Disease-Specific, Versus Standard, Nutritional Support for the Treatment of Pressure Ulcers in Institutionalized Older Adults: A Randomized Controlled Trial

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OBJECTIVES: To investigate whether a disease-specific nutritional approach is more beneficial than a standard dietary approach to the healing of pressure ulcers (PUs) in institutionalized elderly patients.

DESIGN: Twelve-week follow-up randomized controlled trial (RCT).

SETTING: Four long-term care facilities in the province of Como, Italy.

PARTICIPANTS: Twenty-eight elderly subjects with Stage II, III, and IV PUs of recent onset (<1-month history).

INTERVENTION: All 28 patients received 30 kcal/kg per day nutritional support; of these, 15 received standard nutrition (hospital diet or standard enteral formula; 16% calories from protein), whereas 13 were administered a disease-specific nutrition treatment consisting of the standard diet plus a 400-mL oral supplement or specific enteral formula enriched with protein (20% of the total calories), arginine, zinc, and vitamin C ($P<.001$ for all nutrients vs control).

MEASUREMENTS: Ulcer healing was evaluated using the Pressure Ulcer Scale for Healing (PUSH; 0 = complete healing, 17 = greatest severity) tool and area measurement (mm^2 and %).

RESULTS: The sampled groups were well matched for age, sex, nutritional status, oral intake, type of feeding, and ulcer severity. After 12 weeks, both groups showed significant improvement ($P<.001$). The treatment produced a higher rate of healing, the PUSH score revealing a significant difference at Week 12 (-6.1 ± 2.7 vs -3.3 ± 2.4; $P<.05$) and the reduction in ulcer surface area significantly higher in the treated patients already by Week 8 ($-1{,}140.9 \pm 669.2\,mm^2$ vs $-571.7 \pm 391.3\,mm^2$; $P<.05$ and $\sim 57\%$ vs $\sim 33\%$; $P<.02$).

CONCLUSION: The rate of PU healing appears to accelerate when a nutrition formula enriched with protein, arginine, zinc, and vitamin C is administered, making such a formula preferable to a standardized one, but the present data require further confirmation by high-quality RCTs conducted on a larger scale. **J Am Geriatr Soc 57:1395–1402, 2009.**

Key words: pressure ulcers; nutrition; elderly; protein; arginine; zinc; vitamin C

All over the world, the incidence and prevalence of pressure ulcers (PUs) has reached significant proportions in long-term geriatric wards, with 3% to 30% of those admitted to institutions having PUs.[1–3] The consequences of this escalation in PUs are substantial and can be seen in the significant association with morbidity, mortality, length of "hospital" stay, and overall health costs,[2,4,5] but adherence to comprehensive prevention protocols has been shown to lead to a consistent reduction in ulcer incidence.[1,2] Preventing and treating PUs requires a complex interaction of interventions. In this respect, although avoiding (removing/redistributing) persistent pressure at bony sites is still the most important measure,[6] delivering adequate nutritional care has now been recognized as being of additional benefit.[1–4,6–9] In fact, in frail elderly patients, PUs and malnutrition frequently coexist,[10,11] and certain nutritional factors, such as recent weight loss,[12] impaired food intake, and low protein dietary intake,[11,13] appear to be associated with PU development. In addition, recent meta-analyses have clearly highlighted an association between enteral nutrition support, particularly with high protein content, and significantly lower PU incidence.[2,14] Unfortunately, particularly with regard to treatment, similar robust evidence from randomized controlled trials (RCTs) is still lacking, and no high-level nutritional recommendations have been produced.[14] The energy requirements of elderly patients

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with PUs and other comorbidities do not seem any greater than those of risk-matched controls.[15] In any case, adequate energy should be delivered to cover requirements and to promote new tissue synthesis. Preliminary experience supports the use of protein-enriched formulas in the healing of PUs.[16–18] Although earlier investigations into the healing process failed to demonstrate any consistent benefit from single-nutrient supplementation,[10] the recent literature provides some evidence of potential benefits that could derive from the concomitant supplementation of arginine, zinc, and antioxidant vitamins.[18,19] Accordingly, companies selling nutritional supplements are trying to achieve improvements in the field by producing putative "disease specific" formulations and to clarify the mechanisms involved, but until now, no high-quality trial has been designed to test the efficacy of such formulations. The present study was undertaken to evaluate the use of a disease-specific nutritional treatment enriched in protein, arginine, zinc, and vitamin C and to compare it with a standard protocol for improving the rate of PU healing.

