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Effects of ω-3 supplementation on the nutritional status, immune, and inflammatory profiles of gastric cancer patients: A randomized controlled trial

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ABSTRACT

Objective: The aim of this study was to study the effect of ω-3 supplementation on the nutritional status and the immune and inflammatory profiles of patients with gastric cancer during antineoplastic pretreatment.
Methods: This was a randomized, open, controlled longitudinal study with intervention in outpatient patients with gastric cancer. Sixty-eight patients were randomized into two groups and received either a formula enriched with ω-3 (intervention group [IG]) or standard formula without ω-3 (control group) for 30 d consecutively. Nutritional status (based on patient-generated subjective global assessment, bioimpedance, and anthropometric measurements) and immune and inflammatory parameters were collected before and after supplementation. Results were expressed as frequency, median, and interquartile intervals and were compared by non-parametric test. $P < 0.05$ was considered statistically significant.
Results: Thirty-four patients were included in each group. Of the patients, 64.7% were men, 44.1% were older than 60 years, and 45.6% had stage III disease. There was an increase in C-reactive protein in the control group before and after supplementation, in addition to the worsening in some anthropometric parameters, such as arm muscle area and arm muscle circumference. There was maintenance of the immune profile in both groups. An increase in weight gain was observed in the IG but not in the control group (1.2 [0.9–9] versus 0.7 kg [0.4–1.3]; $P = 0.03$), as was a reduction of interleukin-6 (5.7 [4.1–6.4] versus 6.3 pg/mL [5.6–8.6]; $P = 0.03$) and a maintenance of nutritional status, after supplementation.
Conclusions: Supplementation with ω-3 leads to weight gain, reduction in the inflammatory profile, and maintenance of the nutritional and immune profiles of these patients, but further studies are needed to examine changes in body composition.

Introduction

Gastric cancer is considered a disease with a poor prognosis, where the only curative therapy is surgical resection during the early stages [1–4]. Among the different types of cancer that affect the gastrointestinal tract, gastric cancer is one of the most common, being the fifth most common malignancy in the world and third leading cause of cancer death in both sexes [1–3]. More than 50% of gastric cancer cases occur in individuals >50 y of age. The distribution of this disease in the world is inversely proportional to the country's socioeconomic level [5,6].

Weight loss often is present in patients with cancer and may be evident in 30% to 80% of these patients, depending on the type of

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tumor [7]. This unintentional weight loss, which can lead to malnutrition, is sometimes the first sign noticed by the patient, but in some people it may occur only during the course of disease progression or treatment. Weight loss in patients with cancer is associated with poor outcomes such as reduced response to therapy, increased complications and infections, worsening of quality of life, and decreased survival [8-11].

During the development of cancer, transformed cells have self-sufficiency of growth factors and insensitivity to growth inhibitory factors and apoptosis. In addition, they stimulate the activation of immune system cells, triggering an inflammatory response. Among the main mechanisms of activation of the inflammatory response is the production of cytokines, which are associated with the development of cachexia, influencing anorexia, increased energy expenditure, and weight loss [12,13].

Studies have shown that effective nutritional intervention in pretreatment in patients with cancer is beneficial, reducing hospital costs, loss of follow-up in treatment, postoperative infection, and hospital length of stay by increasing their immunity. Nutritional supplements associated with dietary counseling have demonstrated an increase in dietary intake and prevention of weight loss associated with antineoplastic therapy [14].

Supplementation with ω-3 fatty acid is one of the therapies that has been proposed in an attempt to reverse the catabolism observed in a large percentage of patients with cancer and cachexia by attenuating the inflammatory response. This supplementation helps reduce the formation of proinflammatory cytokines, favoring the metabolic tolerance of energetic substrates and attenuating protein catabolism, with the aim of improving the prognosis of these patients [15,16]. Owing to the anti-inflammatory effect of ω-3s, daily supplementation with 2 g of eicosapentaenoic acid (EPA) may help stabilize unintentional weight loss in patients with cancer [14,17].

