

Applied nutritional investigation

Impact of fish oil and melatonin on cachexia in patients with advanced gastrointestinal cancer: A randomized pilot study

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Abstract

Objective: The effect of fish oil (FO), melatonin (MLT), or their combination and dietary advice on cachexia and biochemistry variables reflecting cachexia were investigated in patients with advanced gastrointestinal cancer.

Methods: Twenty-four patients not amenable to standard anticancer treatment and with documented weight loss and/or decreased serum albumin were included. They were randomized to 30 mL/d of FO, which provided 4.9 g of eicosapentaenoic acid and 3.2 g of docosahexanoic acid, or 18 mg/d of MLT for 4 wk. During the next 4 wk, all patients had FO and MLT. Serum or plasma was analyzed for tumor necrosis factor- α , interleukin-1 β , soluble interleukin-2 receptor, interleukin-6, and interleukin-8 and the fatty acids eicosapentaenoic acid, docosahexanoic acid, arachidonic acid, and linoleic acid.

Results: Serum levels of eicosapentaenoic acid and docosahexanoic acid increased as expected with FO. No major changes in biochemical variables and cytokines were observed with any intervention. In the FO group, 5 of 13 patients (38%) showed weight stabilization or gain compared with 3 of 11 patients (27%) in the MLT group. After combining interventions, approximately 63% of patients showed such responses.

Conclusions: FO, MLT, or their combination did not induce major biochemical changes indicative of a strong anticachectic effect. Nonetheless, the interventions used may have produced a weight-stabilizing effect. © 2005 Elsevier Inc. All rights reserved.

Keywords:

Gastrointestinal cancer; Cachexia; Fish oil; Melatonin

Introduction

Cachexia is common in many tumor types in the advanced setting, especially so in, for example, cancers of the pancreas, lung, and colon, and is a major clinical problem with considerable effect on a patient's quality of life (QoL). Cancer cachexia is manifested as weight loss with depletion of skeletal muscle and adipose tissue, accelerated total protein turnover, and increased gluconeogenesis and resting energy expenditure [1]. The best way to reverse cancer

cachexia is to provide efficient control of the cancer. However, in patients with advanced cancer, such therapy is frequently not available or provides only short-term beneficial effects. Nutritional support alone is not sufficient to counteract cachexia [1], indicating that specific mechanisms are responsible for the phenomenon.

Cancer cachexia is reminiscent of an inflammatory process, identified by an acute-phase protein response (APPR) with increased levels of C-reactive protein (CRP) and fibrinogen, which are poor prognostic factors in advanced cancer [2,3]. Knowledge of the pathophysiology behind cancer cachexia has expanded considerably during recent years. Thus, various cytokines produced by host immune cells in response to tumor seem to be causally related to the metabolic abnormalities [1,4].

Interleukin (IL) 1 β is a potent anorexia-producing agent

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that causes increased resting energy expenditure, skeletal protein wasting, and leptin release [4]. IL-6 is associated with weight loss and increased hepatic protein synthesis and acts on the hypothalamus to impair eating activity [5]. Tumor necrosis factor- α (TNF- α) is also a potent anorexia-producing agent because it promotes skeletal protein wasting, inhibits lipoprotein lipase, and decreases synthesis of lipids [6]. High levels of TNF- α are seen in weight-losing patients with pancreatic cancer [5].

The effect of other cytokines is less well established in this context. However, IL-2, a key T-cell cytokine primarily produced by T cells of the T helper-1 type, interacts with a specific membrane IL-2 receptor, detectable in plasma as soluble IL-2 receptor (sIL-2R). Soluble IL-2R is high in cancer patients, is most pronounced in those with cachexia, and correlates with prealbumin, transferrin, and survival rate [7]. IL-8 is a proinflammatory cytokine that is involved in the regulation of satiety and modulates the APPR [8]. Peptides seemingly produced by tumors and that specifically induce proteolysis and lipolysis have been isolated recently [1,3].