MATERIALS AND METHODS

A RCT with a 12-week follow-up was performed, with data collected over a 5-month period (November 2007–March 2008). Residents of long-term care aged 65 and older admitted to four different facilities of the province of Como (Italy) were screened for PUs. Subjects were considered eligible if they had Stage II, III, or IV lesions as assessed according to the revised (2007) National Pressure Ulcer Advisory Panel staging system.[20] Patients fed orally and through feeding tubes were included. Exclusion criteria were presence of acute illness (e.g, infection) or chronic disease (e.g., diabetes mellitus, peripheral vascular disease, autoimmune or neoplastic disorders) possibly affecting the nutritional intervention and healing process, positive culture from PU swab sampling, use of immunosuppressive therapies, development of the lesion more than 1 month before evaluation, and lack of dietary adherence ($<85\%$ of prescription). Informed consent was obtained from all patients enrolled.

Allocation to the intervention groups was defined according to a computer-generated randomization list.

This study was performed in adherence to the principles established by the Declaration of Helsinki, and the ethics committees of the institutions involved gave final approval.

Nutritional Interventions

All patients received nutritional support of at least 30 kcal/kg per day regardless of feeding method; no modification was made for patients who were already receiving more than 30 kcal/kg per day before enrollment in the study.

Treatment Group

In participants who were fed orally, two bottles (400 mL) of a high-energy enriched formula (Cubitan, Nutricia, Milan, Italy), which provided a total of 500 kcal, 34 g protein, 6 g arginine, 500 mg vitamin C, and 18 mg zinc, were administered along with a standard hospital diet to reach the estimated energy requirements.

In participants who were tube fed, 1,000 mL of a high-protein formula (20% energy from protein; Cubison, Nutricia) enriched with arginine, zinc, and vitamin C (in 100 mL: 100 kcal, 5.5 g protein, 0.85 g arginine, 38 mg vitamin C, and 2 mg zinc) were infused together with appropriate volumes of an isocaloric standard formula (Nutrison; 16% energy from protein, in 100 mL: 100 kcal, 4.0 g protein, 0 g arginine, 10 mg vitamin C, and 1.2 mg zinc) to reach the energy requirements.

Control Group

In participants who were orally fed, the nutritional treatment consisted of a standard hospital diet (16% energy from protein) without any additional supplement. In subjects who were tube fed, energy and the infusion of appropriate volumes of a standard formula satisfied protein requirements (Nutrison).

PU Care

All patients received similar wound care according to standard protocols used in the wards. Local pressure to the areas was avoided, or at least reduced, using a turning and repositioning program, a dynamic air mattress on the bed, and a gel cushion for when sitting out of bed. The same professional nurse, who was blinded to the nutritional interventions, always applied topical treatments, in accordance with accepted guidelines;[6] the treatment depended on lesion depth and position, amount of exudate, type of tissue in the wound base, and presence of infection. In this last case, local antibiotic therapy was delivered according to germ isolation and antibiogram results. Systemic therapy was instituted only in the presence of bacteriemia or sepsis, defined as fever ($>38^{\circ}$C) or hypothermia ($<36^{\circ}$C) and one or more positive blood cultures for pathogenic organisms.

Nutritional and PU Assessments

Anthropometric and biochemical data were collected at the beginning (baseline) and at the end (Week 12) of the study. Weight, to the nearest 0.1 kg, was measured using the same calibrated scale. For subjects who were bedridden, a chair scale or a hoist provided with a weighing device was used. Estimated height was derived to the nearest 0.5 cm from knee height using anthropometric calipers according to standard procedures,[21] and body mass index (BMI) was calculated. Any history of recent weight loss was obtained retrospectively from the clinical register of the patients. A biochemical examination, after 8 to 12 hours fasting, included total blood count, liver function tests, urea, creatinine, electrolytes, total protein evaluation, albumin, transferrin, glucose, total cholesterol, and serum zinc.

Nutrition-related risk of complications was graded using the Geriatric Nutritional Risk Index, which is based on the combined predictive value of albumin and low body weight ([1.489 $\times$ albumin, g/L]+[41.7 $\times$ present/ideal body weight]). This tool was recently introduced into clinical practice because of its significant association with the occurrence of major outcomes, such as pressure ulcers, infection, and death. Given the frequent difficulties associated with elderly patient participation in nutritional assessment, the feasibility of such a tool has also been highlighted in different settings, particularly in long-term care facilities.[22,23]

Nutritional intake before and during the study was assessed as follows. Types and amounts of infused formula were collected from the clinical register of every patient receiving enteral administration. In participants who were orally fed, the same well-trained dietitian weighed and recorded the amount of food delivered to and left by the patients at three main meals (breakfast, lunch, dinner). In this way, the average daily protein (g/d), vitamin C (mg/d), arginine (g/d), and zinc (mg/d) intake was computed manually using the Italian National Table of Food Composition.[24] The analysis for the treatment group included the nutritional supplement contribution. The mean of three consecutive days was considered for the statistical analyses, and throughout the study, a weekly assessment was made of dietary compliance. Data were also normalized for patient body weight (g or mg/kg per day).

