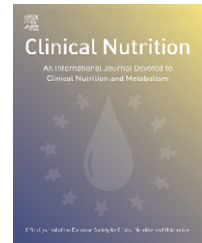




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ORIGINAL ARTICLE

# A diet enriched in eicosapentanoic acid, gamma-linolenic acid and antioxidants in the prevention of new pressure ulcer formation in critically ill patients with acute lung injury: A randomized, prospective, controlled study

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## KEYWORDS

Fish oil;  
Pressure ulcer;  
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## Summary

**Background & aims:** Pressure ulcers are a significant burden in the ICU. Many factors have found to be associated with pressure ulcers including malnutrition. While it has been recognized that high protein diets decrease the incidence of pressure ulcers, the role of lipids as well as vitamins and antioxidants remains unclear. The aim of this study was to evaluate the preventive and healing effects of an enteral diet enriched in eicosapentanoic acid (EPA) and gamma-linolenic acid (GLA) and vitamins (vitamins A, C and E) on pressure ulcers.

**Methods:** One hundred patients with acute lung injury were included in a larger study evaluating the effects of lipids and vitamins on respiratory function. A secondary end point, occurrence and healing of pressure ulcers was included. A diet enriched in lipids (EPA, GLA) and vitamins (vitamins A, C and E) was compared with a diet similar in macronutrient composition. The occurrence and healing of pressure ulcers was evaluated according to the National Pressure Ulcer Panel. Nutritional assessment included calorie intake, resting energy expenditure, levels of serum prealbumin, albumin, vitamins A and E, zinc and copper. C-reactive protein and procalcitonin were also measured.

**Results:** Patient's age, severity of disease and gender distribution were similar in the two groups. The study group had a higher body mass index. At baseline, the pressure ulcer

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score was similar in the two groups A significantly lower rate of occurrence of new pressure ulcers was observed in the study group compared to the control group ( $p < 0.05$ ). No difference was observed in the healing of existing pressure ulcers in the study as opposed to the control group. There was no significant difference in the nutritional parameters between the two groups.

**Conclusions:** A diet enriched with EPA, GLA and vitamins A, C and E is associated with a significantly lower occurrence of new pressure ulcers in critically ill patients with acute lung injury.

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## Introduction

A pressure ulcer is a local area of tissue inflammation and injury that develops when soft tissue is compressed between bone and an external surface.<sup>1</sup> Pressure ulcers may be the result of immobility, excessive mechanical load, incontinence, advanced age and malnutrition.<sup>2</sup> ICU patients have higher risks to create pressure ulcers, due to a catabolic state, use of noradrenaline and mainly because of an inflammatory state.<sup>3</sup> Impaired nutrition may influence tissue vulnerability to extrinsic factors such as pressure.<sup>4,5</sup> The European Pressure Ulcer Advisory Panel Recent has recently issued nutritional guidelines for the prevention and treatment of pressure ulcers.<sup>6</sup> While the importance of protein-calorie rich supplementation is recognized, the value of vitamin and trace element supplementation is unclear.<sup>7</sup> A recent study found that a diet enriched with arginine, vitamin C, and zinc given to a small set of patients improved the rate of healing of pressure ulcers when compared with a standard diet.<sup>8</sup>

The purpose of this prospective, randomized study was to compare the incidence and the healing of pressure ulcers in a sample of critically ill, mechanically ventilated patients suffering from acute lung injury between those receiving a diet enriched in lipids (eicosapentanoic acid (EPA), gamma-linolenic acid (GLA)), vitamins A, C and E to a comparable diet of macronutrients. This aim was defined as a secondary end point in a larger study.<sup>9</sup>

## Material and methods

One hundred patients suffering from acute lung injury defined by a  $\text{PaO}_2/\text{FIO}_2$  ratio below 250 were included in this prospective, randomized, non-blinded study. Exclusion criteria included patients with head trauma, cerebral bleeding, coagulation disorders, those receiving steroids in a dose  $> 0.25$  mg/kg/day methylprednisolone or non-steroidal anti-inflammatory agents, patients less than 18 years and pregnant patients. Diarrhea was noted and patients were excluded if loose stools were occurring in more than three times. The study was prospective, randomized and not blinded. The control group received a ready to feed, high fat, low carbohydrate, enteral formula (Pulmocare, Ross Laboratories, Abbott, Chicago, USA). The study group received a formula with the same macronutrient composition but with additions of EPA, GLA and vitamins A, C and E (Oxepa, Ross Laboratories) (see Table 1). Resting energy

expenditure was measured using an indirect calorimeter (Deltatrac II, datex-Ohmeda, Helsinki, Finland) and at least 50% of the  $\text{REE} \times 1.25$  was administered to patients in both groups from the first day according to randomization. Enteral feeding was then rapidly increased to reach  $1.25 \times \text{REE}$  from the second day. Daily enteral intake was recorded.

