wounds was conducted at the Kuala Lumpur Hospital, Malaysia, three with venous ulcers, two with diabetic foot ulcers (DFU) and one with a below-the-knee stump, whereby the patients received a protein-based nutritional supplement twice daily. Monitoring of key parameters that affect wound healing; albumin level, wound size progress, appetite and side effects was done on a weekly basis, over a duration of four weeks. The protein-based nutritional formula used for this study was a wound supplement, fortified with high levels of micronutrients arginine, glutamine and leucine, multivitamin and minerals, plus edible birds' nest. The aim of the study was to establish the role of protein-based nutritional supplements in providing wound nutrition, to progress healing in chronic wounds. The blood indices showed improvement in the blood albumin level, wound size reduced and there were no side effects or toxicity. The patients' appetite also improved. We can conclude that proper nutrition is crucial in wound healing.

**Harikrishna KR Nair** is the Head of Wound Care Unit, Department of Internal Medicine, Hospital Kuala Lumpur; **Sylvia SY Chong** is a Research Assistant, Wound Care Unit, Department of Internal Medicine, Hospital Kuala Lumpur

A study by Kaiser et al (2010) showed that prevalence of malnourishment in hospitals is 39% out of 1384 patients and 14% out of 1586 patients in nursing homes, while prevalence of at-risk malnourishment in hospitals is 47% and 53% in nursing homes. Prevalence of malnourishment and at-risk malnourishment combined, totals to 86% in

hospitals and 67% in nursing homes.

The concept of preparing the wound bed was updated in 2007 to consider the whole patient before treating the wound (Sibbald et al, 2007). A full and detailed patient assessment will highlight the underlying aetiology of the wound and other factors that may impede wound healing, such as pain and

poor nutrition (Dealey, 2000).

A systematic review by Pedroni et al (2014) evaluated the impact of malnutrition on the development and severity of pressure ulcers (PU) and revealed, through eight studies, that the risk of developing PUs is higher in malnourished patients. Leigh et al (2012) observed that well-nourished patients displayed greater improvement in healing rates, than malnourished patients. If left untreated, malnutrition can have serious complications. In hospitals, malnourished patients face increased complications, such as infections — particularly a higher risk of infection at surgical sites, slower recovery and an overall higher risk of death. Alarmingly, half of the patients who fall in hospitals are malnourished (Schneider et al, 2004; Agarwal et al, 2013).

The focus of a nutrition assessment should be on evaluating energy intake, weight loss and presence of acute disease, as well as an estimation of the individual's caloric, protein and fluid requirements. The interprofessional team should work with the individual and/or surrogate to develop appropriate and individualised interventions and then monitor and evaluate these, should any changes need to be made (Posthauer et al, 2015).

Hydration plays a vital role in the preservation and repair of skin integrity. For the healing of PUs, 30–40 ml/kg or 1500 ml/d is recommended. Fluid replacement depends on the volume of losses experienced by the patient, for example through draining wounds, fever and gastrointestinal losses, as well as comorbid conditions, such as renal or cardiac disease. Patients who use pressure-relieving air mattresses are prone to excessive sweating and may need extra fluid to compensate for excess fluid loss (Todorovic, 2002).

The European Pressure Ulcer Advisory Panel, National Pressure Injury Advisory Panel and Pan Pacific Pressure Injury Alliance (EPUAP/NPIAP/PPPIA) Nutrition Guidelines (2019) recommend:

- A 30–35 kcal/kg body weight for adults with PU who are malnourished or at risk of malnutrition
- Fortified foods be offered when nutritional requirements cannot be achieved by normal dietary intake
- Oral nutritional supplement and artificial nutrition be considered as strategies for reaching the individuals caloric intake goals.

The EPUAP/NPIAP/PPPIA Nutrition Guidelines (2019) states that proper nutrition can help to support skin and muscles, which can help prevent PUs and promote healing if a pressure

injury occurs. Quality nutrition comprises of:

- Calories: adequate calories help maintain muscle mass and weight
- Protein: repairs and maintains tissue and muscle, which can help PUs heal
- Amino acids: arginine is a conditionally essential amino acid that is critical for wound healing
- Water: proper hydration carries nutrients throughout the body
- Vitamins and minerals: many vitamins and minerals are associated with healing.

