



Effects of an Arginine-enriched Oral Nutritional Supplement on the Healing of Chronic Wounds in Non-Malnourished Patients; A Multicenter Case Series from the Netherlands and Hungary

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Abstract

Aim: To explore the effects of a specific arginine-enriched oral nutritional supplement on the healing of chronic wounds in non-malnourished patients.

Method: A case series using a prepared and Medically Ethically approved evaluation template. Out of three clinical centres in the Netherlands and one in Hungary, 27 patients with arterial leg ulcers, venous leg ulcers, diabetic foot ulcers, and pressure ulcers participated. They consumed a specific ready to drink arginine-enriched oral nutritional supplement daily, in addition to their regular diet and standard wound care, for a maximum of 12 weeks. Main outcome measures were wound healing progress, patients' compliance and rating of the specific nutritional supplement.

Results: Seventeen females and twelve males with a mean age of 73.7 years were included. Within 2 to 12 weeks, complete healing occurred in eight ulcers, thirteen ulcers showed clear signs of healing through decreased wound surface area ranging from 25% to 88% reduction, and three ulcers kept unchanged. Overall, the daily oral nutritional supplements, on average two servings per day (= 400 ml), were almost fully consumed (99.5%), and the patients' rating of the oral nutritional supplement was good.

Conclusion: Extra nutritional support with a specific ready to drink arginine-enriched oral nutritional supplement seems to be beneficial for the healing of different types of chronic wounds. The patients' compliance with the product was very high, and they rated it as good. Further research, especially prospective randomised controlled studies on arginine-enriched oral nutritional supplements in patients with chronic wounds are necessary.

Keywords: Oral nutritional supplementation; Wound healing; Arginine; Zinc; Vitamin C

Introduction

Although many wounds will heal without delay or complications, both acute and chronic wounds may be affected by intrinsic factors such as diabetes and ischemia and extrinsic factors (e.g. infection and under-nutrition) [1]. Wound healing in any tissue follows a predictive sequence of cellular and molecular events leading to the repair of injured tissue [2]. However, some wounds somehow show failure in the healing processes and are then termed chronic wounds [3,4]. In contrast to acute wounds, chronic wounds such as pressure ulcers (PUs), leg ulcers (LUs) and diabetic foot ulcers (DFUs) are more complicated because the physiological process of the wound healing is significantly altered [5]. Wound chronicity is the result of one or more of the following factors: enhanced inflammation and proteolysis, extra cellular matrix degradation, impaired fibroblast migration together with a decrease in collagen synthesis and delayed epithelialization [6].

In the last decade, wound research has led to new and multifaceted wound healing interventions but delayed wound healing is still a major burden for health care in general and patients in particular [7]. The negative impact of chronic wounds on patients' quality of life in terms of ulcer pain, sleep, mobility, social interaction is profound [8-10]. Worldwide, the chronic wound burden lies chiefly within the elderly

population [6,11,12] and the morbidity accompanying age-related delay in healing, is readily acknowledged [11,12]. In 2013 in the Netherlands, a multi-centre cross-sectional point-prevalence measurement on chronic wounds in nursing home patients was conducted [13]. Out of 1514 patients, 63 patients had one or more chronic wounds, which resulted in a prevalence of 4.2%. Almost half (46%) of these wounds were PUs.

A good nutritional status contributes to a good health status, independence and quality of life, especially in older individuals. Nutrition is a relevant mediator for the preservation of skin tissue, strengthening of tissue resistance, and promoting tissue repair [14-16]. Skin regeneration is a vital aspect of wound healing, facilitated by adequate nutrition. Adequate nutritional support therefore plays a pivotal role in wound healing. However, based on the results of two randomized controlled trials in patients with PUs, it appears that some nutrients play an active role in wound healing independently of protein and energy provision [17,18]. In the study of van Anholt et al, the authors had used the same specific high protein, arginine- and micronutrients-enriched oral nutritional supplement (ONS) in non-malnourished PU patients and showed beneficial effects: accelerated PU healing and decreased wound care intensity (significantly fewer dressings required per week and less time spent per week on changing the dressings), which is likely to decrease overall costs of PU treatment [17]. The OligoElement Sore Trial of Cereda et al showed

that the additional provision of arginine, zinc, and antioxidants in the nutritional support in malnourished PU patients improved PU healing [18]. Strength of this large multicenter, blinded RCT study was that specific micronutrients were given within the content of appropriate nutritional care and both groups received a similar high-protein, high-calorie support to promote new tissue synthesis.