**Table 1** Composition of the two formulas (MTC are medium chain triglycerides).

Nutrient	Control	EPA+GLA
<b>Protein</b>		
% of total calories	16.7	16.7
g/L	62.6	62.5
Source	87% sodium caseinate 13% calcium caseinate	87% sodium caseinate 13% calcium caseinate
<b>Carbohydrate:</b>		
% of total calories	28.1	28.1
g/L	105.7	105.5
Source	46% maltodextrin 54% sucrose	45% maltodextrin 55% sucrose
<b>Lipids</b>		
% of total calories	55.2	55.2
g/L	92.1	93.7
Source	55.8% canola oil 20% MCT 14% corn oil 7% high oleic safflower oil 3.2% soy lecithin	31.8% canola oil 25% MCT 20% fish oil 3.2% soy lecithin
<b>Vitamins:</b>		
Vitamin E (IU/L)	85	317
Vitamin C (mg/L)	317	844
$\beta$ -carotene (mg/L)	—	5.0
Taurine (mg/L)	160	316
L-carnitine (mg/L)	160	181
Caloric density (kcal/mL)	1.5	1.5
Osmolality (mOsm/kg/ $\text{H}_2\text{O}$ )	475	493

Anthropometric and nutritional parameters including age, sex, weight and height, body mass index (BMI), APACHE II score,<sup>10</sup> prealbumin and albumin levels were measured (every 3 days). In 28 randomized patients, blood samples were taken for analysis of vitamins A and E (HPLC inditector UV) as well as C-reactive protein and procalcitonin (Hitachi 747 automatic analyzer) for markers of inflammation.

The occurrence and the state of pressure ulcers were checked daily and graded according to the National Pressure Ulcer Advisory Panel.<sup>6</sup> Grade 1 is described as the skin showing no resolution of the redness after pressure release. Grade 2 was characterized by a wound appearing as bullous, where the pressure ulcer looks like a blister, an abrasion or a shallow crater. The epidermis is peeled away or cracked open, creating a portal of entry for microbes. Grade 3 is defined as full-thickness skin loss involving subcutaneous tissue up to the fascia while Grade 4 looks like a crater of damaged tissue extending from the tissues to the muscle and the bone. Occurrence and healing of present ulcers were assessed using these criteria each morning by one of the researchers.

### Statistical analysis

For every variable, means, medians and standard deviations were calculated. An ANOVA with repeated measures was used to test the significance of the differences between the dependent variables. For non-dependent variables, the Chi-square test was used to detect associations between variables.

### Results

One hundred patients were included in the study. Five were excluded because of diarrhea or food intolerance (gastric residue larger than 250 mL). Patients' characteristics are summarized in Table 2. On admission, 14 out of 49 patients from the control group had a pressure ulcer (Grade 1:  $n = 6$ , Grade 2:  $n = 7$  and Grade 3:  $n = 1$ ). Seven patients in the study group out of 46 were suffering from pressure ulcers on

ICU admission (Grade 1:  $n = 5$ , Grade 2:  $n = 1$  and Grade 3:  $n = 1$ ). This difference was not found to be statistically different. The number of pressure ulcers increased from 14 to 23 (day 4) and 24 (day 7) in the control group as opposed to an increase of 7 to 12 (day 4 and 15 (day 7) in the study group. There was significantly less pressure ulcers occurrence in the patients receiving the study formulas as opposed to the control group (see Figure 1) (15 vs. 24,  $p < 0.05$ ). Table 3 shows the variations of pressure ulcers according to severity and time. The number of pressure ulcers did not significantly decrease (control group 1/24 pressure ulcers; study group 2/15 pressure ulcers). On day 4, 23 out of 49 had a pressure ulcer in the control group while only 12 out of 46 were suffering from a pressure ulcer in the study group ( $X^2(1) = 3.52$ ,  $p < 0.05$ ). At day 7, 24 patients had a pressure ulcer while only 15 patients from the study group were having a wound ( $X^2(1) = 3.52$ ,  $p < 0.05$ ).