The majority of the clinical trials, which included small groups of patients with advanced cancer or those undergoing anticancer treatment, reported improvements in appetite, energy intake, body weight, and lean body mass [18-21]. However, there were some randomized trials that failed to demonstrate any benefit [22,23].

To our knowledge, the effects of supplementation with ω-3 in the pretreatment of patients with gastric cancer have not been studied. For these reasons, the aim of the present study was to compare the nutritional status and the immune and inflammatory profiles of this group of patients before and after use of nutritional supplements with ω-3.

Material and methods

This was a randomized, open, controlled longitudinal study with nutritional intervention. Inclusion criteria included the following:

- patients with gastric cancer who were in pretreatment,
- age 40 to 65 y,
- patients at the Nutrition outpatient clinic of Hospital do Câncer I / Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), from July 2015 to July 2017,
- patients diagnosed with adenocarcinoma by clinical diagnosis and histopathology confirmation.

The project was approved by the local ethics committee and by the Brazilian Clinical Trials Registry (ReBec)

Tumor stage was defined by clinical staging and TNM classification, depending on the tumor. Stage I was considered in situ (Tis or stage 0); localized extension; grade I; TNM T1, N0, and M0; or histologic grade 1 (well differentiated). Stage II was considered: grade II; TNM T2, N0, and M0; or histologic grade 2 (moderately well differentiated). Stage 3 was considered: regional, grade III; TNM T3, N1-3, M0; or histological grade 3 (poorly differentiated). Stage 4 was considered: distant extension; grade IV; TNM T4, N1-3, M1; or histological grade 4 (undifferentiated) [24].

Patients with chronic liver disease (CHILD-PUGH B and C), HIV/AIDS, severe congestive heart failure, chronic renal disease, or diabetes mellitus; patients already on chemotherapy or radiotherapeutic treatment; patients with another diagnosis of cancer in the period up to 5 y previously; patients with an infection or inflammatory disease focus; and patients who refuse to sign the informed consent form for participation in the study were excluded from the study.

The trial used a parallel-group design with individual participant random assignment conducted using sequences generated by www.random.org. Allocation (1:1 ratio) was conducted using a locked spreadsheet that assigned participants to treatment groups. Investigators were involved in both prescription of the supplement and participant testing so they were not blinded to group allocation. Group allocation was not discussed with participants; however, it was likely clear to them based on the supplement they were provided and the group to which they were assigned.

In the first evaluation, patients underwent an interview to ascertain clinical history, presence of smoking, and level of physical activity. Nutritional assessment was performed using anthropometric data such as weight, height, mid-upper arm circumference (MUAC), triceps skinfold thickness (TSF), mid arm muscle circumference (MAMC), mid arm muscle area (AMA), skeletal muscle mass index (SMI) by electrical bioimpedance (BIA) and 24-h food recall questionnaire. In addition, it was used the patient-generated subjective global assessment (PG-SGA) and patients were classified as A (well-nourished), B (moderate/suspected malnutrition), or C (severely malnourished) [25,26]. A blood sample was collected to evaluate the nutritional status (albumin and prealbumin); to evaluate the inflammatory profile through serum concentrations of interleukin (IL)-6 and C-reactive protein (CRP); and to evaluate the immune profile, quantification of T cells and their CD3 markers, CD4, and CD8. Other information, such as presence of comorbidities and staging of the disease, were gathered from medical records.

After this initial evaluation and randomization, the control group (41 patients) received standard formula supplementation without ω-3, and the intervention group (42 patients) received supplementation of a formula enriched with ω-3, fractionated in two steps of 200 mL/d each, adding an additional 560 kcal and 29 g/d protein (Novasource GI Control, Nestlé) or 600 kcal, 24 g/d protein, and 3.2 g/d of ω-3 EPA/docosahexaenoic acid (DHA; Prosure, Abbott, Ireland), respectively. Also, all patients were advised to consume a healthy diet with low lipid content (~20% of the total calories), in the consistency tolerated by the patient, according to the nutritional needs of each patient (30 kcal/d based on their actual weight), because this type of diet is recommended to patients with gastric cancer in order to avoid or decrease symptoms such as nausea, vomiting, and early satiety, which are very common with this disease and therefore would contribute to better acceptance. The use of the nutritional supplement was additional and taken over the period of 30 d consecutively, which corresponds to the mean time of pretreatment complementary exams.