The same well-trained operator (AG), who was blind to the nutritional interventions performed PU assessments at defined time points: baseline and Weeks 2, 4, 6, 8, and 12. In patients with multiple lesions, the most severe lesion was considered for the analysis. Changes (improvement or deterioration) in ulcer healing were monitored and described using the Pressure Ulcer Scale for Healing (PUSH) tool.[25] This tool assigns subscores according to surface area (length × width), exudate amount, and tissue type in the ulcer bed. Thus, a final total score categorizes lesion severity through a scale ranging from 0 (completely healed) to 17 (greatest severity). Finally, to avoid any possible bias in patient enrollment, an assessment was made of the patients' baseline risk for PU development; this was computed using the Norton Scale, one of the first-developed risk-assessment scales and one that is still widely used because of its relative ease of use and its accuracy, and compared with the specialist nurse's clinical judgment.[26,27] The Norton Scale is made up of five subscales that measure the functional capabilities (physical condition, mental status, activity, mobility, and incontinence) of the person at risk. Each subscale assigns a score of 1 to 4 points (1 for low level and 4 for highest level of functioning), contributing to a total score ranging from 5 to 20.

Outcomes

The primary endpoint was PU healing, as described by reduction in PUSH score and lesion area (mm^2 and %). Secondary endpoints were improvements in nutritional variables (weight, BMI, and biochemistry), infection occurrence (days of antibiotic therapy), and hospitalization.

Statistical Analysis

Data are presented as means ± standard deviations. Differences in proportions were assessed using the chi-square or Fisher exact test where appropriate. Comparisons of between-group and within-group quantitative variables were performed using unpaired and paired, respectively, Student *t*-tests. The Mann-Whitney *U*-test was used for nonhomogeneous distribution of variance. Reduction in PUSH score and PU area from baseline to 12-week follow-up was analyzed using analysis of variance (ANOVA) for repeated measures (Dunnett test for post hoc comparison of means). Finally, multiple regression analyses were performed to test, where possible, the independent contributions of specific nutrients (protein, arginine, vitamin C, and zinc), energy intake, and overall formula (independent variables) to ulcer healing. Such healing (and degree of healing) is defined as decrease (Δ) in PUSH score and percentage of reduction in ulcer area (dependent variables). All statistical analyses were performed using STATISTIX 7.0 (Analytical Software, Tallahassee, FL). The level of significance was established as $P < .05$.

RESULTS

In total, 371 elderly long-term care residents were screened; of these, 39 (10.5%) presenting with PUs (Stages II, III, and IV) were considered eligible for inclusion in the study. Nine of these were excluded according to the exclusion criteria (3 with a >1-month history of PU, 3 with diabetes mellitus, 2 with terminal neoplastic disease, and 1 with peripheral vascular disease), leaving 30 patients (77%; 18 women and 12 men) to be randomly allocated to the treatment or control group. Two patients (both with a single lesion) in the treatment group died within the first 4 weeks of the follow-up period (on Days 15 and 22). As a result, the final analysis sample consisted of 28 participants (13 in the treatment group and 15 in the control group). Thus, the analyses cannot be considered intention to treat, although any possible bias to results may be partly excluded on the grounds that nutritional intervention can only be considered effective if it produces a reduction of 20% to 40% in the PU in the first 4 weeks.[28]

Demographic and Clinical Features of the Study Sample

The baseline demographic and clinical features of the population and the location and number of ulcers at the different sites are presented in Table 1. As shown, no differences across these variables were detected between groups, and the location of the ulcers was comparable. Of the participants recruited, 18 were tube fed (64.3%; 9 in the treatment group (69.2%) and 9 in the control group (60%); $P = .71$, Fisher exact test), and 15 had more than one lesion (10 in the treatment group (76.9%) and 5 in the control group (33.3%); $P = .03$, Fisher exact test).

Biochemical Variables

At baseline, the study groups were well matched for biochemical parameters (Table 2), although at the end of the study period, the enriched formula nutritional intervention resulted in significantly higher zinc serum levels ($P < .01$ vs baseline). Moreover, after 12 weeks, the control group showed lower serum zinc levels than the treatment group ($P < .03$) and a significant increase in total lymphocyte count ($P < .002$ vs baseline).