The studies of van Anholt et al and Cereda et al have shown that adequate nutritional support by an arginine-enriched ONS significantly improved the healing of PUs [17,18]. Subsequently, the question was whether this effect also counts for diabetic foot ulcers (DFUs), arterial leg ulcers (ALUs), and venous leg ulcers (VLUs). Therefore, a multicenter case series has been conducted to explore the effect of a specific arginine-enriched ONS and the healing process in different types of chronic wounds.

Objectives

The objective of the case series was to evaluate the effect of an arginine-enriched ONS in non-malnourished patients with a DFU, LU, or PU. The primary outcome measures were: 1) wound healing progress (complete healing and wound size reduction), 2) patients' compliance to the specific ONS, and 3) patients' rating of the specific ONS.

Methods

A convenience sample of patients with chronic wounds was recruited from three Dutch clinical centres: two nursing homes and one community wound centre, and one clinical health centre in Hungary. The wounds existed for at least three weeks and remained unchanged or worsened despite the centre's standard wound care. This wound chronicity represented a rationale for the prescription of an arginine-enriched ONS. If the patient had several wounds, the most severe ulcer was selected for follow-up. All patients were non-malnourished i.e., with a normal BMI and no signs of undesired weight loss or insufficient nutritional intake. Permission was sought and received from the Medical Ethics Committee of Maastricht University to undertake the case series using the evaluation template to record data. The patients received a comprehensive explanation of the study before providing informed consent. Patient anonymity and confidentiality were maintained throughout the evaluation period. Table 1 shows the general inclusion/exclusion criteria that were applied to all patients.

Table 2 refers to the additional specific inclusion criteria for patients with a DFU, LU or PU respectively.

In order to consume at least 5g arginine per day, all participants were daily offered one to three servings of a specific ready to drink arginine-enriched ONS (Cubitan®, Nutricia) in addition to their centre's regular diet and centre's standard wound care, for a maximum of 12 weeks or until complete healing. The physician of the participants determined the number of ONS servings taking into account the renal function. One serving (200mL) provides 250 kcal, 20 g protein, 3 g L-arginine, 250 mg vitamin C, 38 mg vitamin E (α-TE), 9 mg zinc, 1.5 mg carotenoids). At study start, wound existence (3-4 weeks, 5-12 weeks, >12 weeks), wound location, and patients' mobility (bedfast, chairfast, walks occasionally, walks frequently) (Tables 3) were recorded.

Besides patient characteristics, information on wound surface area (WSA) (length x width), daily ONS servings (1, 2, 3), compliance per serving (100%, 75%, 50%, 25%, 0%), patients' ONS rating (excellent, very good, good, moderate, bad), and photographs of the wounds were recorded monthly over the twelve-week period.

PUs were categorised/staged in line with the NPUAP-EPUAP-PPPIA Guidelines in 2014 [19]. A Pressure Ulcer Scale for Healing (PUSH) was generated for all PU patients [20]. The PUSH score categorises the PU and generates a score in relation to; WSA (length x width), level of exudate (none, light, moderate, heavy), and type of tissue (closed, epithelial tissue, granulation tissue, slough, and necrotic tissue). The sum of the sub-scores provides the total PUSH score and comparison of these scores over time provides guidance on the status of the ulcer as regards improvement or worsening.

LUs were divided in ALUs and VLUs through measurement of the Ankle Brachial Pressure Index (ABPI). DFUs were graded in line with Wagner's classification [21].