After 30 d, the patients returned and all nutritional, immune, and inflammatory evaluation procedures were again performed.

Patients who did not tolerate the use of nutritional supplementation or who did not use the supplement in the prescribed amount, that is, adherence to supplementation was <80% of the prescribed amount, were removed from the study. In addition, the use of nutritional supplementation was monitored weekly by telephone contact and patients were asked to bring in the second set of supplement bottles that were not used and the empty bottles of supplements.

Anthropometric measurements including body mass index (BMI), TSF, MUAC, MAMC, and mid AMA were performed by trained dietitians to monitor the nutritional status at each period of the study. Body mass index was calculated as weight (kg) divided by height (m^2), and nutritional status was determined according to the World Health Organization for adults [27] and Pan-American Health Organization for older people over 60 years [28]. MUAC was measured in millimeters using a standard measuring tape, and TSF was obtained at the same point as for MUAC, using the Lange skinfold caliper (Santa Cruz, CA, USA). MAMC and AMA were derived from MAC and TSF by using standard formulas. Serum albumin was quantified by the bromocressol green method and serum prealbumin by turbidimetric method using specific kits and according to laboratory routine. Patients with albumin values >3.5g/dL and prealbumin between 0.20 and 0.40 g/dL were within the normal range [29].

To access means of dietary energy (kcal/d and kcal·kg·d^{-1}) and dietary protein (g/d and g·kg·d^{-1}), two 24-h food recall questionnaires were completed. These short questionnaires asked for a record of all food and drink, including supplementation, taken during the day before study entry and after supplementation.

A Biodynamics Model 450 tetrapolar BIA was used. Patients fasted for ≥2 h with an empty bladder [30], lying in dorsal decubitus with arms relaxed throughout the body without touching it and with the legs stretched and separated, avoiding touching the hands on the trunk [31].

The BIA analysis was performed by placing four small electrodes on the hand and right foot of the reclining patient. Resistance and electrical reactance were measured at 50 Hz, using electrodes positioned on the anterior surface of the foot

at the distal end of the second metatarsal and on the surface the distal end of the hand in the third metacarpal [30,31].

AMA was performed to evaluate the muscle mass of the patients, correcting the bone mass, and was obtained through the equation proposed by Frisancho [32]:

$$\text{AMA}\ (\text{cm}^2) = [\text{MUAC}\ (\text{cm}) - \pi \times \text{TSF}\ (\text{mm})/10)]^2/4 \times \pi.$$

Muscle mass was corrected by weight, height, sex, and age, and therefore the SMI was calculated using data obtained from the evaluation performed by electrical BIA. This was obtained by the equation proposed by Janssen et al. [33]:

$$\text{SMM (skeletal muscle mass)} = (\text{height}^2\ [\text{m}]/\text{resistance} \times 0.401) + (\text{sex}\ [*] \times 3.825) + (\text{age} \times [-0.071]) + 5.102$$

where sex (*) equals either 1 for men and 0 for women. The SMI (kg/m^2) = SMM/height^2 (m).

For the purpose of muscle mass classification, the cutoff value for sarcopenia was SMI <6.76 kg/m^2 for women and SMI <10.76 kg/m^2 for men, according to Janssen et al. [33]. Patients with sarcopenia and CRP >1 mg/dL or IL-6 higher than the median of the group were considered to have cachexia [10].