Food Intake and Adherence to Interventions

Average daily dietary intake data are presented in Table 3. At baseline, there were no significant differences in total and weight-normalized (/kg/d) energy, protein, arginine, zinc, or vitamin C intake. In both groups, the intervention protocols resulted in a significant increase in energy and all of the considered nutrients. As expected, allocation to the treatment protocol was associated with significantly higher protein (1.5 vs 1.2 g/kg per day), arginine, zinc, and vitamin C intake ($P < .001$ for all). Total dietary adherence

Table 1. Baseline Demographic and Clinical Features of the Population

Variable	Treatment (n = 13)	Control (n = 15)
Male:female*	4:9	6:9
Age, mean ± SD	82.1 ± 9.6	81.4 ± 9.9
Body mass index, kg/m^2, mean ± SD	20.8 ± 3.2	23.1 ± 5.0
Percentage weight loss, mean ± SD	− 5.7 ± 5.0	− 3.6 ± 3.1
Geriatric Nutritional Risk Index, mean ± SD (range)	81.4 ± 11.9 (62.9–101.1)	80.8 ± 9.3 (65.1–96.1)
Norton index, mean ± SD (range)	6.8 ± 1.6 (5–11)	8.7 ± 4.0 (5–17)
Oral feeding:tube feeding*	4:9	6:9
Diagnoses, n		
Vascular dementia	4	5
Alzheimer's disease	3	2
Cerebrovascular accident	4	5
Psychiatric disorders	2	2
Multiple sclerosis	—	1
Pressure ulcers, n		
Stage		
II	2	3
III	4	4
IV	7	8
Location		
Sacrum	5	8
Back	0	1
Foot	4	3
Ankle	4	3
Number of lesions†		
1	3	10
2	7	2
3	2	3
4	1	0

Statistical comparisons between groups were performed by unpaired Student *t*-test, Mann-Whitney *U*-test (for not Gaussian distribution) or Fisher exact test (categorical variables).

No significant differences were detected between the treatment and control groups.

P = *.71, † .03, Fisher exact test.

(percentage of food consumed to that delivered) was high (94.3% control; 94.7% treatment), and oral supplement consumption was successful. Thus, all patients reached the 85% or greater proposed cutoff. Oral nutritional support was well accepted, and none of the patients developed any adverse reaction to the supplements.

Primary Endpoint (PU Healing)

With regard to the trial's primary endpoint, the provision of adequate amounts of energy ($\geq$30 kcal/kg per day) and protein ($\geq$1.2 g/kg per day) was effective in improving PU healing (ANOVA for repeated-measures analysis, $P<.001$ for both interventions; Figure 1A and B). Table 4 shows the time-course progression of the healing-process indexes of both groups. Disease-specific nutritional treatment was associated with a significantly higher rate of PU healing. The differences in the interventions became statistically significant in PUSH score at Week 12 ($P<.05$) and in ulcer area from Week 8 ($P<.05$). Overall, the patients treated with the enriched formula showed a significantly higher mean reduction in PU area (Figure 1C; $\sim$ 57% vs $\sim$ 33% at Week 8, $P<.02$; $\sim$ 72% vs $\sim$ 45% at Week 12, $P<.005$). Complete healing was documented for only one patient in the treatment group. Furthermore, the effect of single nutrients and that of the overall "treatment factor" on wound healing were explored. In the overall population, separately adjusted (sex, age, and tube feeding) univariate linear regression models revealed a significant association between a lower (Δ) PUSH score (dependent variable) and greater arginine intake (Δmg/kg per day; coefficient of determination (R^2) = 0.31, $P<.05$) and the use of a disease-specific formula ($R^2 = 0.37$, $P<.02$), although the grater arginine (Δmg/kg per day), vitamin C (Δmg/kg per day), and zinc (Δmg/kg per day) intake, as well as the use of the whole formula, had a significant effect in reducing the (Δ%) PU area (separate models adjusted for sex, age, and tube feeding: $R^2 = 0.42$, $P<.01$; $R^2 = 0.43$, $P<.01$; $R^2 = 0.40$, $P<.02$; $R^2 = 0.50$, $P<.01$, respectively). Moreover, there was no significant effect on wound healing (ΔPUSH and area) despite the increased energy (Δkcal/kg per day) and protein (Δg/kg per day) support. Therefore, whether there remained a significant independent association with single nutrients was tested also after including the factor "use of whole formula" (coded as 0 = control and 1 = treatment) in models previously showing an association. Only the factor "use of whole formula" was significantly associated ($R^2 \geq 0.42$, $P<.03$ in all the analyses), whereas the other variables did not enter the model.

