Peer-reviewed | Manuscript received: August 22, 2013 | Revision accepted: January 06, 2014

Nutritional intervention and arginine supplementation in a malnourished patient with peripheral vascular disease (PVD)[1]

A case study

Theodora Steindl-Schönhuber, Hermine König, Gerald Lohr, Linz/Austria

Summary

This case report describes a nutritional approach to the treatment of a patient with peripheral arterial occlusive disease (PVD), intestinal inflammation, weight loss, poor nutritional status and a poorly healing ulcer. The successful treatment was supported by nutritional interventions, including arginine supplementation.

Keywords: arginine, peripheral vascular disease (PVD), ulcer, nutritional deficiency, wound management, clinical nutrition

Citation:
Steindl-Schönhuber T, König H, Lohr G (2014) Nutritional intervention and arginine supplementation in a malnourished patient with peripheral vascular disease – a case study. Ernahrungs Umschau 61(4): 64–69

This article is available online:
DOI 10.4455/eu.2014.012

Introduction

A 75-year old male patient with ulcerous, necrotic and gangrenous peripheral vascular disease (PVD; Fontaine stage IV) was admitted to hospital with recurrent diarrhoea, vomiting, loss of appetite and weight loss of 15 kg within the preceding 4 months. He also had a poorly healing ulcer on the ball of the foot after amputation of a toe.

Dietary treatment was included in the interdisciplinary therapeutic approach. As the nutritional team was aware, there have been few publications on the influence and prevalence of malnutrition or possible specific dietary recommendations for patients with PVD. However, PVD is linked to reduced perfusion and thus to impaired wound healing. Malnutrition is an additional important risk factor. Moreover, PVD often affects older patients, who are at increased risk of malnutrition [1–3]. Recommendations for wound healing include adequate supplies of energy, protein and fluid, together with nutritional screening, supported by high protein nutritional supplements if required [3–5]. The amino acid arginine is involved in wound healing through a variety of mechanisms – improved vascular function, tissue synthesis and the immune response – and it has been suggested that arginine supplementation could be used in wound treatment (◆ Box 1) [4, 6].

The objective was to develop and apply a nutritional treatment with arginine which was appropriate for the gastrointestinal symptoms, the underlying disease, the impaired wound healing and the malnutrition and which assured optimal support for the other treatments (drugs, wound management, etc.).

[1]This is a revised version of a poster presentation during the congress Nutrition 2013 (6–8 June 2013, Zurich/Switzerland).

Methods

Nutritional therapy and arginine supplementation

Because of the patient's reduced nutritional status and the planned medical investigations, slow gastroenterological transition to a normal diet was supported by parenteral nutrition (700 kcal/day for 7 days) and fat-free, rapidly absorbed formula (twice daily). After the gastrointestinal symptoms had improved, the patient's nutrition was based on a light balanced diet, with fully balanced liquid formula twice daily. To heal the ulcer, an arginine supplement was given (5 g three times daily for 2 weeks, then twice daily for 7 weeks). The arginine was administered in the form of L-arginine hydrochloride. This was filled into powder bags in the hospital pharmacy and either dissolved in 150–200 mL fluid or stirred into yoghurt or mushy foods.

Other therapy

The patient's blood parameters and tumour markers were measured, coupled to diagnostic testing for in-

Glossary:

gangrene = tissue necrosis

mesalazine = anti-inflammatory drug

myeloid (stem) cell = bone marrow cell from which the cells of the immune system – e. g. granulocytes, monocytes, dendritic cells and mast cells – are formed.

necrosis = death of single or several cells or tissue in the living organism

Arginine and PVD

Action in blood vessels

The endothelial enzyme nitric oxide synthase catalyses the formation of nitric oxide (NO) from the amino acid L-arginine (◆ Figure 5). This is the sole precursor of NO. For maximal cellular production of NO, adequate levels of the substrate L-arginine must be available. NO has numerous favourable effects on blood vessels and is therefore regarded as a factor that protects blood vessels. The most important effects are considered to be vascular dilatation, increased perfusion and the inhibition of arteriosclerosis by decreasing platelet aggregation and adhesion [12, 13].