Serum IL-6 levels were determined using enzyme-linked immunosorbent assay (ELISA) kit Ready Seat-Go from eBioscience, according to the manufacturer's instructions. All samples were tested in duplicate wells and the means of the duplicates were reported. When the concentrations were between the blank and the lower detection limit of the assay, the values of the limit were included in the data analysis (2 pg/mL). For those samples with concentrations above the detection limit of the assay, the values were obtained from the standard curve [34]. High-sensitivity CRP was measured by turbidimetric method using specific kits and according to laboratory routine.

Immune parameters were evaluated as total number of leukocytes (μL), lymphocytes (μL) and lymphocyte subsets (CD4, CD8, and CD4/CD8 ratio). At least 1×10^6 cells/mL were evaluated in the flow cytometry device (Facscam, Becton Dickinson, Mountainview, CA, USA) using the Cell Quest program with software Infinicity. Antibodies CD4-FITC, CD8-PE, CD3 PerCP, and CD3-FITC were purchased from BD Biosciences.

The primary endpoint evaluated was weight modification, and the secondary outcomes were lean mass gain and reduction of proinflammatory cytokines. For the calculation of weight and lean mass gain, the difference between weight and muscle mass of the phase after supplementation with the initial phase, before nutritional supplementation, was performed only with patients who experienced weight gain.

The study concluded in July 2017 when the supplement was discontinued by the manufacturer.

Statistical analysis

We were unable to locate any studies using ω-3 supplementation (oral liquid formula) only during the preoperative period of patients with gastric cancer, with the outcome of weight gain. Based on our experience and the results of the first patients included in the protocol (pilot study), we considered that a total weight gain of 2 kg would be feasible for the proposed period of supplementation. We used a sample size calculation platform (www.lee.dante.br/pesquisa/amostragem) to compare the average of two populations. Assuming a weight gain of 2 kg (SD ± 2.0) for the intervention group, and considering a sampling error of 5%, a confidence level of 95% and two-tailed hypothesis test, the minimum total number of patients for the present study should be 52, with 26 patients in each group.

Categorical variables were expressed as frequency and percentage, and the χ^2 test or Fisher's exact test were used when necessary. The Kolmogorov–Smirnov test was used to test for the normality of data. We chose to use non-parametric tests, and the results of continuous variables were expressed as median and interquartile interval. The variables were compared between groups by Mann-Whitney and Kruskal-Wallis test, with a 95% confidence interval and a statistical significance of $P < 0.05$.

Spearman coefficient was used for the correlation between continuous variables. SPSS software, version 17 (IBM, Armonk, NY, UA) was used for the statistical analysis.

Results

We screened 286 patients with gastric cancer. After verification of the inclusion and exclusion criteria, 83 patients remained in the study. The randomization of patients is described in Figure 1.