Inclusion criteria
The patient is aged between 18 years and 95 years.
The patient is able to drink ONS.
The patient is not malnourished i.e., with a normal BMI and no signs of undesired weight loss or insufficient nutritional intake.
The patient has a regular diet.
The patient has standard wound care.
The patient has a life expectancy > 6 months.
The patient has a DFU, LU or PU that exists for at least 3 weeks and remained unchanged or worsened despite standard wound care.
If the case study starts in a clinical centre, the patient is able to visit the clinical centre once per two weeks after discharge.
Patient has provided informed consent.
Expected duration specific arginine-enriched ONS use >1 month.
Exclusion criteria
The patient in a severe medical condition e.g. ICU patients, sepsis, serious infection, malignancy requiring chemotherapy, recent (<3 months) myocardial infarction, organ failure, anaemia, and the acute phase after stroke (first two weeks).
The patient is suffering from drugs or alcohol in the opinion of the health care practitioner.
The patient has a protein restricted diet.
The patient used specific arginine-enriched ONS over the last 2 weeks.
The patient requires other oral nutritional supplements / tube feeds during the course of the case series.
The patient is malnourished i.e., has >5% weight loss in the previous month or >10% weight loss in the previous 6 months

Table 1: General inclusion/exclusion criteria.

Diabetic foot ulcer (DFU):
The patient has a DFU > grade II (Wagner's classification).
The patient has a DFU but not a PU or LU.
Leg ulcer (LU):
The patient has a LU with a size >1 cm ² .
The patient has a LU but not a DFU or a PU.
Pressure ulcer (PU):
The patient has a PU category/grade >II.
The patient has a PU but not a DFU or LU.

Table 2: Additional specific inclusion criteria per wound type.

Bedfast: Confined to bed.
Chairfast: Occasional slight changes in body or extremity position but unable to make frequent or significant changes independently.
Walks occasionally: Walks occasionally during day, but for very short distance, with or without assistance. Spends majority of each shift in bed or chair.
Walks frequently: Walks outside room at least twice a day and inside room at least once every two hours during waking hours.

Table 3: Definitions of patient mobility.

Trained and instructed research assistants were responsible for collecting the data among the participants. All data was anonymised and analysed using Microsoft Excel.

Results

Twenty-nine non-malnourished patients were included i.e., seventeen females and twelve males with a mean age of 73.7 years ranging from 50-95 years. The mean BMI was 27.6 and overall mobility ranged between chairfast (N=8), walks occasionally (N=8), and walks frequently (N=13). The chronic wounds involved, were DFU (N=9), ALU (N=5), VLU (N=8), and PU (N=7).

Overall at study start, the wounds existed between >12 weeks

(N=21), 5-12 weeks (N=3), and 3-4 weeks (N=5).

Within 2 to 12 weeks, complete healing occurred in ten ulcers (3 DFUs, 3 VLUs, 4 PUs), thirteen ulcers showed clear signs of healing through decreased WSA ranging from 25% to 88% reduction (6 DFU, 3 ALUs, 4 VLUs), and three ulcers kept unchanged (2 ALUs, 1 VLU). Three PU patients were lost to follow (one deceased, one hospital admission post stroke, and one withdrew due to cognitive decline). Overall, the patients used 2 ONS servings per day (= 400 ml), consumed 99.5% per serving, and rated the ONS as good. Tables 4, 5, 6 and 7 show the characteristics and ONS data of DFU, ALU, VLU and PU patients respectively.

DFU patients (N=9)	1	2	3	4	5	6	7	8	9
Age	79	89	55	50	62	63	54	69	53
Gender	male	female	female	male	female	male	male	male	male
BMI	25.7	32.7	27.3	41.5	26.7	36.6	29	35.9	36.3
Main diagnose	stroke	hypertension	DM	DM	DM, hypertension	DM	DM	DM, hypertension	DM
Mobility	walks occasionally	walks occasionally	walks frequently	walks frequently	walks frequently	walks frequently	walks frequently	walks frequently	walks frequently
Regular diet	yes	yes	yes	yes	yes	yes	yes	yes	yes
Wound existence	>12 weeks	5-12 weeks	>12 weeks	>12 weeks	>12 weeks	>12 weeks	>12 weeks	>12 weeks	>12 weeks
Wound location	left heel	left foot, 2 nd toe	left foot	left foot, 2 nd toe	right foot, hallux	left foot, plantare	left foot, plantare	left foot, 2 nd toe	left foot, transmetatarsal amputation
DFU grade	III	II	II	II	II	II	II	II	III
WSA* at start	20 cm ²	1 cm ²	6.29 cm ²	3.28 cm ²	0.61 cm ²	1.16 cm ²	1.45 cm ²	1.45 cm ²	57.49 cm ²
Effect on healing									
completely healed in weeks	-	12	-	-	-	-	12	12	-
% decreased WSA* (in weeks)	60% (8) ¹	100%	82% (12)	45% (12)	72% (12)	58% (12)	100%	100%	88% (12)
ONS° servings/day	1	2	2	2	2	2	2	2	2
ONS° compliance/serving	100%	100%	100%	100%	100%	100%	100%	100%	100%
ONS° rating	very good	good	very good	very good	very good	very good	very good	good	very good