Different pharmacologic agents have been used to manage cancer cachexia, and limited improvements in appetite and some weight gain have been observed [1]. However, the effects are modest, and to more substantially improve the management of cancer cachexia, approaches that exploit the pathophysiology of cachexia need to be considered. One mechanistically sound approach is the administration of ω -3 polyunsaturated fatty acids (ω -3 FAs), notably eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA), which are plentiful in fish oil (FO). The ω -3 FAs are suggested to influence the development of cachexia by interfering with the catabolic processes that act on muscle and adipose tissue rather than as a nutritional supplement [9]. The ω -3 FAs might affect cytokine production and activity by interfering with the cyclo-oxygenase and lipoxygenase signaling pathways. Mostly studied in advanced pancreatic cancer, large doses of FO seem to partly counteract the cachectic process in this disease [10,11].

Another potentially interesting but less studied approach is the use of melatonin (MLT), a hormone produced by the pineal gland that participates in the regulation of biological rhythms and in the control of cell differentiation and proliferation [12]. MLT is suggested to inhibit tumor growth and stimulate host antitumor defense [13,14], decrease TNF- α , enhance survival, and increase the objective response rate when combined with chemotherapy [15].

The primary aim of the present study was to determine whether short-term intervention with large doses of FO and/or MLT combined with dietary advice in patients with advanced gastrointestinal cancer could influence a broad spectrum of variables presumed to reflect the development of cachexia, notably cytokines. Secondly, we also studied clinical benefit as indicated by food intake, body weight, and QoL. FO and MLT have been studied in this setting, but

data are limited and have not been studied in parallel or in combination.

Materials and methods

Trial outline

The study was a one-center, randomized, non-placebo-controlled, open study performed between January 1998 and May 2000. It was approved by the research ethics committee of the Faculty of Medicine, University of Uppsala (Uppsala, Sweden).

Patients who had advanced gastrointestinal cancer, visited the outpatient clinic, and fulfilled the inclusion criteria were asked to participate. Briefly, patients had to have metastatic or locally advanced gastrointestinal cancer not amenable to curative or standard palliative treatment, greater than 10% weight loss during the previous 6 mo, a serum albumin level no higher than 35 g/l, Karnofsky's performance status of at least 60, and, in the case of ongoing chemotherapy, at least two courses before beginning the study with therapy to continue. Concomitant medication with anticoagulative agents was not allowed; however, in the case of medication with non-steroidal anti-inflammatory drugs or corticosteroids, medication must have begun at least 2 wk before study inclusion. After baseline assessments, patients were given standard dietary advice and were randomized to a 4-wk intervention with FO or MLT followed by study assessments and a new 4-wk intervention period with FO and MLT and final assessments. Twenty-four patients were included and randomized. Key demographic data of patients at the start of intervention are presented in Table 1.

Assessments of biochemistry, performance status, QoL, and food intake

Blood samples for analyses of blood hemoglobin, serum albumin, serum lactate dehydrogenase, CRP, and plasma fibrinogen were obtained in the morning after overnight fasting at baseline and after each 4-wk intervention period. At the same time, serum was obtained and frozen at -70°C within 4 h of sampling for subsequent analyses of TNF- α , IL-1 β , IL-6, IL-8, sIL-2R, EPA, DHA, linoleic acid, and arachidonic acid.

Performance status was measured with Karnofsky's performance status, and QoL was assessed by the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC-QLQ-C30) [16] at baseline and during the last weeks of the first and second intervention periods. The EORTC-QLQ-C30 is a 30-item cancer-specific questionnaire that consists of five functional scales (physical, emotional, cognitive, social, and role), three symptom scales (fatigue, pain, and nausea/vomiting), a global health or QoL scale, and six single items that assess symptoms and finan-

Table 1
Demographic data for the patients who started intervention

	Fish oil (<i>n</i> = 13)	Melatonin (<i>n</i> = 11)
Men/women	7/6	7/4
Diagnoses		
Pancreatic	5	3
Biliary	1	3
Adenocarcinoma (unknown primary tumor)	2	
Colorectal	4	4
Gastric	1	1
Age (y), mean \pm SD	66 \pm 9	69 \pm 10
Age range	52–78	53–83
Weight (kg) 6 mo previously, median (range)	70 (45–115)	69 (40–90)
Weight (kg) at baseline, median (range)	56.6 (35–101)	61.8 (33–80)
Weight loss in previous 6 mo (%)	–13.2 (8.4)	–10.8 (8)
BMI (kg/m ²) 6 mo previously	24.9 (3.8)	23.8 (4.8)
BMI (kg/m ²) at inclusion	21.6 (4.1)	21.1 (4.8)
Karnofsky's performance status at inclusion median (range)	80 (60–90)	70 (40–90)
Chemotherapy		
Previous	4	3
Ongoing	2	

BMI, body mass index

cial effects of disease. Raw scores are linearly transformed to produce standard scores in the range of 0 to 100 for each scale and for single items. Higher scores on the functional and global health scales indicate better functioning, whereas higher scores on the symptom scale represent more symptoms.