Effect on collagen synthesis

Under physiological conditions, supplementation with arginine is unnecessary. Humans can synthesise arginine themselves as part of the urea cycle. Arginine is regarded as semi-essential as, under special conditions, including growth and injury, collagen synthesis may be enhanced to such an extent that the requirements for arginine exceed the quantities produced in the body. Arginine stimulates collagen formation and thus has a favourable effect on wound healing. Collagen mainly consists of the amino acids glycine (ca. one third), proline (12 %) and hydroxyproline (10 %), as well as other amino acids. Proline and the hydroxyproline derived from it are formed biochemically from glutamate, which interacts through arginine and ornithine over the urea cycle [14–16].

Effects in the immune system

In myeloid cells, arginine is mainly metabolised by inducible nitric oxide synthase (iNOS), a special form of the enzyme, to give NO, or by the enzyme arginase, to give urea and ornithine. The stimuli for enzyme induction include various interleukins, tumour necrosis factor-α, interferon-α and -β, various prostaglandins, catecholamines and endotoxins. Enhanced iNOS expression indicates a cellular immune response and enhanced arginase expression a humoral immune response. Enhanced arginase expression plays a role in injuries, sepsis, some infections, after operations and in cancer, and leads to arginine depletion. As a consequence, the T-cell mediated immune response is suppressed, as T-lymphocytes depend on arginine for a series of key biological processes (including proliferation, function, memory and T-cell-receptor formation). It is assumed that these suppressed immune functions can be positively affected by arginine administration. Resting T-cells use little arginine. However, arginine is greatly enhanced in activated T-cells, as the activity of the arginine transporter is increased. Another indication of the importance of arginine in functional T-cells is that, when arginine is deficient, these can form arginine from citrulline by up-regulation of a specific enzyme [17, 18].

Box 1: **Excursus arginine – PVD: mechanisms of vascular function and wound healing**

Parameter	Start of therapy	Follow-up after 2 months	Reference values
BIA measurement			
phase angle	2.6	3.2	men ≥ 4.5
BCM (active body cell mass)	15.7 kg	21.6 kg	
BCM index[1]	5.3 kg/m^2	7.3 kg/m^2	men 7.5–10 kg/m^2
weight	69.4 kg	76.8 kg	
Blood parameters			
CRP	3.8 mg/dL	1.2 mg/dL	≤ 1.0 mg/dL
total cholesterol	84 mg/dL	158 mg/dL	100–200 mg/dL
HDL	24.4 mg/dL	34.7 mg/dL	≥ 35 mg/dL for men
total protein	6.8 g/dL	7.2 g/dL	6.0–8.0 g/dL
albumin (abs.)	3.25 g/dL	3.6 g/dL	3.6–5 g/dL
other parameters			
BMI	23.7 kg/m^2	26.0 kg/m^2	24–29[2] kg/m^2

Tab. 1: **Changes during therapy in the parameters of the nutritional status and body composition**
[1]BCM index: BCM/(height in m)^2
[2]as reference value for normal weight in persons aged over 65 years; 20 is the threshold for malnutrition [1, 8]
BCM = body cell mass; BMI = body mass index; CRP = C-reactive protein; HDL = high density lipoprotein

fection, gastroscopy and coloscopy. The diagnosis was made of erosive gastroduodenitis, with mild discontinuous colitis and ileitis. Anti-inflammatory treatment was then started with mesalazine and proton pump inhibitors. The patient had already had vascular treatment in another hospital, with percutaneous transluminal angioplasty of the *Arteria femoralis superficialis*. He had an appointment with a surgeon in our hospital who considered that no further surgery was necessary. The patient's ulcer was treated by our wound management team.

Management on discharge

Before the patient was discharged, he was advised in detail about optimal nutrition at home, with respect to tolerability and malnutrition. This discussion also covered the further use of arginine and of high calorie oral nutritional supplements containing fibre (twice daily).