The Prevention and Treatment of Pressure Ulcers Clinical Practice Guideline highlights four keys areas — prevention, intervention, collaboration and action — to prevent and treat pressure ulcers with good nutrition (EPUAP/NPIAP/PPPIA, 2019):

#### 1. Prevention

- Validated malnutrition screening
- Early intervention
- Flexible nutrition planning

#### 2. Intervention

- Food first
- Fortified foods for increased nutrients
- Oral nutritional supplements (ONS)

#### 3. Collaboration

- Timely collaboration
- Plan to achieve clinical goals
- Adapt to medical changes

#### 4. Action

- Albumin and pre-albumin are NOT sensitive measures of nutrition status
- Provide high-protein snacks
- Expand flavours to increase intake.

The protein-based nutritional supplement ingredient arginine is well researched and proven to be beneficial in polytrauma (Beitl et al, 2016), wound healing and PUs (Leigh et al, 2012; Chow and Barbul, 2014; Choo et al, 2013). It increases collagen deposition and is a metabolic substrate for the synthesis of nitric oxide, which helps vasodilatation by improving blood flow. Glutamine protects against inflammatory injury by inducing expression of heat shock proteins, providing cellular protection in inflammation, injury and stress (Chow and Barbul, 2014; Little, 2013; Saghaleini et al, 2018; Neyens et al, 2017). Branched-chain amino acids (BCAAs), such as leucine, isoleucine and valine, prevent the breakdown of muscle proteins that can occur after trauma or severe stress. BCAAs enable growth hormone production, help wound healing and have been shown to reduce negative nitrogen balance in the body and decrease

stress index. They are particularly helpful in severe insults, such as cases of burn, trauma and sepsis (Tamanna et al, 2014; Gomes et al, 2018). Correct traces of vitamin A, vitamin C, vitamin E, zinc, copper and selenium balance is pivotal for wound healing (Mirastschijski et al, 2013; Oliveira et al; 2017; Ubbink et al, 2014). EBN ingredient N-acetylneuraminic acid (sialic acid) is a food rich in glyconutrients, such as collagen and amino acids, which was proven in the 1980s to have EGF-like activity (Kong et al, 1987). Scientific research carried out many years later showed that EBD is able to strengthen immunity, anti-inflammatory and mitogenic activity to promote the regenerative and proliferative ability of human adult stem cell, human adipose-derived stem cells (hADSCs) but not cancer cells (Aswir and Wan Nazaimoon, 2011; Roh et al, 2012; Vimala et al, 2012; Yida et al, 2015; Chua et al, 2013).

### Objective

To establish the role of protein-based nutritional supplements in providing wound nutrition for the healing of chronic wounds.

### Methods

#### Study design

This study was done by recruiting patients who have wounds with associated serum hypoalbuminemia. Patients who presented with chronic wounds to the Wound Care Unit, Kuala Lumpur Hospital, Malaysia (WCUHKL) had to undergo blood screening for serum albumin.

This study conformed to the guidelines set out in the Declaration of Helsinki of Ethical Principles for Medical Research involving Human Subjects. The study was approved by the Kuala Lumpur Hospital Review Board (local institution board). The study objectives and potential risks involved were explained to the patient in detail. Informed consent and permission to use wound photographs and case details for publication/research purposes were obtained.

### Clinical assessment

Participants were given standard of care by a WCUHKL nurse, which involved wound assessment, wound bed preparation, debridement and application of wound dressings that were appropriate to wound aetiology.

### Methodology

Patients received a 30g sachet (mixed with 200ml of water) of protein-based nutritional supplement twice daily, for a duration of four weeks. All patients received standard of care, whereby the diabetic foot ulcers (DFU) were offloaded and compression was used on the venous ulcer cases. Weekly follow-up visits were planned with monitoring of key parameters; albumin level, wound size, side effects and appetite.