DFU= Diabetic Foot Ulcer BMI= Body Mass Index * = Wound Surface Area ° = Oral Nutritional Supplementation ¹= hospital admission after 8 weeks

Table 4: Characteristics of diabetic foot ulcer patients and ONS data.

ALU patients (N=5)	1	2	3	4	5
Age	81	71	85	84	76
Gender	female	male	female	female	female
BMI	24	26.1	22.2	23	23.4
Main diagnose	diabetes	PVD ¹	hypertension	hypertension	diabetes
Mobility	walks occasionally	walks frequently	walks frequently	walks occasionally	walks occasionally
Regular diet	yes	yes	yes	yes	yes
Wound existence	>12 weeks	>12 weeks	>12 weeks	>12 weeks	>12 weeks
Wound location	left leg	right leg	left leg	right leg	left leg
WSA* at start	45 cm ²	46 cm ²	6.6 cm ²	16 cm ²	12 cm ²
Effect on healing:					
% decreased WSA* unchanged	33%	53%	-	-	75%
	-	-	x	x	-
ONS° servings/day	1	2	2	1	2
ONS° compliance/serving	100%	100%	100%	100%	100%
ONS° rating	excellent	good	good	good	good

¹= Peripheral Vascular Disease ; * = Wound Surface Area; ° = Oral Nutritional Supplementation ; ALU= Arterial Leg Ulcer; BMI= Body Mass Index

Table 5: Characteristics of arterial leg ulcer patients and ONS data.

VLU patients (N=8)	1	2	3	4	5	6	7	8
Age	75	78	77	95	85	82	76	86
Gender	male	female	female	female	female	female	female	female
BMI	32.5	22.3	34.6	25.8	34	29.4	28.2	38
Main diagnose	hypertension	hypertension	hypertension	diabetes	diabetes	hypertension	hypertension	hypertension
Mobility	walks freq	walks freq	walks occasion	walks occasion	chair-fast	walks freq	walks occasion	chair-fast
Regular diet	yes	yes	yes	yes	yes	yes	yes	yes
Wound existence:								
3-4 weeks	-	-	-	-	x	-	-	-
>12 weeks	x	x	x	x	-	x	x	x
Wound location	left leg	right leg	right leg	left leg	left leg	right leg	left leg	left leg
WSA* at start in cm ²	5	1	0.5	6	24	12	36	17
Effect on healing:								
completely healed in weeks	12	8	-	-	-	8	-	-
% decreased WSA*	100%	100%	-	25%	66%	100%	85%	65%
unchanged	-	-	x	-	-	-	-	-
ONS° servings/day	1	1	1	1	2	2	2	2
ONS° compliance/serving	100%	100%	100%	100%	100%	100%	100%	100%
ONS° rating	good	very good	very good	good	good	good	good	good

*= Wound Surface Area; °= Oral Nutritional Supplementation; VLU= Venous Leg Ulcer; BMI= Body Mass Index

Table 6: Characteristics of venous leg ulcer patients and ONS data.