Secondary Endpoints

With regard to secondary outcome, none of the patients required hospitalization to treat complications, although the control group had a slightly higher occurrence of infectious complications (9 subjects vs 3 subjects; $P = .07$, Fisher exact test) and a significantly greater number of days of antibiotic therapy (103 vs 36; $P<.001$, two-sample proportion test).

DISCUSSION

Malnutrition in elderly populations is associated with poor clinical outcome and is an indicator of risk not only for greater mortality, but also for a variety of other complications.[22,23,29] The prevalence of protein-energy malnutrition in nursing home residents ranges from 23% to 85%, and a structured approach to its ad hoc management has been proposed.[30] Unfortunately, there is only limited evidence of the effect of nutritional intervention in preventing PUs.[2] Indeed PUs remain a common problem, but early treatment, including nutrition, might be effective in improving some wound-healing indices, thus reducing morbidity, mortality, length of stay, and overall health costs.[2,4,5,9] Nutritional status is a factor that can be influenced positively, and delivering high-quality nutritional care is an easy process.[7] In this scenario, the present RCT clearly suggests that disease-specific nutritional support is feasible and safe and in selected cases should be preferred to the standard

Table 2. Changes in Clinical and Biochemical Parameters Over the Study

	Mean ± Standard Deviation (Range)			Mean ± Standard Deviation (Range)		
	Treatment			Control		
Parameter	Baseline	Week 12	Change	Baseline	Week 12	Change
Weight gain, kg	53.6 ± 8.8	55.5 ± 9.4	1.8 ± 2.7	64.3 ± 13.6	65.0 ± 12.9	0.7 ± 2.6
Body mass index, kg/m^2	20.8 ± 3.2	21.5 ± 3.3	0.7 ± 1.1	23.0 ± 5.0	23.3 ± 4.7	0.3 ± 0.8
Total protein, g/L	63.6 ± 8.4	66.9 ± 6.5	3.3 ± 7.0	63.4 ± 6.7	65.6 ± 4.5	2.2 ± 4.5
Albumin, g/L	29.2 ± 8.5	30.6 ± 5.0	1.4 ± 7.2	27.9 ± 5.6	29.2 ± 4.8	1.3 ± 3.4
Transferrin, mg/dL	171.3 ± 44.1	179.5 ± 57.2	8.2 ± 29.0	161.3 ± 45.7	158.7 ± 33.8	− 2.6 ± 25.3
Total cholesterol, mg/dL	150.5 ± 40.7	161.2 ± 51.5	10.6 ± 23.6	138.6 ± 30.2	147.1 ± 25.3	8.5 ± 18.5
Hemoglobin, g/L	11.4 ± 1.8	11.6 ± 1.7	0.2 ± 1.5	11.1 ± 1.3	11.2 ± 1.4	0.1 ± 0.7
Lymphocytes/mm^3	1,999 ± 898.8	2,017 ± 650	18 ± 647	1,585 ± 500	2,156 ± 615[‡]	571 ± 538
Zinc, μg/dL	346.0 ± 285.5	453.5 ± 267.6*[†]	107.5 ± 106.6	272.9 ± 260.8	240.3 ± 181.6	− 32.5 ± 87.1
Geriatric Nutritional Risk Index score	81.4 ± 11.9 (62.9–101.1)	84.2 ± 8.7 (65.0–102.3)	2.8 ± 10.3 (− 16.6–17.4)	80.8 ± 9.3 (65.1–96.1)	83.1 ± 7.6 (72.8–102.3)	2.2 ± 5.6 (− 4.6–17.2)

Statistical comparisons were performed as follows: unpaired Student *t*-test or Mann-Whitney *U*-test (between intervention groups).
* $P < .03$; paired Student *t*-test (within single intervention group compared with baseline).
$P <$ [†].01, [‡].002.

approach for improving the rate of PU healing. Unfortunately, there is little literature addressing this issue, and much of the available data are not sufficiently comparable—population and setting heterogeneity, supplement duration variability, nonhomogeneous healing measurement—to allow an evaluation of consistent effects.[2] Along with this, consideration must also be given to the fact that the only well-documented evidence for the use of disease-specific nutrition concerns the use of diabetes-specific formulas in the management of glycemic control.[31]

Despite this "literature lack," recent overviews of the use of enteral nutrition in PU treatment report a trend