A 4-d food diary was kept at baseline and at the end of each intervention period. A booklet with meal-size photographs facilitated estimation of food intake. The intake reported was transferred to weight values and then calculated and compared with the Nordic nutrition recommendations [17]. Dietary advice was given by the dietitian based on the diary and according to Nordic recommendations, i.e., 30% of calories should be from fat, 10% to 15% from protein, and 55% to 60% from carbohydrates. The recommended levels were adjusted for age, sex, weight, and physical activity. This advice differed from that mostly given to patients with advanced cancer, which suggests energy-dense food with at least 35% of calories provided by fat. Advice was given to the patient, and in most cases the spouse was present during the consultation.

Pharmacologic interventions

Patients who are randomized to start FO (FO group) received 30 mL/d of an FO mixture (ACO Omega 3, Pharmacia, Stockholm, Sweden), 15 mL in the morning and 15 mL in the evening, with meals. During the study, production

of ACO Omega 3 ceased, so from patient number 21 and onward Eskimo 3 (Cardinova, Uppsala, Sweden), an equivalent product, was used. The FO contained 18% EPA and 12% DHA, and 30 mL provided 4.9 g of EPA and 3.2 g of DHA. Patients who were randomized to start MLT (MLT group) received six capsules, each of which contained 3 mg of MLT, in the evening, i.e., 18 mg/d. In the second intervention period, all patients underwent both interventions.

Patients brought back all bottles and packages, empty or not, for assessment of compliance. In the FO group, changes in plasma FAs were also used to assess compliance. A doubling of the level of EPA in plasma was regarded an indication of good compliance. For MLT compliance was assessed from empty packages returned.

Analysis of fatty acids and cytokines

FAs were extracted with chloroform and methanol. Phospholipids were separated by thin-layer chromatography, and, after transmethylation, FA methyl esters were separated by gas-liquid chromatography [18]. Results are presented as percentage of all FAs detected.

Commercial cytokine enzyme-linked immunosorbent kits for measurements of serum or plasma levels of circulating TNF- α , IL-1 β , IL-6, IL-8, and IL-2R were obtained from R&D Systems (Abingdon, United Kingdom), and analyses were performed according to the manufacturer's instructions. For measurement of TNF- α and IL-1 β , high-sensitivity kits were used (measurement ranges of 0.5 to 32 pg/mL and 0.125 to 8 pg/mL of serum, respectively); for sIL-2R and IL-8, standard-sensitivity kits were used (measurement ranges of 78 to 5000 pg/mL and 31.2 to 2200 pg/mL, respectively). Levels of IL-6 differed considerably across patients. Therefore, high-sensitivity kits (0.156 to 10 pg/mL) were used alternatively with standard-sensitivity kits (3.12 to 300 pg/mL), with all sera investigated in parallel on the same plate. For IL-6, data from the kit that provided the most complete information concerning changes in serum IL-6 levels during the study period were used.

Statistical analyses

Mann-Whitney U test and Wilcoxon's matched-pairs signed-rank test were used for inference calculations of differences in medians for unpaired and paired data, respectively, and Student's *t* test was used for inference on mean values. Correlations were calculated by Spearman's rank correlation coefficient and survival rate by log-rank test.

Data presentation

Data are presented for the 24 patients who started the intervention, are based on the randomization groups, and mostly are presented as medians and ranges. Changes in biochemistry and cytokines after an intervention period are

Table 2

Baseline median (range) values in randomization groups and median changes (%) from baseline to period 1, from periods 1 to 2, and from baseline to period 2 for numbers of patients indicated