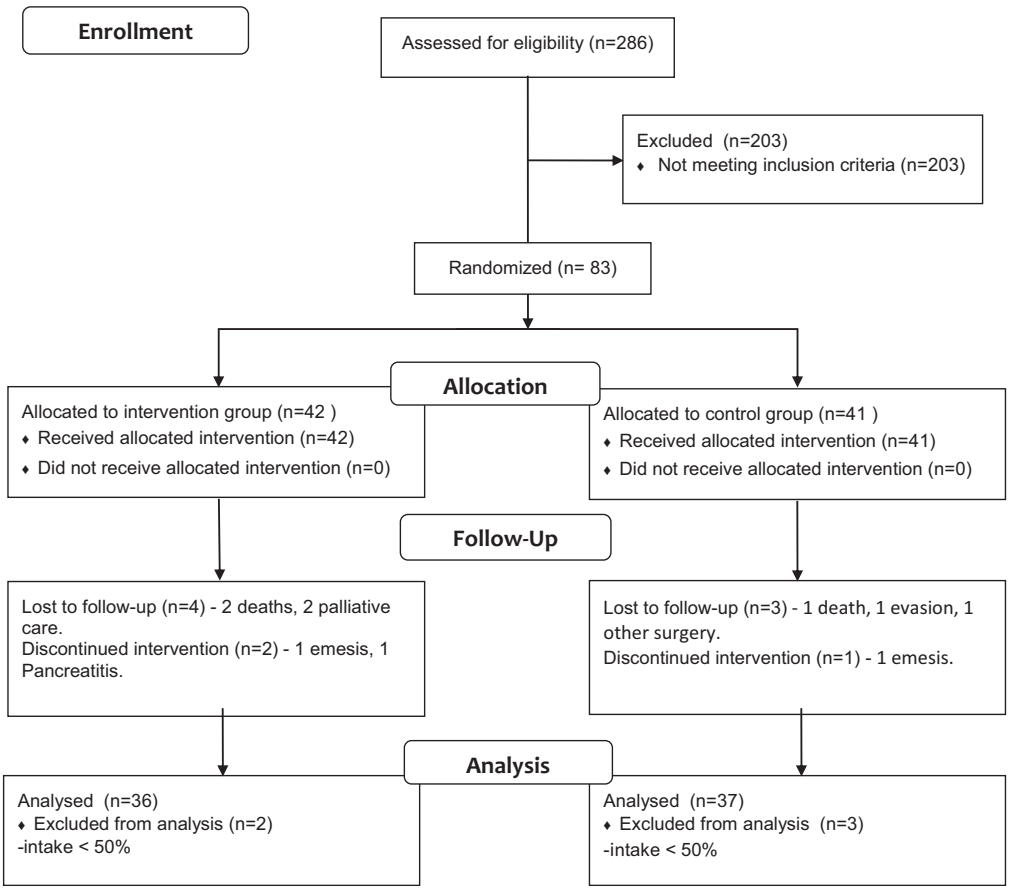

Fig. 1. Participant flow diagram.

During the 30 d, there was loss of follow-up, leaving 68 patients to complete the study, with 34 in each group. The initial characteristics of the patients are described in Table 1.

Of the 68 patients who completed the study, 64.7% were male and 55.9% were adults. The participants had a median age of 58 y in both groups, and 53% of the patients were in the most advanced stage of the disease (stages III and IV) at the time of the beginning of the research. It is important to note that in relation to the staging of the disease in the initial phase, no statistical difference was identified between groups. In relation to the initial nutritional assessment performed through PG-SGA, 72.1% of the patients presented moderate/suspected malnutrition or were severely malnourished (B + C).

In the initial phase, no statistical difference was observed between the parameters evaluated when compared between the control and intervention groups. This demonstrated that the two groups in the initial phase were similar. Also, 58 patients had BIA analysis. In the initial phase, we observed that 38.2% of patients had sarcopenia and 19.1% had cachexia. Table 2 shows the characteristics of the groups before and after supplementation.

In the beginning of the study, all of the patients had a low daily caloric intake (<30 kcal/kg); after nutritional intervention it was increased, not considering the additional calories from the supplement. In addition, maintenance of the inflammatory, immune, and nutritional profiles were observed in the patients in the intervention group. Both groups presented scores >8 points in the PG-SGA, indicating the need for early nutritional intervention and management of gastrointestinal symptoms.

Table 1
Characteristics of the patients*

Variables	Baseline (N = 68) %
Sex	
Male	64.7
Female	35.3
Age range	
Adult (40-59)	55.9
>60 y	44.1
PS	
0	47.1
1	42.6
2	4.4
No information	5.9
Staging	
I	4.4
II	25.0
III	45.6
IV	7.4
No information	17.6
Physical activity	
Yes	10.3
No	89.7
Smoker	
Yes	26.5
No	73.5
Alcohol consumption	
Yes	2.9
No	97.1
Family history of cancer	
Yes	67.6
No	32.4
Systemic arterial hypertension	
Yes	23.5
No	76.5
PG-SGA classification	
A	27.9
B	61.8
C	10.3

PG-SGA, patient-generated subjective global assessment; PS, performance status.
*Results presented in frequency.