### Potential source of bias

Selection bias will be present in this pilot study as the participants were selected only from the pool of patients with hypoalbuminemia at the WCUHKL and therefore may not represent the wider population.

### Results

We recruited six patients who had chronic wounds ranging from four months to two and a half years, all had an increase in their albumin levels after four weeks of receiving the protein-based nutritional supplement (*Table 1*). The increase ranged from 30 to 61%, which is a good marker as protein is the building block for wound healing. In addition, the wound size, which was measured routinely in terms of length and width, also showed improvement (*Table 2*). All patients received standard of care whereby the DFUs were offloaded and compression used on patients with venous ulcers. There were no side effects or untoward reactions in all cases. Patients were satisfied with the product, especially its taste and reported an increase in their appetite.

**Table 1. Albumin levels while on twice daily protein-based nutritional supplements**

Patient	Albumin level (normal range: 35–55 g/l)				
	Start	Week 1	Week 2	Week 3	Week 4
Patient 1: 47kg	25	37.7	40	40.3	40.4
Patient 2: 56kg	25	31	30.5	33.8	32.6
Patient 3: 58kg	25	40	39.2	40.1	39.9
Patient 4: 74kg	29.7	32.5	35	38	42.2
Patient 5: 47kg	30	34.7	37.2	38	39.4
Patient 6: 75kg	24	28	30	34	38.3

**Table 2. Patients' wound measurements while on twice daily protein-based nutritional supplements**

Patient	Wound measurement in cm <sup>2</sup>				
	Start	Week 1	Week 2	Week 3	Week 4
Patient 1: Venous ulcer	88	70	60	57	49.5
Patient 2: Diabetic foot ulcer	120	91	87.5	84	74.75
Patient 3: Venous ulcer	54	51	46.75	44	37.5
Patient 4: Diabetic foot ulcer	2.25	1.95	1.69	1.3	1.5
Patient 5: Venous ulcer	351	332.5	323.75	306	227.5
Patient 6: BKA stump	30	27.5	11	5	1.5

**Case 1**

69-year-old female  
Venous ulcer since March 2019 (6 months)

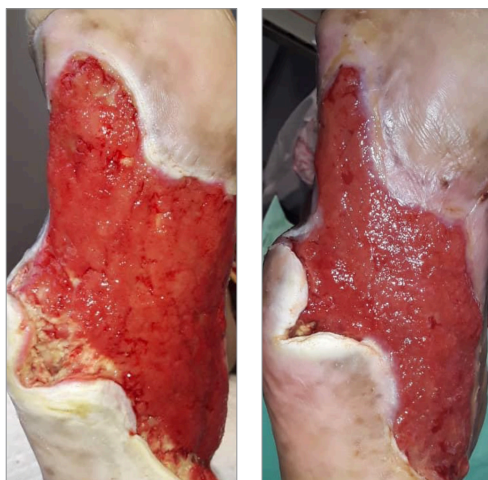


Day 1

Day 28

**Case 2**

67-year-old female  
Diabetic foot ulcer since June 2019 (3 months)



Day 1

Day 27

**Case 3**

80-year-old female  
Venous ulcer since March 2017 (6 months)



Day 1

Day 30

**Case 4**

65-year-old male  
Diabetic foot ulcer since May 2019 (4 months)



Day 1



Day 31

## Case 5

66-year-old male  
Venous ulcer since July 2019 (2 months)



Day 1



Day 30

## Case 6

60-year-old male  
BKA stump wound since August 2019  
(1.5 months)



Day 1



Day 31

## Discussion

Nutrition plays a vital role throughout all stages of wound healing. NHS Improvement (2014) highlighted the fact that nutritional status plays a critical role in the wound healing process. The study highlighted protein, energy fluid, vitamin A, C, B complex, zinc, iron and copper as being nutritional components, essential for wound healing. Various recent studies have concluded that micronutrients, such as arginine, glutamine and BCAA (leucine) are important components of wound healing.