Reference values		Baseline		Baseline to period 1		Periods 1 to 2		Baseline to period 2	
		FO (n = 13)	MLT (n = 11)	FO (n = 11)	MLT (n = 9)	FO (n = 10)	MLT (n = 6)	FO (n = 10)	MLT (n = 6)
B-Hb	Women: 115–151 g/L Men: 133–167 g/L	126 (87–163)	113 (82–144)	−3.3	−0.8	−6.1	−6.0	−8.2*	−0.9
S-Alb	37–48 g/L	39 (27–48)	34 (27–40)	−2.4	−2.9	−2.9	−5.1	−2.4	+2.6
S-LDH	3.8–6.7 μ kat/L	6.9 (4.6–16.4)	8.6 (4.4–40)	+8.7	+32.5	−2.7	+10.5	+3.9	+18.0
S-CRP	0–10 mg/L	22.5 (10–124)	63 (10–229)	+11.7	+62.0	+8.3	+22	\pm 0.0	\pm 0.0
P-Fibrin	2.0–3.6 g/L	4.8 (3.1–8.7)	6.1 (3.2–8.4)	+8.5	−1.9	−7.9	−0.4	−3.4	−9.4
TNF- α	NA	4.6 (2.1–16.4)	6.8 (3.7–12.1)	−2.3	\pm 0	+13.0	+4.3	+22.5	−6.7
IL-1 β	NA	0.125 (0.125–2.36)	0.25 (0.125–1.18)	\pm 0.0	\pm 0.0	\pm 0.0	\pm 0.0	\pm 0.0	+23.2
sIL-2r	NA	1992 (1408–6375)	3699 (1814–6129) [†]	+5.0	−1.8	+17.8	−4.4	+23.0	−14.0
IL-6	NA	4.7 (1.5–7.6)	4.9 (1.4–18.9)	−5.3	+10.0	+6.0	+17.7	+17.9	\pm 0.0
IL-8	NA	31.2 (31.2–240)	80.7 (31.2–309)	\pm 0.0	+21.9	\pm 0.0	\pm 0.0	\pm 0.0	+9.4

B-Hb, blood hemoglobin; FO, fish oil; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; IL-8, interleukin-8; MLT, melatonin; NA, not applicable; P-fibrin, plasma fibrinogen; S-Alb, serum albumin; S-CRP, serum C-reactive protein; sIL-2R, soluble interleukin-2 receptor; S-LDH, serum lactate dehydrogenase; TNF- α , tumor necrosis factor- α

* Statistically significant changes across assessment I to III within groups, $P = 0.01$.

[†] Statistically significant difference between groups, $P = 0.02$.

shown as the difference versus baseline or the previous assessment, as applicable, for patients who remained in the trial at that point. These changes are presented as percentages. Concentrations of FAs, in percentages of total FAs, are presented as means at each assessment. Weight development is presented as loss or gain of kilograms at each assessment. Energy intake is presented as mean value at inclusion and changes during the study period. In a subgroup analysis, patients with good compliance to their supplement over 4 wk are presented in a corresponding way with values at baseline, i.e., the assessment closest to the start of the intervention and changes after 4 wk. In a responder analysis, patients with weight stabilization or gain were counted as responders, and those with weight loss or who provided no data were counted as non-responders.

Results

Compliance and adverse events

Two patients in each group did not accomplish the first intervention period, one patient in each group died due to progressive disease, and one in each group dropped out because of progressive disease. After the second intervention period, one patient in the FO group and three in the MLT group dropped out due to progressive disease. During the first intervention period, eight patients (62%) in the FO group had good compliance. In the MLT group, five patients (45%) took 100% of the MLT, two had 75%, and four took 50% or less of the amount prescribed. Among patients who started supplementation with FO during the second period, five (62%) showed good compliance. Among patients who started MLT at this period, 100% compliance was seen in four (36%).

Very few side effects considered related to the interventions

were recorded. After the first period, one patient in the FO group reported grade 3 anorexia (National Cancer Institute common toxicity criteria [CTC]) and one in the MLT group reported grade 3 fatigue, and these developments were likely related to the study drugs. After the second period, one patient in the FO group reported grade 3 anorexia, one in the MLT group developed grade 3 toxicity of the central nervous system, one in the MLT group had grade 3 paraesthesia, and one in the FO group reported heartburn and grade 2 belching.