Regarding inflammatory parameters evaluated in the control group, an increase in the inflammatory profile, and worsening of some anthropometric parameters with statistical significance, was observed. There was an increase in the median of the CRP, CRP-to-albumin ratio, and IL-6 after supplementation.

A negative correlation of the IL-6 was found with MAMC ($r^2 = -0.31$, $P = 0.03$), weight gain (WG) ($r^2 = -0.31$, $P = 0.02$), and AMA ($r^2 = -0.32$, $P = 0.02$). That is, the higher the IL-6 levels, the lower the parameters of MAMC and AMA and the smaller the WG.

A positive correlation between WG and SMI ($r^2 = 0.407$ and $P = 0.04$) was found in the intervention group; that is, the higher the WG, the better the SMI. In the control group, a negative correlation was found between IL-6 and AMA (r^2 −0.453, $P = 0.02$), meaning higher concentrations of IL-6 lead to lower AMA.

Thirty-seven (54.4%) patients gained or maintained weight. Of these, 21 were in the intervention group. These patients had an increased in SMI compared with patients who had lost weight. However, both groups maintained body fat according to TSF (Table 3).

Discussion

The epidemiologic profile of the patients in this study, including most being male with age >50 y, was similar in reference centers worldwide [35–40]. At the time of the first evaluation (initial phase), the majority of the patients presented moderate or suspected malnutrition or were severely malnourished. Signs and symptoms of gastric cancer can lead to reduced food intake and, consequently, malnutrition, sarcopenia, and cachexia [40–44]. For this reason, nutritional intervention should be performed throughout the antineoplastic treatment and should begin before treatment begins [36,45].

Studies of body composition analysis by computed tomography (CT) in patients with gastric tumors in several stages, considering only the reduction of lean mass, found that 20.6% to 49.4% of them had sarcopenia [46–49]. Even using different evaluation techniques (BIA × CT), the findings are compatible with the present study.

In a review of the literature by Van der Meij et al. [50], supplementation with ω-3 had benefits in weight gain, but not in lean mass. A similar result was observed in the present study, when the groups were compared before and after nutritional supplementation. However, it was possible to show that patients who gained or maintained weight had higher SMI than those who lost weight.

These findings are corroborated by several studies including as Murphy et al. [51], in which 40 patients with lung cancer were allocated to two groups, intervention and control. The intervention group received 2.5 g/d of EPA/DHA for 10 wk. Weight maintenance was observed in the intervention group, in addition to greater lean mass gain. A mean weight loss of 2.3 kg and lower lean mass gains were observed in the control group. In the same study, 69% of the patients in the intervention group maintained lean mass versus 29% in the control group, but in general they lost 1 kg of lean mass. In the study by Ida et al. [39], 124 patients with gastric cancer were randomized and allocated into two groups (supplementation without EPA and intervention with 2.2 g of EPA), 7 d before surgery and 21 d after surgery, and weight loss after surgery at two times (1 and 3 mo after surgery). No statistical difference was observed in the weight loss of the two groups at the two points of evaluation. There also was no statistical difference in the complication rates and postoperative mortality of the two groups.

Ryan et al. [52] analyzed 53 surgical patients with esophageal cancer. Patients were supplemented for 5 d before surgery and 21 d after surgery (28 patients received EPA 2.2 g/d and 25 patients received standard supplementation). Maintenance of body composition in the group supplemented with EPA was observed,

Table 2
Comparison between the initial phase and the phase after nutritional supplementation of the intervention group and control group*