Table 3. Average Dietary Intake, Both Groups, Throughout the Study

	Mean ± SD				Mean ± SD				
	Treatment Group				Control Group				
Nutrient	Before	Study Value	Change	*P*-Value*	Before	Study Value	Change	*P*-Value*	*P*-Value
Energy, kcal/d	1,441 ± 262	1,586 ± 211	145 ± 167	.01	1,532 ± 230	1,848 ± 309	316 ± 239	.002	.02
Carbohydrates, %	51.5 ± 3.5	49.0 ± 3.5	− 2.5 ± 0.8	< .001	51.0 ± 5.3	51.3 ± 4.9	0.3 ± 0.9	.12	.20
Proteins, %	16.1 ± 0.2	19.7 ± 0.9	3.6 ± 0.8	< .001	16.6 ± 2.1	16.4 ± 1.1	− 0.2 ± 1.1	.64	< .001
Fat									
%	32.4 ± 3.5	31.3 ± 3.6	− 1.1 ± 1.3	.01	32.4 ± 4.9	32.3 ± 4.8	− 0.1 ± 0.6	.38	.58
kcal/kg per day	27.3 ± 5.5	30.0 ± 4.0	2.7 ± 3.0	.01	24.8 ± 6.6	29.4 ± 4.7	4.6 ± 3.1	< .001	.74
Protein, g/kg per day	1.1 ± 0.2	1.5 ± 0.2	0.4 ± 0.1	< .001	1.0 ± 0.3	1.2 ± 0.2	0.2 ± 0.1	< .001	.001
Arginine	2,004 ± 885	9,822 ± 888	7,818 ± 1,695	< .001	2,322 ± 930	2,888 ± 1,402	566 ± 663	.001	< .001
From protein, mg/d			227 ± 466				566 ± 663		
From formula									
mg/d			7,590 ± 1,261				—		
mg/kg/d	39 ± 22	186.0 ± 22.4	146.5 ± 26.5	< .001	38.3 ± 21	46.0 ± 22.4	7.7 ± 7.6	.002	< .001
Zinc									
μg/d	14.1 ± 5.9	26.7 ± 2.4	12.6 ± 4.3	< .001	14.5 ± 5.4	17.5 ± 6.1	3.0 ± 2.2	< .001	< .001
μg/kg per day	0.26 ± 0.10	0.51 ± 0.07	0.24 ± 0.11	< .001	0.23 ± 0.11	0.27 ± 0.08	0.05 ± 0.03	< .001	< .001
Vitamin C									
mg/d	127.8 ± 32.3	492.5 ± 69.2	364.7 ± 86.0	< .001	144.0 ± 46.9	201.4 ± 57.9	57.4 ± 66.0	.007	< .001
mg/kg per day	2.4 ± 0.5	9.5 ± 2.7	7.1 ± 2.7	< .001	2.3 ± 0.6	3.2 ± 0.9	0.9 ± 1.1	.007	< .001

Changes are calculated as time point versus baseline; ns = not significant.
P-values are provided according to statistical analyses using paired Student *t*-tests (* within single study group vs baseline), unpaired Student *t*-test or Mann-Whitney *U*-test (between-group comparison; normal and nonnormal distribution, respectively).
No significant differences in baseline values were detected between the groups.
SD = standard deviation.