Patients BMI at baseline was significantly higher ( $28.9 \pm 6.2$  vs.  $26.5 \pm 5.4 \text{ kg/m}^2$ ,  $p = 0.05$ ) in the study group. Patients received 75% of their REE within 48 h of admission. Severity of the illness was not significantly improved in either group as shown by the levels of

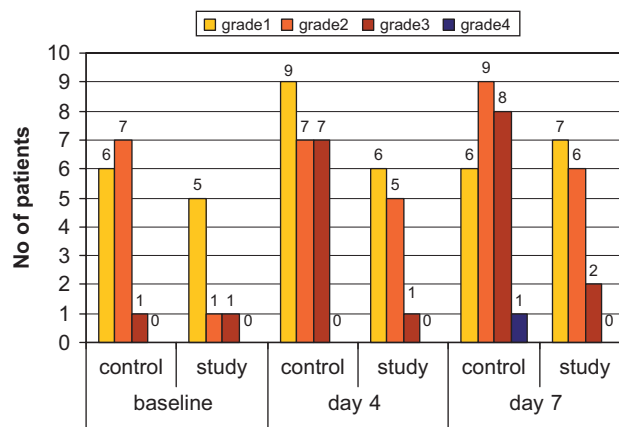


Figure 1 New onset of pressure ulcers during the hospitalization.

Table 2 Baseline patient characteristics.

	Control diet ( $n = 49$ )	EPA+GLA diet ( $n = 46$ )	<i>P</i>
Mean age (yr)*	62.3 (17.2)	57.0 (18.7)	NS
Diagnostic category for ICU admission <sup>†</sup>			
Medical ( $n$ )	34 (69.4)	28 (60.9)	
Surgical ( $n$ )	15 (30.6)	18 (39.1)	
Trauma ( $n$ )			
Gender <sup>†</sup>			
Male	28 (57.1)	29 (63.0)	
Female	21 (42.9)	17 (37.0)	
APACHE II (score)*	22.6 (6.9)	22.6 (6.7)	NS

EPA—eicosapentaenoic acid; GLA—gamma linolenic acid.

\*Data are presented as mean  $\pm$  SD.

<sup>†</sup>Data are presented as number of cases and percentage of the total.

**Table 3** Pressure ulcer status in the control group and in the study group.

	Baseline		Day 4		Day 7	
	Control	Study	Control	Study	Control	Study
Pressure ulcer total number	14(28.5)	7(15.2)	23(46.9)	12(26.1)	24(49.0)	15(32.6)
Grade 1	6(42.8)	5(71.4)	9(39.2)	6(50.0)	6(25.0)	7(46.7)
Grade 2	7(50.0)	1(14.3)	7(30.4)	5(41.7)	9(37.5)	6(40.0)
Grade 3	1(7.2)	1(14.3)	7(30.4)	1(8.3)	8(33.3)	2(13.3)
Grade 4	0	0	0	0	1(4.2)	0
Pressure ulcer total number	14(28.5)	7(15.2)	23(46.9)	12(26.1)	24(49.0)	15(32.6)
Worse			9(39.1)	1(8.3)	6(25.0)	4(26.7)
No change			4(17.4)	4(33.3)	17(70.8)	8(53.4)
Recover			1(4.4)	2(16.7)	0	0
New			9(39.1)	5(41.7)	1(4.2)	3(19.9)

**Table 4** Nutritional parameters at baseline and after 7 days regarding estimated and measured energy expenditure (HB is Harris benedict equation, REE is resting energy expenditure obtained by indirect calorimetry). BMI is body mass index.

	Control diet		EPA+GLA		p-value
	Day 1	Day 7	Day 1	Day 7	
BMI (kg/m <sup>2</sup> )	26.5±5.4		28.9±6.2		0.05
Nutritional intake (kcal/d)	1055±378 (57%)	1420±437 (71%)	1053±351 (49%)	1624±512 (69%)	NS
Albumin (g/dL)	2.01±0.62	1.98±0.55	2.14±0.61	2.16±0.74	NS
Prealbumin (g/dL)	9.76±4.0	11.52±5.20	9.97±5.41	12.79±7.56	NS
REE (kcal/day)	1850±334	1992±510	2132±625	2326±495*	0.01
Harris Benedict (kcal/day)	1471±238		1569±293		NS
Vitamin A (µg/dL)	28.0±15.4	33.3±16.2	18.7±16.5	24.1±18.7	NS
Vitamin E (mg/dL)	0.96±0.44	1.38±0.36	1.17±0.58	1.74±0.43	NS

BMI—body mass index; NS—non significant. REE—resting energy expenditure.

prealbumin and albumin (Table 4). Levels of vitamins A and E increased significantly from baseline to day 14, however, there was no significant difference between the two groups (Table 4). C-reactive protein and procalcitonin levels rose during the first week of hospitalization in both groups and decreased afterward in the two groups, in relation with the disease.

## Discussion

This study reports the prevention and improved healing of pressure ulcer using a specific nutrient formula. Only a few studies have demonstrated the effectiveness of nutrition in the prevention and healing of pressure ulcers. A previous study of gastric cancer patients demonstrated better healing of pressure ulcers using arginine, zinc and vitamin C.<sup>8</sup> In another study assessing surgical wounds in patients undergoing surgery for gastric cancer,<sup>11</sup> hydroxyproline deposition in a subcutaneously placed catheter was increased after supplementation with an arginine and fish oil-enriched diet.