Biochemistry, cytokines, and fatty acids

Median baseline values for biochemistry were beyond the normal range for most parameters in both groups (Table 2). The lower values for hemoglobin and albumin and higher values for lactate dehydrogenase, CRP, and fibrinogen in the MLT group indicated that those patients were more deteriorated at baseline than were those in the FO group. At baseline TNF- α , IL-6, and sIL-2R were detectable in 24 patients (100%), IL-1 β in 10 (42%), and IL-8 in 12 (50%). There was an indication that patients in the MLT group were in poorer health, with generally higher baseline cytokine values, compared with patients in the FO group. However, this was statistically significant only for sIL-2R ($P = 0.02$).

At baseline and for all patients, all cytokines, except IL-1 β , for which there were too few detectable values, correlated statistically significantly with CRP and fibrinogen (Spearman's rank $r = 0.53$ to 0.70 , $P < 0.01$ to 0.001 , not shown).

After the initial 4 wk on FO or MLT, there were no major and systematic changes in biochemistry or cytokines (Table 2). The only statistically significant change from baseline during the study was seen for B-hemoglobin in the FO

Table 3

Serum fatty acid distribution as percentage of total fatty acids at baseline and assessments II and III.* Reference values are for healthy volunteers [18].

	Baseline		Assessment II		Assessment III		Reference values [†]
	FO	MLT	FO	MLT	FO	MLT	
Linoleic acid (18:2 ω -6)	17.7 (2.4)	19.0 (2.4)	13.9 (3.7)	20.5 (2.8)	14.1 (4.5)	14.9 (3.0)	23.4 (2.6)
AA (20:4 ω -6)	7.8 (1.9)	6.5 (1.7)	7.1 (1.3)	6.0 (1.8)	7.0 (2.0)	6.0 (0.5)	7.9 (1.0)
EPA (20:5 ω -3)	1.3 (0.5)	1.2 (1.0)	6.0 [‡] (3.5)	1.0 (0.4)	7.2 (5.2)	7.9 [‡] (3.5)	1.5 (0.5)
DHA (22:6 ω -3)	4.4 (1.3)	3.6 (0.9)	6.3 [‡] (1.9)	3.4 (1.1)	6.0 (2.5)	4.8 (2.4)	4.7 (0.9)

AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FO, fish oil; MLT, melatonin

* Values are mean (standard deviation).

[†] Values are for healthy subjects [18].

[‡] Statistically significant difference between groups, $P \leq 0.001$.

[§] Statistically significant change between assessments II and III, $P = 0.006$.

group ($P = 0.01$). When analyzing all patients together, the only statistically significant changes were increases in IL-6 over the first intervention period ($P = 0.04$) and in IL-8 over both intervention periods ($P = 0.03$, data not shown).

At baseline, mean values of FA distribution in plasma were similar to those in healthy volunteers [18] and with essentially no differences between groups. After the first 4 wk of FO intervention, linoleic acid decreased, whereas EPA and DHA increased. Differences between mean values in the FO and MLT groups were statistically significant at assessment II. At assessment III, linoleic acid decreased and EPA and DHA increased in the MLT group and reached the same levels as those in the FO group. The change for EPA in the MLT group was statistically significant (Table 3).

Energy intake and weight

At baseline and before dietary consultation, mean energy intakes \pm standard deviation were 1750 ± 707 kcal and 1495 ± 400 kcal in the FO and MLT groups, respectively, representing 93% and 82%, of the recommended intake (Nordic nutrition recommendations). At the end of each intervention period, the FO group showed a decrease in intake by -65 and -196 kcal, respectively. In the MLT group, mean energy intake increased by 187 and 19 kcal, respectively. Commercial supplements were used by approximately 50% of patients during the study period. Supplements generally provided 4 to 500 kcal/d, which corresponded to approximately 25% of total energy intake. The energy provided by FO was not included in the calculations (30 mL provides 280 kcal).

After the first intervention period, median weight losses were 0.6 and 1.8 kg in the FO and MLT groups, respectively. During the second intervention period, both groups showed median weight gains of 0.2 and 0.8 kg, respectively (not significant). With respect to weight response, there were five responders (38%) during the first intervention period in the FO group and three (27%) in the MLT group (Fig. 1). Over both intervention periods, eight patients (62%) responded in the FO group compared with seven (64%) in the MLT group. There were no clinical signs of fluid retention in any patient during the trial.