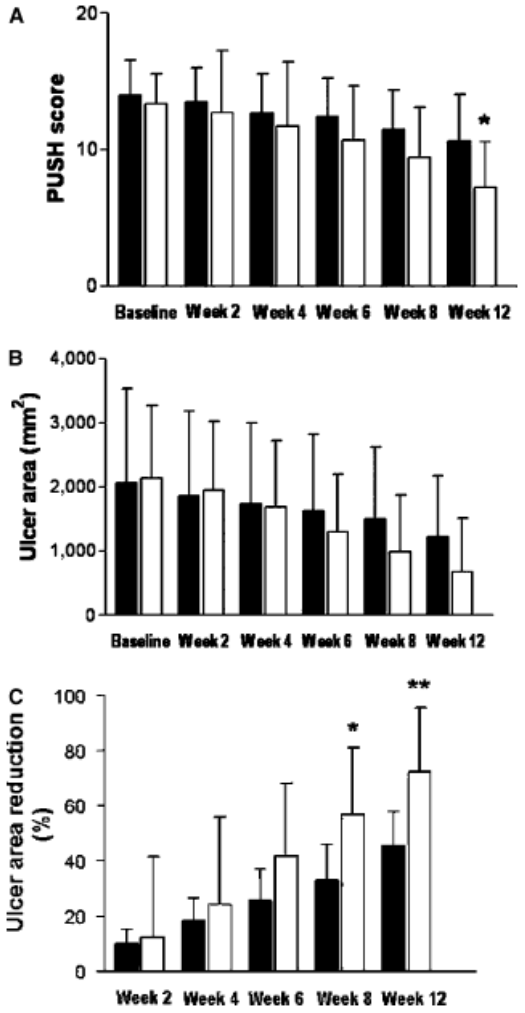

Figure 1. Trend of healing process over the study period: □, treatment; ■, control. (A) Pressure Ulcer Scale for Healing (PUSH) score: analysis of variance (ANOVA) for repeated measures, $P<.001$ in both groups (Dunnett post hoc comparison, $P<.01$ from week 6); *treatment significantly different from control at the same time point (Mann-Whitney *U*-test; $P<.02$). (B) Pressure ulcer area: ANOVA for repeated measures, $P<.001$ in both groups (Dunnett post hoc comparison, $P<.01$ from week 6); no statistically significant differences were detected between groups at any time points. (C) Percentage of decrease in pressure ulcer area: treatment significantly different from control at Weeks 8 and 12 (Mann-Whitney *U*-test; $*P<.02$ and $**P<.005$, respectively).

toward better healing using specific-nutrient supplementation.[2,19] Accordingly, the present study has effectively investigated this issue, particularly with regard to the lack of energy and protein intake contribution, and revealed that reaching the target of 30 kcal/kg per day did not seem to produce any significant effect on wound healing. Moreover, the controls showed a slightly greater increase in calorie intake (4.6 ± 3.1 kcal/kg per day) than the treated patients (2.7 ± 3.0 kcal/kg per day, $P=.13$). Energy requirements do not seem to be a critical factor in patients with PUs,[15] and the recommendations suggest treating malnutrition using a nutritional support ranging from 25 to 35 kcal/kg per day.[15,32,33] Similarly, there was no confirmation of the expected significant effect with regard to protein intake, and previous studies, which reported a significant anabolic effect from short-term supplementation of 1.5 g/kg per day in undernourished elderly subjects,[34] suggest improvement in healing of existing lesions using high-protein-content (~ 1.8 g/kg per day) treatments.[2,10,16,17] Alternatively, aging is frequently associated with unbalanced protein turnover,[35] and increasing intake beyond 1.5 g/kg per day may not improve nitrogen balance and may cause dehydration.[10,36] Perhaps the supplementation used in the current trial was not enough to produce an effect on the rate of healing. It is also possible that the effect of the overall treatment formula might have masked the healing effect. Accordingly, it is not possible to provide any practical suggestion for the amount of protein that should be provided in a nutritional supplement, but in the light of previous experience with complicated patients[13] and in agreement with recent reassessments in healthy older adults,[37] intake of 1.5 g/kg per day might be a positive step. Finally, it cannot be excluded that reaching a higher intake of calories and protein would have additionally benefited the rate of healing.

As anticipated above, these findings support the role of specific nutrients in the healing process, although the effect of the overall disease-specific formula seems to predominate. This is what the multivariate analyses revealed, but the results should be interpreted cautiously, especially in view of the small sample size of the study.

Few high-quality clinical trials have investigated the therapeutic application of nutritional factors. Moreover, specific nutrients (zinc and vitamin C) have usually been studied independently, and trials have failed to demonstrate a significant difference in the rate of healing of patients who are not deficient, even when supplemented with above-therapeutic dosages.[10] Alternatively, it is well accepted that vitamin C is essential for wound repair, and zinc might be implicated in delayed healing, also through impaired immune function.[38] Along with this, the administration of the semi-essential amino acid arginine has shown pleiotropic effects in healthy older adults (elevation of serum insulin-like growth factor concentrations and improvement of nitrogen balance and immune response and antioxidant proprieties),[39,40] but no study in patients with PUs has been conducted to evaluate its supplementation alone. However, a recent animal model experience describes better wound healing with enhanced expression and deposition of extracellular matrix major components (e.g., type I and III collagen).[41] Moreover, the significant contribution of an insulin-related anabolic effect, secondary not only to nutritional repletion, but also to the independent arginine effect, cannot be excluded.[42]

Finally, only two RCTs have preliminarily investigated the efficacy of pooled supplementary arginine, zinc, and vitamin C.[18,19] A short-term (2- or 3-week follow-up) three-treatment comparison was performed (normal hospital diet vs high-protein vs high-protein plus additional arginine, zinc, and antioxidant vitamin), but the improved rate of healing was reported as inconclusive in the combined-treatment group of both studies. Unfortunately, major biases and shortcomings were detected. In the first trial,[18] the data on wound healing, obtained using a "PU status tool," were presented only graphically. Moreover, no information was provided on PU area reduction, dietary