Evaluation of the clinical course and nutritional status

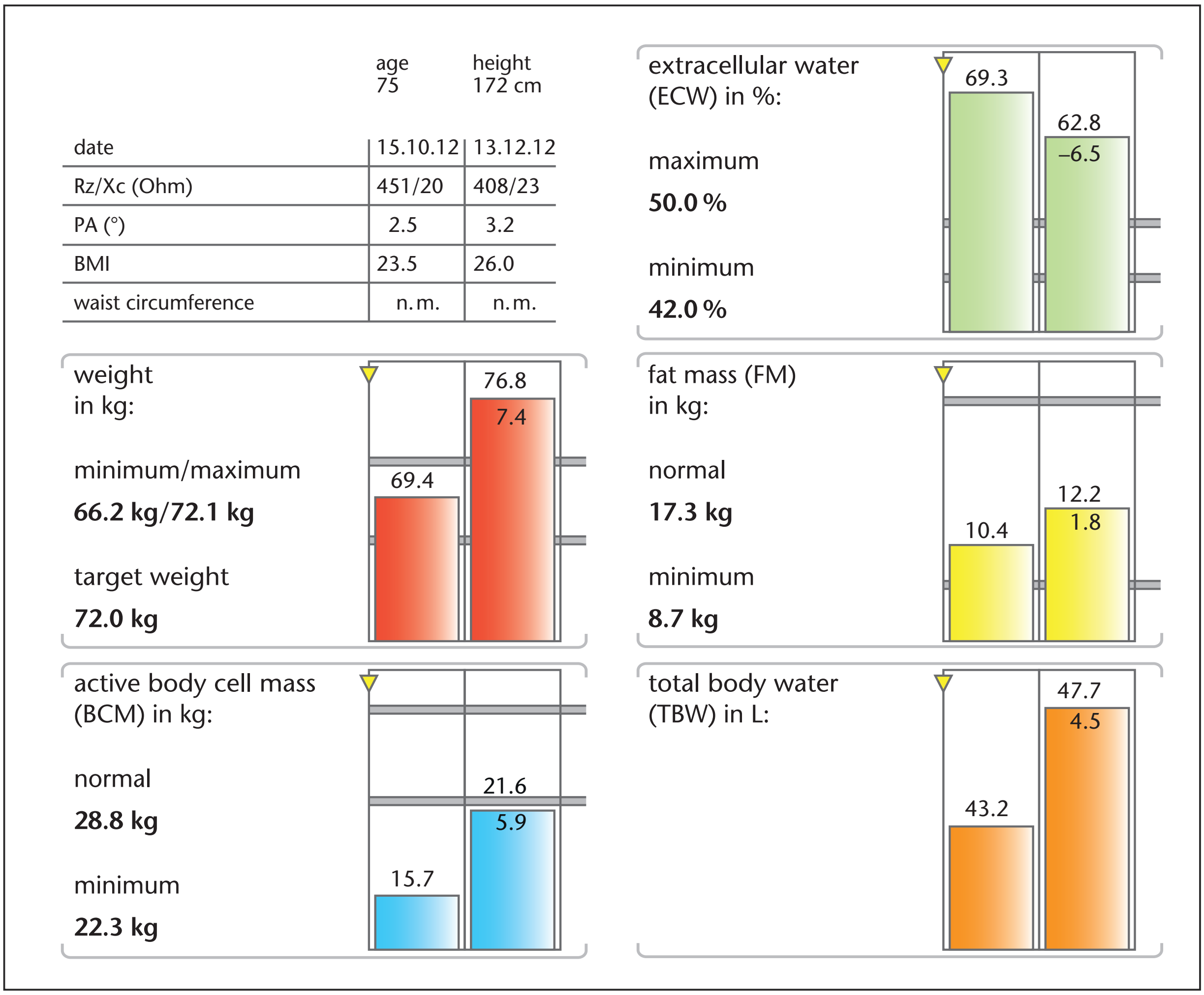
The following parameters were measured at the start of therapy and at the follow-up two months later:

- blood parameters (inflammation, cholesterol, protein values)
- gastrointestinal symptoms
- ulcer appearance and structure
- body composition with bioelectric impedance analysis (BIA)
- patient's subjective analysis of his health

Results

A few days after the start of therapy, the patient's vomiting and diarrhoea improved and his appetite increased. The mean oral energy supply in the hospital was 2,200 kcal, which was a very satisfactory value. Mean protein supply was 55 g, which meant a great improvement. The patient was discharged after 14 days. With the recommended oral nutritional supplement at home, the calorie supply increased by 600 kcal and 24 g protein per day.

Fig. 1: **Ulcer, 0.5 cm diameter with visibly free plantar vein (left), clearly advanced ulcer healing after 2 months (right)**



date	15.10.12	13.12.12
Rz/Xc (Ohm)	451/20	408/23
PA (°)	2.5	3.2
BMI	23.5	26.0
waist circumference	n. m.	n. m.

Fig. 2: **Results of the BIA measurement: block diagram at start of therapy (left) and after 2 months (right)**
BCM = body cell mass; BMI = body mass index; n. m. = not measured; PA = phase angle alpha; Rz = resistance; Xc = reactance

At the follow-up after two months, it was found that the state of the wound had greatly improved (◆Figure 1). Angiography confirmed that the treated vessel had remained open. The patient's nutritional status and body composition were better (◆Table 1, ◆Figures 2 and 3), and the laboratory parameters normalised (◆Table 1). The patient's well-being and energy were enhanced. He was happy that his general condition had become much better.

Discussion

As recommended in current guidelines on geriatric nutrition [7], it was attempted to optimise the therapy of this patient by combining and continuously adjusting individual nutritional medical measures, supported by good and active collaboration between physicians, dieticians, wound managers, pharmacists, domestic nurses, and of course the patient himself (◆Figure 4).

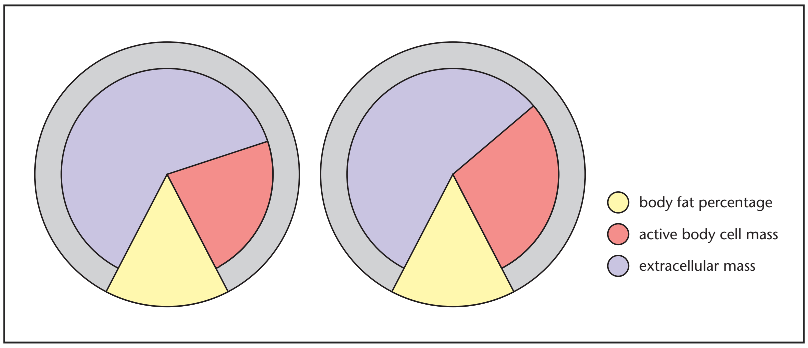


Fig. 3: **Results of BIA measurement: three compartment model at the start of therapy (left) and after 2 months (right)**