Performance status, QoL, and survival rate

With respect to Karnofsky's performance status, the median baseline value of 80 (range = 60–90) in the FO group changed to 70 (range = 60–90) after the first intervention period and returned to 80 (range = 60–90) after the second period. In the MLT group, the median baseline value of 70 (range = 40–90) changed to 65 (range = 40–90) after the first period and remained at 65 (range = 60–90) after the second period. There were no statistically significant differences in Karnofsky's performance status between groups at randomization or during the study.

At baseline, 22 patients answered the EORTC-QLQ-C-30; the second time, it was answered by 18 patients; the third time, it was answered by 16 patients. At baseline the only statistically significant differences between the FO and MLT groups, indicating lower QoL in the MLT group, were found in the scales for physical functioning, with mean values of 72 and 44 ($P = 0.003$) for the FO and MLT groups, respectively, and for role functioning, with mean values of 54 and 22 ($P = 0.02$), respectively. Scores for global QoL were low at baseline, 45 and 43, and a slight but insignificant increase occurred during the study period. Appetite scores, 61 and 60, decreased markedly during the first 4 wk in both groups. However, these changes were not statistically significant. At the second assessment, there was a statistically significant decrease in physical functioning and financial difficulties in the FO group ($P = 0.002$ and 0.04, respectively). The mean score for pain increased in the FO group during the first 4 wk ($P = 0.004$).

There was no statistically significant difference in overall survival rate between groups. Median survival periods were 142 d (range = 8–645) in the FO group and 179 d (range = 55–313) in the MLT group.

Subgroup analyses

To further explore the data and expand the possibility of finding relevant changes, subgroup analyses were performed. When considering patients with good compliance during any intervention period, there were no major or significant system-