The protein-based nutritional supplement introduced in the pilot study contains ingredients recognised scientifically to provide benefit in helping wound recovery. In addition to that, edible birds' nests (EBN) were added into

the sachet powder drink. EBN has epidermal growth factor (EGF)-like activity that will help to aid skin and tissue regeneration.

Arginine, an amino acid, is recommended by EPUAP/NPIAP/PPPIA Nutrition Guidelines (2019) for adults with a PU. It is the best-studied component of immunonutrition for wound healing (Chow and Barbul, 2014). It increases collagen deposition and is a metabolic substrate for the synthesis of nitric oxide, causing vasodilation and improved blood flow (Choo et al, 2013). Another amino acid, glutamine, acts as a fuel source for fibroblasts and epithelial cells (Saghaleini et al, 2018). It protects against inflammatory injury by inducing expression of heat shock protein, providing cellular protection in inflammation, injury and stress (Wischemeyer, 2002; Little, 2013; Neyens et al, 2017).

BCAAs, such as leucine, isoleucine and valine, avoid protein catabolism, preventing the breakdown of muscle proteins that can occur after trauma or severe stress (Gomes et al, 2018). BCAAs enable growth hormone production, help in wound healing and have been shown to reduce negative nitrogen balance in the body and decrease stress index. It helps in severe insults like cases of burn, trauma and sepsis (Tamanna et al, 2014).

Correct trace element vitamin A, vitamin C, vitamin E, zinc, copper and selenium balance is pivotal for wound healing. Some micronutrients, such as selenium and the vitamins A, C and E, may deactivate free radicals and potentially accelerate wound healing (Mirastschijski et al, 2013; Oliveira et al, 2017). Review data shows that most of these vitamins and minerals are cofactors in the wound healing process, where a depletion in serum levels might constitute delayed healing (Ubbink et al, 2014).

EBN was shown to have EGF-like activity, which appears to play a crucial role in normal cellular processes, such as proliferation, differentiation and development. Kong et al (1987) documented that birds' nest containing EGF can help to promote and activate the synthesis of DNA, thus cell proliferation for the first time. Aswir and Wan Nazaimoon (2011) *in vitro* study results showed that EBN can influence the production of anti-inflammatory TNF- $\alpha$  in cells. The effects of EBN extracts on the production of these pro-inflammatory molecules, NO and TNF- $\alpha$  were assessed using an *in vitro* model (Vimala et al, 2012). The results from this finding suggest that EBN extract has potent inhibitory activity against TNF- $\alpha$  and NO, as there was significant inhibition by some of the EBN samples. In their animal

study, Yida et al (2015) demonstrated that EBN attenuated high fat diet-induced oxidative stress and inflammation, partly through transcriptional regulation of hepatic antioxidant and inflammation-related genes, better than Simvastatin. The results also indicated that other post-transcriptional mechanisms may be involved in the antioxidant and anti-inflammatory effects of EBN. It strongly promotes the proliferation of hADSCs but not cancer cells. Its effects were mediated via the expression of IL-6 and VEGF (Roh et al, 2012). The effects of EBN extract is also tested on human adipose-derived stem cells. The results demonstrated mitogenic activity and promote the regenerative ability of human adult stem cells. With all these cellular-based data, the use of EBN extract in regenerative medicine is encouraging (Chua et al, 2013).

### Conclusion

One of the hurdles patients recovering from

a wound face is enough uptake of essential nutrition. Weak patients might not have the appetite to take in enough food to generate sufficient energy and nutrients for their wounds to heal. Epigran Protein drinks, added to the daily diet, provide energy, fluid, various vitamins and minerals, essential micronutrient of arginine, glutamine, BCAAs and EBD to aid the wound healing process. Epigran Protein has proven to be effective in increasing the albumin levels and can help in the area reduction of chronic wounds. Therefore, it is a good nutritional supplement to be used with concurrent dressings, as per standard of care. There were no reported side effects and it was well tolerated by all patients.

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### Declaration of interest:

Soza Healthcare sponsored the protein-based nutritional supplement (Epigran Protein) used for this study. The author has no conflicts of interest to declare.

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