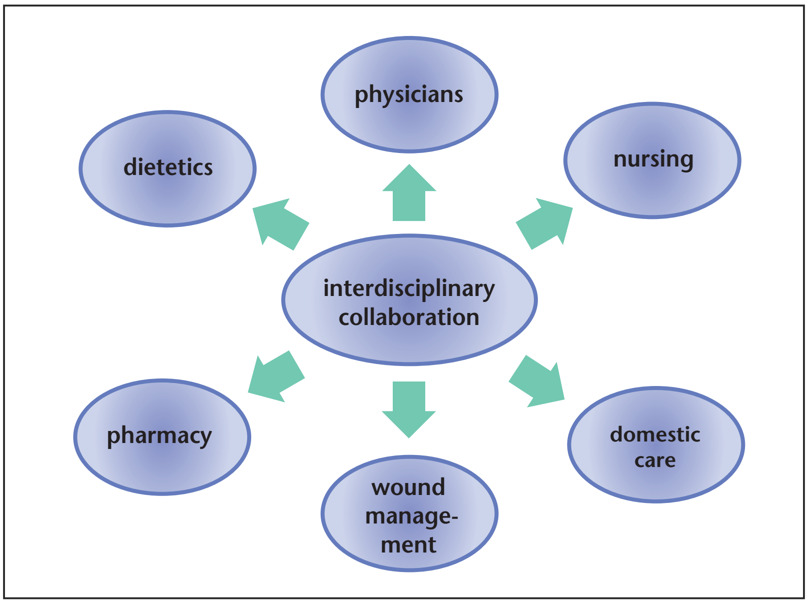


Fig. 4: **Interdisciplinary collaboration for a successful therapeutic concept, including nutritional treatment**

Nutritional parameters

Particularly in geriatrics, a reduced nutritional status, as in the present case, presents a poor prognosis with respect to morbidity and mortality, when accompanied by deficits in protein status and body composition (see results of the BIA measurement ◆Table 1), together with marked unplanned weight loss [1, 2]. In addition to the causal therapy of the diagnosed intestinal inflammation a comprehensive nutritional therapy was therefore initiated, and this was clearly successful after two months. In the results of the BIA measurements, the increase in phase angle and active body cell mass are especially relevant, as low values indicate malnutrition and the loss of functional metabolically active areas, such as skeletal muscle.

The increase in weight and the consequent increase in BMI are also linked to the favourable changes in nutritional status. It should be born in mind that normal weight in older people corresponds to high range BMI [8]. During therapy, the patient reached a BMI value that is more advantageous for his age, as shown in ◆Table 1.

The success of the therapy was evident in the increases in albumin and total protein, which indicated improved plasma protein synthesis. The latter decreases when the supply of amino acids and energy is inadequate, but recovers relatively rapidly, once metabolism has stabilised [2]. Total cholesterol may be lowered in malnutrition, particularly in older individuals; this increased markedly during treatment [2, 9]. HDL-cholesterol was initially greatly reduced, but recovered to a low normal value on follow-up.

The patient's intestinal inflammation was an important cause of his poor nutritional status. The authors would consider it interesting to establish whether there is an inherent relationship between PVD and malnutrition; literature on this subject is sparse. Some small studies have indicated that malnutrition is frequent in patients with critical ischemia of the extremities and may be a predictor of the course of the disease and the therapy [10, 11]. Larger studies are needed to investigate these links.

Wound situation

As the patient had been under considerable stress for an extended period, he was highly motivated to continue the therapy – including the arginine supplementation – when he went home. The wound situation had greatly improved after two months. The authors consider that this was partially due to the administration of arginine, although the general improvement in nutritional status and the increased protein supply will also have favoured healing. It should be emphasised that the ulcer was only healed after nutritional intervention and improvement in the nutritional status, even though vascular perfusion was sat-

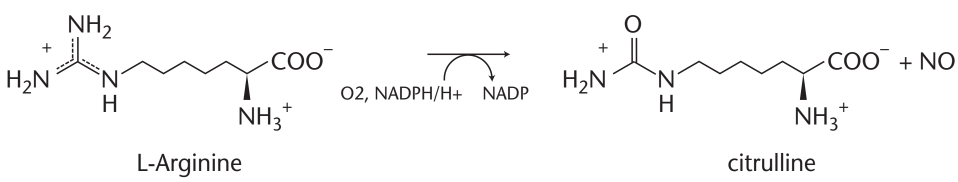


Fig. 5: **Biosynthesis of nitrogen monoxide from arginine by oxidation with the enzyme nitric oxide synthase**

isfactory after surgical treatment. This shows the importance of holistic treatment of disorders in wound healing. This must include the nutritional status and it may be misleading just to concentrate on the vascular system.

Conclusion

Specific nutritional intervention can make a major contribution to the successful treatment of malnourished PVD patients. Arginine supplementation can be used to improve wound healing. As this was a single case study (n = 1), it is unclear to what extent this supplementation contributed to the cure. Large interventional studies would be needed to validate the effect of arginine. Important components include the continuation of treatment at home, patient compliance and the incorporation of the measures into an overall therapeutic concept.