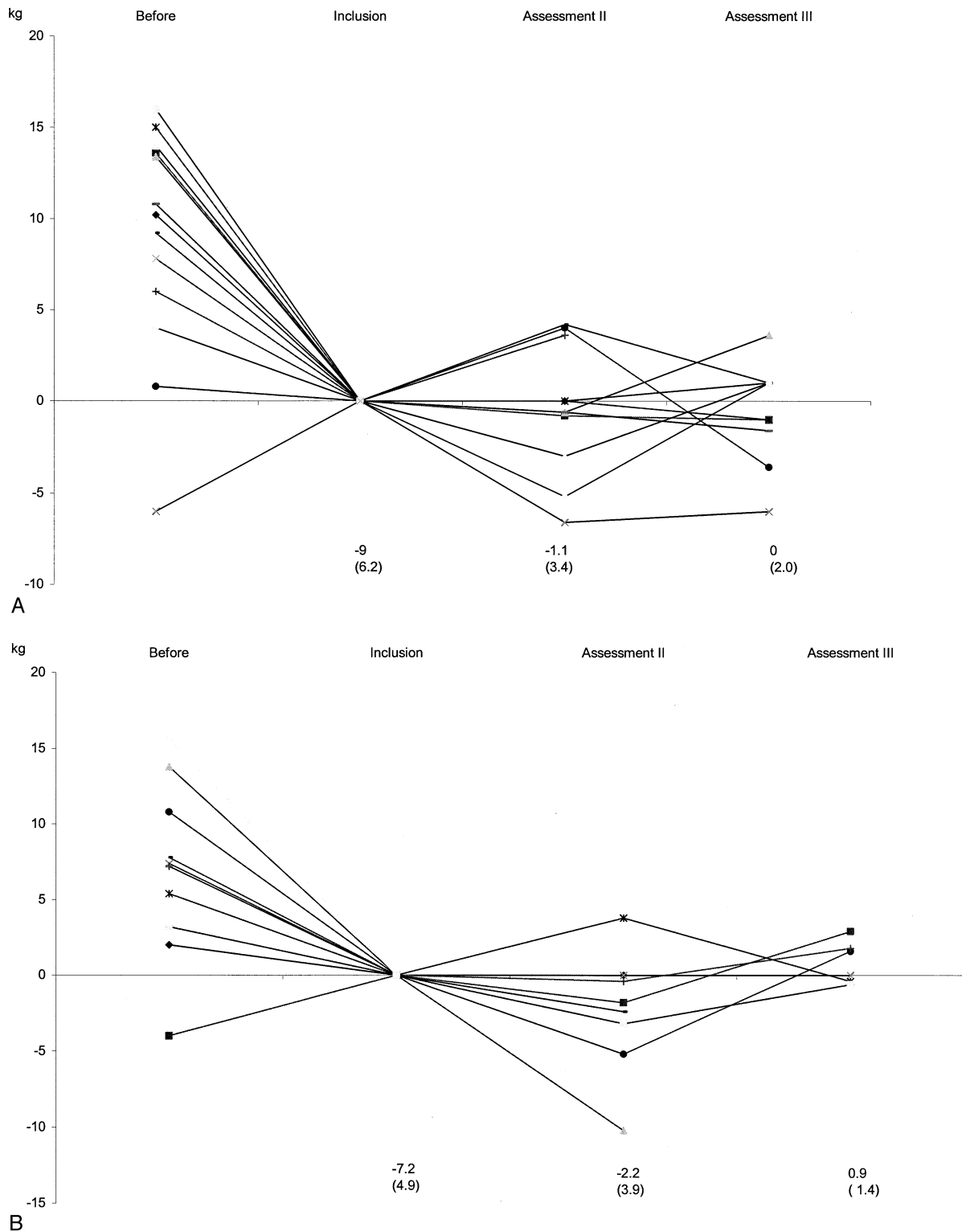


Fig. 1. Weight change (kg) during the previous 6 mo to inclusion, inclusion to assessment II, and assessment II to III in subjects receiving (A) fish oil or (B) melatonin. Each line represents one patient. Mean weight changes (standard deviations) are indicated at the bottom.

atic changes in biochemistry and cytokines within or between the FO and MLT groups (data not shown).

To investigate whether a beneficial effect from FO and MLT might be restricted to patients who had pancreatic

cancer, this subgroup of eight patients was analyzed separately. This subgroup showed results that corresponded with the entire patient group, i.e., no major and consistent changes in biochemistry and cytokines were observed.

However, after the second intervention period, six of eight patients (75%) were weight responders.

Discussion

This randomized pilot trial aimed at further elucidating the role, if any, of intervention with FO and/or MLT in patients who had advanced gastrointestinal cancer and documented weight loss. It was originally planned to include 30 patients in each arm. Unfortunately, the number of patients who participated in the protocol was smaller than expected, frequently due to rapidly progressive disease. Although the final number of patients was limited, the extensive set of analyses performed and the inclusion of FO and MLT for intervention make the data generated interesting.

The FO and MLT interventions were generally well tolerated, alone and in combination. Plasma FAs changed in accord with corresponding findings in healthy individuals on a similar dose of FO [18], indicating that a severe cancer-associated inflammatory state does not prohibit the FA response expected from large-dose FO. Further, plasma levels of malonaldehyde and vitamin E did not change after starting FO (not shown), indicating that the large amount of polyunsaturated FAs provided did not increase lipid peroxidation.

Subjects had documented weight loss, poor QoL scores, biochemical indicators of advanced disease, and levels of CRP, fibrinogen, and cytokine compatible with a vigorous inflammatory response. Given the proposed anti-inflammatory effect being a key mechanism of action for ω -3 FAs in FO and MLT [6,13], such effects should have been readily detected in the patients studied.

However, FO, MLT, and their combination did not induce any major or consistent changes in CRP, fibrinogen, and cytokines indicative of inflammation suppression. However, this could be interpreted as a stabilization of the APPR, which would be compatible with previous small studies in which administration of FO, at doses smaller than that used in the present study, did not decrease APPR [11], except for small and/or temporary decreases in CRP [19,20].

Serum measurements of factors involved in inflammation may poorly reflect activity in tissues because the stimulated production *ex vivo* of IL-6 from peripheral blood mononuclear cells isolated from cachectic patients treated with FO decreased, whereas there was no change in serum levels [19]. Further, cytokine production might show diurnal rhythms, making time points for sampling critical and increasing the “noise” against which therapeutic changes should be contrasted [21]. Alternatively, patients’ level of inflammation may have been too advanced for the interventions to counteract.

In a previous study in cachectic patients who had advanced cancer, 20 mg/d of MLT in a time-dependent fashion decreased serum levels of TNF to approximately 50% at

2 mo, indicative of an anti-inflammatory response [13]. MLT at a similar dose demonstrated no anti-inflammatory effects in the present study. The reason for this discrepancy is not clear because the patients in these trials seemingly were similarly advanced. However, the number of patients on MLT for this period was small, thus decreasing the power to detect changes.