Variables	Intervention group: initial phase (n=34)	Intervention group: after supplementation (n=34)	*P*-value*	Control group: initial phase n=34)	Control group: after supplementation (n=34)	*P*-value†	*P*-value‡
Weight (kg)	63.5 (58.1–69.8)	64.6 (58.9–69.2)	0.33	66.1 (71.7–75.4)	66.1 (52–75.3)	0.56	0.67
Weight gain (kg)		1.2 (0.9–2)			0.7 (0.4–1.3)		**0.03**
PG-SGA classification	10.5 (5–15)	5.5 (2–9)	**0.00**	8.5 (5–12)	6 (2–9.2)	**0.00**	0.89
BMI (kg/m^2)	24.2 (20.4–26.3)	23.8 (21.3–26.6)	0.31	22.8 (20.1–28.3)	22.5 (20.3–28.2)	0.75	0.76
SMI (kg/m^2)	9 (8–10.2)	9.1 (8.5–10.5	0.78	9.7 (7.7–10.9)	8.7 (7.4–10.2)	0.69	0.37
TSF (mm)	13 (8–20)	15 (8.7–20)	0.20	14.5 (7–19.2)	14.5 (6.7–20)	0.06	0.50
MAMC (cm)	23.9 (22–25.4)	23.6 (22–26.7)	0.55	24 (22.2–26.2)	23.3 (21.7–26.1)	**0.01**	0.69
AMA (cm^2)	45.7 (38–51.5)	44.1 (39.6–56.1)	0.09	45.7 (38.9–54.4)	43.2 (36.7–54.4)	**0.03**	0.61
Albumin (g/dL)	4.3 (3.8–4.6)	4.1 (3.7–4.5)	0.12	4.4 (4.1–4.7)	4.3 (3.8–4.5)	**0.02**	0.27
CRP (mg/dL)	0.4 (0.1–1.1)	0.8 (0.1–1.8)	0.22	0.2 (0.1–1.3)	0.4 (0.1–2.8)	**0.00**	0.86
CRP/Albumin	0.1 (0–0.3)	0.23 (0–0.5)	0.08	0.05 (0–0.3)	0.1 (0–0.7)	**0.04**	0.83
CD4 (%)	41.4 (32.4–50.3)	37.1 (28.9–42.8)	0.57	39 (33.5–44.8)	41.5 (31–49.8)	0.32	0.14
CD8 (%)	22.8 (16.7–30)	25.6 (19.3–28.2)	0.84	22.7 (18.6–31.1)	22.6 (16.7–30.3)	0.59	0.57
CD4/CD8	1.7 (1–2.5)	1.3 (1–1.7)	0.47	1.7 (1.2–2.3)	1.9 (1.2–2.5)	0.25	0.09
IL-6 (pg/mL)	5.7 (4.8–6.3)	5.7 (4.1–6.4)	0.45	5.9 (5.3–7.6)	6.3 (5.6–8.6)	**0.00**	**0.03**
kcal / 24h	1248.5 (934.7–1485.2)	1873.8 (1174.6–1995.2)	**0.00**	1364 (1058.5–1813.6)	1747.4 (1361.5–2289.7)	**0.01**	0.78
kcal/kg	18.9 (14.5–25.5)	27.3 (19.9–35.6)	**0.00**	21.3 (14.2–27.2)	27.2 (18.8–36)	0.10	0.63
Protein/24 h (g)	64.1 (44.2–92.2)	82.4 (63.3–113.3)	**0.01**	83.7 (55.5–96.8)	97 (65.3–121.6)	0.75	0.50
Protein g/kg	0.9 (0.7–1.3)	1.4 (1–1.8)	**0.01**	1 (0.7–1.8)	1.6 (1–2)	**0.05**	0.58

AMA, mid arm muscle area; BMI, body mass index; CD4, T-helper lymphocytes; CD8, T-cytotoxic lymphocytes; CRP, C-reactive protein; IL, interleukin; MAMC, mid arm muscle circumference; PG-SGA, patient-generated subjective global assessment; SMI, skeletal muscle index; TSF, triceps skinfold.
Data presented as median and interquartile range and Mann-Whitney's nonparametric test. Values in bold are statistically significant.
*Statistical difference between before and after supplementation in intervention group.
†Statistical difference between before and after supplementation in control group.
‡Statistical difference between intervention group and control group after supplementation; by Mann-Whitney test.

compared with loss of 1.9 kg of lean mass in the standard group, with statistical significance ($P = 0.03$).