We wish to thank our hospital – Krankenhaus der Barmherzigen Brüder Linz – for assuming the costs that were additional to those for normal inpatient treatment (e. g. arginine supplementation).

Mag. Dr. Theodora Steindl-Schönhuber[1]
Diätologin Hermine König[2]
Dr. Gerald Lohr[3]
Krankenhaus der Barmherzigen Brüder Linz
Seilerstätte 2, 4020 Linz/Österreich

[1]Anstaltsapotheke
E-Mail: theodora.steindl@bblinz.at
[2]Diätologie
[3]Abteilung für Innere Medizin

Conflict of Interest
The authors declare no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

References

1. *Volkert D (2004) Ernährungszustand, Energie- und Substratstoffwechsel im Alter. Leitlinie Enterale Ernährung der DGEM und DGG. Ernährungs Umschau 51: 396–403*
2. *Hackl JM. Ermittlung des Ernährungsstatus. In: Stein J, Jauch KW (Hg). Praxishandbuch klinische Ernährung und Infusionstherapie. J.M. Springer Verlag, Berlin Heidelberg New York (2003)*
3. *Posthauer ME, Dorner B, Collins N (2010) Nutrition a critical component in wound healing. Adv Skin Wound Care 23: 560–572*
4. *European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel. Treatment of pressure ulcers: Quick Reference Guide. National Pressure Ulcer Advisory Panel, Washington DC (2009)*
5. *Benedikt MA, Weitgasser R (2006) Ernährungsmanagement bei Wundpatienten. JEM 8(2): 6–10*
6. *Bai Y, Sun L, Yang T et al. (2009) Increase in fasting vascular endothelial function after short-term oral L-arginine is effective when baseline flow-mediated dilation is low: a meta-analysis of randomized controlled trials. Am J Clin Nutr 89: 77–84*
7. *Volkert D, Bauer JM, Frühwald T et al. (2013) Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin (DGEM) in Zusammenarbeit mit der GESKES, der AKE und der DGG Klinische Ernährung in der Geriatrie. Aktuel Ernährungsmed 38: 164–187*
8. *Küpper C (2010) Mangelernährung im Alter. Ernährungs Umschau 57: 204–211*
9. *Lapin A (2006) Grenzen und Bedeutung der Labordiagnostik bei Mangelernährung im Alter. W.klin.W. 156(5–6): 142–148*
10. *Shah M, Martin A, Myers B et al. (2010) Recognising anaemia and malnutrition in vascular patients with critical limb ischaemia. Ann R Coll Surg Engl 92(6): 495–498*
11. *Shang-Hung C, Yueh-Ju T, Hsin-Hua C et al. (2014) Clinical predictors of long-term outcomes in patients with critical limb ischemia who have undergone endovascular therapy. Angiology 65(4): 315–322*
12. *URL: http://de.wikipedia.org/wiki/Endotheliale_Stickstoffmonoxid-Synthase Zugriff 19.08.13*
13. *Fritsch P. Dermatologie und Venerologie. 2. Aufl., Springer-Verlag, Berlin Heidelberg New York (2004)*
14. *Karlson P, Doenecke D, Koolman J et al. Karlsons Biochemie und Pathobiochemie. 15. Aufl., Thieme Verlag, Stuttgart (2005)*
15. *Biesalski HK, Fürst P, Kasper H et al. Ernährungsmedizin: Nach dem Curriculum Ernährungsmedizin der Bundesärztekammer und der DGE. 3. Aufl., Thieme Verlag, Stuttgart (2004)*
16. *van den Berg F. Angewandte Physiologie. 3. Aufl., Thieme Verlag, Stuttgart (2010)*
17. *Arginin.URL: http://de.wikipedia.org/wiki/Arginin Zugriff 10.08.13*
18. *Popovic PJ, Zeh HJ 3rd, Ochoa JB (2007) Arginine and immunity. J Nutr 137(6 Suppl 2): 1681–1686*

DOI: 10.4455/eu.2014.012