Seemingly compatible with an APPR and cytokine stabilization, the data indicated that both interventions might have a weight-stabilizing effect. Thus, compared with the baseline weight decrease in most patients, many showed small gains or at least weight stabilization during the interventions. Patients with pancreatic cancer in a weight-losing state similar to that of patients in the present study showed a weight loss of almost 3 kg/mo when receiving supportive care alone [11]. With this background, weight stabilization could be considered a clinically relevant effect. Although the number of responders was larger during FO than during MLT interventions, the difference was small. However, the effects observed in weight development might also be related to the dietary advice provided and/or a supportive effect from a close contact with the study team.

These effects should be compared with previous observations of a median weight gain of 1 kg after 3 wk and 2 kg after 7 wk [10], 1 kg after 3 wk [11], or 0.3 kg/mo on FO in patients with advanced pancreatic cancer [20], whereas MLT at 20 mg/d was found to decrease weight loss in patients with advanced cancer compared with supportive care alone [13]. The present data are less convincing but are compatible with such effects.

Effects on cancer cachexia from the combined use of FO and MLT have not been studied previously. Considering previous observations that effects on cachexia from similar interventions might be observed within 4 wk, the present data indicated that the small beneficial effects from FO and MLT are additive. Alternatively, the beneficial effect might need a longer period than 4 wk to fully develop. In any case, a lack of substantial synergy from the combination was reflected by the absence of changes in biochemistry and cytokines.

Although appetite tended to improve during the first intervention period, this response was not accompanied by an increased energy intake from food in the FO group. In a previous trial, FO increased appetite and median energy intake by 370 kcal/d [10]. However, the FO was formulated as a nutritional supplement that provided 610 kcal/d in that trial. In the present study, the prescribed dose of FO provided almost 300 kcal/d, which might have contributed to a weight-stabilizing effect. In contrast, a more specific effect from the ω -3 FAs in the FO is suggested because metabolic abnormalities in cachexia, notably increased resting energy expenditure and fat oxidation, were counteracted in patients with pancreatic cancer who were given FO [22].

Although the lack of statistical significance and the small groups prohibit a clear conclusion, it was interesting to note that the overall median survival tended to be longer for the

MLT group than for the FO group. Because of the more pronounced poor prognostic factors at baseline in this group, a shorter survival compared with the FO group was expected. Although highly speculative, this observation is compatible with a lower rate of disease progression on MLT compared with supportive care alone in advanced cancer [13] and with an improved survival rate from the combination of MLT and chemotherapy compared with chemotherapy alone for advanced solid cancer [15].

What are the roles, if any, of these supplements in the palliative care of patients with advanced cancer? For FO there are limited experiences in pancreatic cancer, indicating that ω -3 FAs from FO counteract some of the key features of cancer cachexia [10,21]. These findings also have strong support in convincing preclinical data in cachexia models in vivo [23]. In addition, there is one controlled trial that showed a survival benefit from large-dose FO combined with vitamin E in patients with advanced cancer [24]. However, at present, neither the quality nor the quantity of the trials is sufficient to recommend inclusion of FO in the standard care of patients with cachexia associated with advanced cancer. More and confirmatory data on the clinical relevance of a small weight gain and counteracted abnormal metabolism are needed.

However, because of the interesting preclinical in vivo data showing that ω -3 FAs suppress cancer growth and metastases [25] and that FO can potentiate the effect but not toxicity of a cytotoxic drug [26], further exploration of the putative beneficial effects of ω -3 FAs in cancer management seems justified.

For MLT, documentation on the cachexia indication has relied on only one, yet fairly large and controlled clinical trial showing decreased weight loss and TNF levels from MLT [13]. Although the present data are partly compatible with such an effect, MLT should be confined to clinical trials until more data, including mechanistic information, are at hand. Taken together, the clinical reports on effects of MLT in cancer, including growth inhibition, slowing of tumor progression, and enhancement of the effect of chemotherapy at decreased toxicity and antiangiogenic activity [5,15,27] are interesting, and further exploration of the putative beneficial effects of MLT in cancer management also seems justified for MLT.

In conclusion, FO, MLT, and their combination did not produce substantial anti-inflammatory effects in cachectic patients with advanced gastrointestinal cancer. However, the weight-stabilizing effect seemingly produced by the combined intervention and previous observations justify their inclusion in additional clinical trials.

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