In the present study, worsening (e.g., decreased albumin levels and increased CRP and IL-6) was observed in some parameters of the control group after supplementation. There was a tendency for worsening of lymphocyte concentrations in this group also. However, when comparing the two groups after supplementation, we observed a significant reduction in IL-6 levels in the intervention group, that is, the control group patients were significantly more inflamed than those in the intervention group.

In the study by Fabian et al. [53], the use of ω-3 in the prevention and survival of breast cancer patients was analyzed after 5 mo of progressive supplementation of EPA/DHA (≤1.8 g/d) with a reduction in tumor necrosis factor-α and IL-6.

There was no statistical difference between CD4 and CD8 levels in either group after supplementation. A similar finding was found by Wei et al. [54], who analyzed the immune response of surgical patients with gastric cancer, supplemented with or without ω-3 3, and after surgery it was observed that there was no statistical difference in CD4 and CD8 levels between the two groups. Rodrigues et al. [55] did not find any statistical differences in the CD4 and CD8 levels when analyzing patients' immune profiles at three time points (initial phase, after standard formula supplementation, and after supplementation with immunomodulators, including ω-3).

In the initial phase and after supplementation, a negative correlation was found between the levels of IL-6 and weight gain and IL-6 and MAMC. In other words, the patients who initially presented higher concentrations of IL-6 gained less weight and presented lower parameters of MAMC in the phase after supplementation. This correlation is related to the increase in inflammation because IL-6 plays an important role in the inflammatory response, inducing the production of acute phase proteins such as CRP, which is associated with weight loss in patients with cancer [8]. Cytokines are involved in the development of cachexia, influencing both anorexia, weight loss, and consequently lower MAMC [8,56,57]. These cytokines also may inhibit food intake, causing adipose tissue to release leptin, a sign of satiety [14].

By stratifying the groups, it was observed that a negative correlation was found between IL-6 and AMA only in the control group and a positive correlation between WG and SMI only in the intervention group. This confirms the importance of the modulation of the inflammatory profile in these oncology patients to guarantee the weight gain and better nutritional parameters that effectively favor the best response to cancer treatment and the best clinical outcome [56,57].

The present study had some limitations. It was not blinded and was done with a specific cancer group in a reference center, which did not allow the generalization of the results for the whole cancer population. The study did not aim to evaluate clinical outcome. The strong points of the work were that it was a randomized controlled study with nutritional counseling and good adherence to a specialized supplement.

Table 3
Differences between patients who gained or maintained weight and patients who lost weight before and after 30 d of supplementation*

Variables	Patients who gained or maintained weight (n = 37)	Patients who lost weight (n = 31)	*P*-value
Δ Weight (kg)	1.1 (0.6 to 2)	−1.2 (−2.4 to −0.4)	<**0.001**
Δ BMI (kg/m^2)	0.39 (0.2 to 0.8)	−0.4 (−0.9 to −0.8)	<**0.001**
Δ TSF (mm)	0 (−1.5 to 1)	0 (−1 to 1)	0.38
Δ SMI (kg/m^2)	0.1 (−0.2 to 0.7)	−0.4 (−0.74 to 0.2)	**0.02**

BMI, body mass index; SMI, skeletal muscle index; TSF, triceps skinfold.
*Data presented as median and interquartile range and Mann-Whitney's non-parametric test. Values in bold are statistically significant.

Conclusion

Gastric cancer patients undergoing protreatment were, under ω-3 and standard supplementation, able to maintain nutritional and immune parameters. Supplementation with ω-3 attenuated the inflammatory response of patients by decreasing the concentrations of CRP and IL-6 compared with the control group. Thus, patients not supplemented with ω-3 were more inflamed than those in the ω-3 intervention group. The use of ω-3 supplements in a therapeutic approach has shown promise in combating cancer cachexia, promoting weight maintenance, and improving lean body mass. Despite the ω-3 effect on proinflammatory cytokines, acute phase proteins, and tumor factors, further studies are necessary to examine changes in body composition.

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