Table 4. Description of Pressure Ulcer Healing Throughout the Study

	Mean ± Standard Deviation							
	Pressure Ulcer Scale for Healing Score*				Ulcer Area (mm^2)			
Time Point	Treatment	Change	Control	Change	Treatment	Change	Control	Change
Baseline	13.5 ± 2.2	—	14.0 ± 2.6	—	2,151 ± 1,135	—	2,069 ± 1,471	—
Week 2	12.8 ± 4.5	− 0.6 ± 3.1	13.5 ± 2.5	− 0.5 ± 0.9	1,966 ± 1,074	− 185 ± 260	1,869 ± 1,312	− 200 ± 213
Week 4	11.8 ± 4.7	− 1.6 ± 3.5	12.7 ± 2.9	− 1.3 ± 1.3	1,706 ± 1,033	− 445 ± 485	1,746 ± 1,257	− 323 ± 264
Week 6	10.8 ± 4.0	− 2.6 ± 2.8	12.4 ± 2.8	− 1.6 ± 1.5	1,315 ± 899	− 836 ± 577	1,629 ± 1,200	− 440 ± 320
Week 8	9.5 ± 3.7	− 3.9 ± 2.7	11.5 ± 2.9	− 2.5 ± 2.0	1,010 ± 881	− 1,141 ± 669‡	1,498 ± 1,126	− 571 ± 391
Week 12	7.4 ± 3.4‡	− 6.1 ± 2.7†	10.7 ± 3.4	− 3.3 ± 2.4	701 ± 835	− 1,450 ± 803‡	1,228 ± 952	− 841 ± 559

* Range 0 = complete healing, 17 = greatest severity.

Changes are calculated as time point versus baseline.

Statistical comparisons of the intervention groups were performed using the Mann-Whitney *U*-test: $P <$ †.02, ‡.05.

intake and adherence, or inclusion and exclusion criteria (e.g., history of ulcer, other illnesses). However, another recent study,[19] despite the small set of patients, was well designed and presented an adequate description of the exclusion and inclusion criteria. Unfortunately, the ulcer status of the different treatment groups was monitored only using the PUSH tool, and unselected biases occurred over the study period, leading to a significant overestimation of the healing power of the enriched formula; patients in the "multiple-supplement" group were older and had a lower baseline BMI and better dietary adherence during the study. Moreover, there was no information given about oral intake before the treatment period, and it cannot be excluded that, in this group, the oral intake was more compromised, thus enhancing the healing effect of nutritional repletion.

Taken together, these considerations support the consistency of the results of the current study, in which many limitations have been overcome. Unfortunately, other limitations must be highlighted: the smallness of the sample and the absence of a control group supplemented only with protein. Only elderly institutionalized people with a recent history of PUs were included, so it was not possible to extend the use of the disease-specific formula to all of the PU patients. Moreover, the orally and tube-fed subjects were analyzed together, and this choice might have strengthened the results through the effect of better adherence to treatment; subjects undergoing oral nutritional support frequently consume supplements at the expense of other food,[43] but providing the results of subgroup analyses would have been of little statistical significance. With regard to statistics, no intention-to-treat analysis was performed, in accordance with the exclusion of dead patients from the treatment group, although it appears that at least 4 weeks of follow-up is required to appreciate the effectiveness of nutritional intervention in the healing of PUs.[28] Finally, it is also possible that the difference found in ulcer healing was partly due to a mild impairment of immunocompetence, as described according to total lymphocyte count, a parameter considered to contribute significantly to lesion development,[10,12,44] even though no significant effect was detected using ad hoc linear regression analysis (data not shown in Results section). Along with this, immune function might have negatively influenced the occurrence of infection in the control group, although the well-known positive effect of nutritional repletion and micronutrient status[45,46] on immune response might support an immune-enhancing effect of the enriched formula. In conclusion, in patients affected by PUs, the use of disease-specific nutritional support should be considered, at least in elderly residents of long-term care with a recent history of PUs. This not only would probably allow shorter healing times, but would also reduce the overall costs of PU care. Further high-quality studies (RCTs) are needed to confirm these preliminary results, which have opened a new field of research. In view of this, the application of disease-specific nutritional protocols and study design should involve major items such as the setting in which PUs occur (hospital–acute care, subacute care, long-term care, home care), the age of the recruited population (young, middle aged, elderly), the history of ulcers (recent onset, chronic disease) and concomitant diseases. Moreover, a pharmacoeconomic evaluation should also be considered to evaluate the cost-effectiveness of using disease-specific formulas.

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