PU patients (N=7) ss	1	2	3	4	5	6	7
Age	52	75	66	80	77	75	66
Gender	male	female	male	female	male	male	female
BMI	24	20	22.9	21	20.5	29.6	28.9
Main diagnose	Huntington	hyper-tension	stroke	hyper-tension	hyper-tension	hip fracture	diabetes
Mobility	chairfast	walks freq	chairfast	chairfast	chairfast	chairfast	chairfast
Regular diet	yes	yes	yes	yes	yes	yes	yes
Wound existence:							
3-4 weeks	-	-	x	x	-	x	x
5-12 weeks	x	x	-	-	-	-	-
>12 weeks	-	-	-	-	x	-	-
Wound location	left shoulder	right ankle	left heel	right hip	right heel	right hip	sacrum
PU grade	IV	IV	II	III	IV	II	II
WSA* at start in cm ²	1	3.75	16	2.25	6	9	4
PUSH score at start	8	10	11	12	14	8	8
PUSH score at end	0	0	0	12	11	10	0
Effect on healing:							
completely healed in weeks	8	8	4	-	-	-	2
lost to follow-up	-	-	-	x ¹	x ²	x ³	-
ONS° servings/day	3	2	2	2	2	2	2
ONS° compliance/serving	100%	100%	100%	50%	100%	75%	100%
ONS° rating	very good	good	good	mode-rate	good	good	good

¹= deceased after 4 weeks; ²= hospital admission after 8 weeks; ³= withdrawal after 5 weeks; (deterioration) *= Wound Surface Area; °= Oral Nutritional Supplementation; PU= Pressure Ulcer; BMI= Body Mass Index; PUSH= Pressure Ulcer Score of Healing

Table 7: Characteristics of pressure ulcer patients and ONS data.

Figure 1 shows some pictures at start (t0) and after 12 weeks (t1) of a DFU, arterial LU and venous LU respectively.

Discussion and conclusion

Twenty-nine non-malnourished patients were included in the case series. Within 2 to 12 weeks, complete healing occurred in ten ulcers (3 DFU, 3 VLUs, 4 PUs), thirteen ulcers showed clear signs of healing through decreased wound surface area ranging from 25% to 88%

reduction (6 DFU, 3 ALUs, 4 VLUs), and three ulcers kept unchanged (2 ALUs, 1 VLU).

Overall, these case series show that use of an arginine-enriched ONS in addition to regular diet and standard wound care seems to be beneficial for the healing of different types of chronic wounds in non-malnourished patients. All primary outcome measures i.e., wound healing progress, patients' compliance with and patients' rate of the specific ONS were generally positive. These findings are in line with



clinical studies showing a positive effect of nutritional supplementation with additional protein, arginine and micronutrients to promote PU healing [17,18,22-30]. In contrast, the findings of two studies were not in line with the findings of these studies [31,32]. A pragmatic randomised trial showed a significant improvement in wound healing in patients receiving standard nutrition supplement compared to wound-specific supplement, although there was a clinically relevant improvement in quality of life and patient satisfaction in the wound-specific ONS group [31]. The other study, a placebo-controlled randomised controlled trial (RCT), showed that the use of specialised amino acids did not appear to reduce PU wound size [32]. However, the OligoElement Sore Trial (OEST), a level 1 study, confirmed that the additional provision of arginine, zinc, and antioxidants in the nutritional support in malnourished PU patients improved PU healing [33]. Strength of this multicenter, double-blinded, placebo-controlled RCT study was that specific micronutrients were given within the content of appropriate nutritional care and both groups received a similar high-protein, high-calorie support to promote new tissue synthesis.

From these case series, it may be assumed that this positive effect also counts for the healing of chronic wounds, other than PUs. Actually, the arginine-enriched ONS is a nutritionally complete supplement, also enriched with arginine, Zinc and vitamin C.

The potential mechanisms involved in the improvement of the wound healing process by arginine, zinc and antioxidants e.g. vitamin C are the following: arginine improves protein anabolism and cellular growth, is a donor of nitric oxide, which increases blood flow to the wound area and acts as an immune response mediator. Zinc contributes

to protein and DNA synthesis, immune function, and cellular proliferation. Vitamin C is involved in collagen synthesis, fibroblast proliferation, and cellular immunity [34,35].

Case series focus on the clinical course of events in terms of patient's response to therapy and therefore they represent real-life care and provide a rationale for future high-quality clinical studies. On the other hand, case series are non-comparative by lacking a control arm so that treatment outcomes in the selected cases cannot be compared with those that did not receive treatment. A case series study involves first experiences as a rationale for future more in depth research." It is therefore recommended that more prospective randomized controlled studies on arginine-enriched ONS are undertaken in patients with chronic wounds other than PUs.

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