Wound healing is a complex biological process. The sequence of events in the wound healing process begins

immediately after injury, with the activation of the coagulation cascade and the initiation of the inflammatory phase. The inflammatory phase plays a central role in wound healing. Cells are involved not only in encountering the invading microbes or new tissue constituents, but also in participating in the tissue repair process.<sup>12,13</sup> Neutrophils, granulocytes as well as monocytes and macrophages are a part of the non-specific cellular defense system for wound cleaning and skin defense. Their nuclei contain proteolytic enzymes which facilitate extensive degradation of detritus and phagocytosis of bacterias. Neutrophils are attracted to the wound site by the action of several chemotactic substances. Since neutrophils, T cells and macrophages release PUFAs on stimulation, it is possible that this could be one of the defense mechanisms of the body to fight infections. High levels of glucose have been demonstrated to increase the inflammatory process and increase infection rate and tight glucose control was shown to decrease sepsis rate and mortality in surgical critically ill patients.<sup>14</sup> Since the calorie intake should be preserved and glucose load could increase hyperglycemia, high-fat based diets could be recommended. PUFAs show antibiotic-like actions.<sup>15</sup> EPA and GLA have been demonstrated to decrease neutrophil and macrophage accumulation in bronchoalveolar lavage

fluid of patients suffering from ARDS.<sup>16</sup> Additionally, a short-time infusion of fish oil-based emulsions (of which EPA/GLA are included) reduced monocyte proinflammatory cytokine generation and adhesive interaction with endothelium.<sup>17</sup> Therefore, both studies show that EPA and GLA can contribute to attenuating the inflammatory process.

In previous studies, the use of EPA+GLA formula was associated with increased prostaglandin levels, in particular LBT5: in patients receiving w-3 enriched lipid infusions, the mononuclear leukocyte membrane fatty acid composition is modified<sup>18</sup> with an increase in LBT5. An increase in arachidonic acid is also observed. It could therefore be hypothesized that supplementation of enteral feeding in critically ill patients with EPA and GLA may prevent the occurrence of new pressure ulcers by decreasing the inflammatory process in high-risk areas.

Clinical trials over the last decade suggest beneficial effects of omega-3 fatty acids (o-3 FA) in parenteral nutrition on recovery and outcome in patients with severe surgical interventions and in the critically ill by lowering the magnitude of the inflammatory response and improving host defense of the inner cell. Lee et al.<sup>19</sup> demonstrated that activation of general proinflammatory pathways, such as NFκB and cyclooxygenase-2 expression by saturated FA and the inhibition of this induction by polyunsaturated FA are mediated through a common signaling pathway derived from toll-like receptor (TLR)-4. TLR-4 conveys signals as a part of innate immunity from the endotoxin receptor (CD) on the surface of macrophages. Consequently, inflammatory receptors, enzymes and cytokines are expressed differently in the process of wound healing. o-3 FA modify cellular receptor functions.<sup>20</sup>

Additionally, the arachidonic acid pathways are activated leading to the production of thromboxane A<sub>2</sub>, which assists the vasoconstriction and platelet aggregation, and prostacyclin (PGI<sub>2</sub>) that causes capillary vasodilatation. Vasodilatation also occurs due to local histamine release from activated mast cells in injured tissue.<sup>21</sup> We assume that, o-3 FA play an active role here and change the capillary vasodilatation in addition. Apart from energy supply, o-3 FA exert immune modulating and organ protective effects. This has been particularly shown for EPA and docosahexaenoic acid (DHA) contained in fish oil. Depending on nutritional intake, o-3 FA are incorporated in the phospholipid pool of cellular membranes and replace the o-6 FA thereby increasing membrane fluidity and influencing lipid mediator and cytokine production. Furthermore, o-3 FA modify the function of membrane-linked enzyme system.<sup>22</sup> Finally a recent study<sup>23,24</sup> adding parenteral fish oil emulsion to the nutrition regimen of rats treated with dexamethasone led to decrease of platelet-derived growth factor-AA in experimental wound tissues, without adverse effects on healing or no aggravation of the dexamethasone effects.

We can conclude that our study using an EPA, GLA and antioxidant-enriched diet administered to critically ventilated patients has not enough data to support the suggestion that this specialized nutrition support is influencing significantly pressure ulcer occurrence. It may prevent their progression in severe (Grade 3) existing pressure ulcers. This hypothesis has to be demonstrated by a prospective randomized study designed for this purpose.

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