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Clinical Impact of Highly Purified, Whey Proteins in Patients Affected With Colorectal Cancer Undergoing Chemotherapy: Preliminary Results of a Placebo-Controlled Study

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Abstract

Background and Aims: Sarcopenia, the loss of both lean body and skeletal muscle mass, may interfere in cancer patients outcome. As investigated, whey proteins could prevent the onset of sarcopenia. We have conducted a study to evaluate the effects of whey protein in colorectal cancer patients, undergoing 5-fluorouracil-based chemotherapy. **Methods:** After written informed consent, patients were blind randomized 1:1 to whey protein (ProLYOtin; arm A) versus placebo (arm B). The patients were assessed both physically and nutritionally before chemotherapy and after 3 (T2) and 6 months (T3) by body impedance assessment, L3-computed tomography scan, Mini Nutritional Assessment (MNA), and Malnutrition Universal Screening Tool (MUST) tests. **Results:** Forty-seven patients were included in this preliminary analysis. Baseline characteristics were well balanced between the 2 arms. During chemotherapy, 33 patients were reevaluated: anthropometric parameters (lean body mass from 68.5% to 71.2% vs 68.7% to 66.3%, and sarcopenia from 84% to 54% and 83% to 77% from baseline to T2 evaluation in arms A and B, respectively), nutritional status (MNA >24 = 100% [A] vs 73.7% [B]), and toxicity (no adverse effects in 86% [A] vs 29% [B] and 94% [A] vs 29% [B] for hematological and gastrointestinal toxicities, respectively) resulted to be significantly different. At univariate analysis, a condition of malnutrition risk according to MUST (relative risk [RR] = 7.5, $P = .02$) or MNA (RR = 1.45, $P = .02$) and ProLYOtin intake (RR = 0.12, $P = .01$) were found to be significantly predictive of chemotherapy toxicity. **Conclusions:** At present, our study shows how whey protein could be an important therapeutic option to improve nutritional status, and particularly to prevent severe toxicity during chemotherapy.

Keywords

colorectal cancer, protein supplementation, whey protein, adjuvant chemotherapy, toxicity, malnutrition, sarcopenia

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Introduction

Sarcopenia—the loss of both skeletal muscle mass and function—may be present independently of body weight and has been shown to negatively interfere with outcome of cancer patients.[1] Some studies have found that reduction in both muscle skeletal tissue and lean body mass (LBM) during chemotherapy correlated with toxicity and worse survival expectancy.[2,3] In sarcopenic patients, the smaller volume of drug distribution with a greater concentration of the same

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drugs in the time unit may explain the greater toxicity that affects these patients more than others.[2,3] Therefore, sarcopenia is becoming increasingly considered a prognostic as well as a predictive factor in chemotherapy response.[4,5]

Recent data point out that the anorexia-cachexia syndrome and the risk of malnutrition and overt malnutrition are present since the first oncological visit.[6] However, it has been demonstrated that whey protein supplements could be a suitable nutritional intervention to improve the muscular protein synthesis to favor gain of LBM and to prevent malnutrition and sarcopenia[7,8]; they also may have intrinsic anticancer properties.[9] Based on the currently available evidence, we propose an exploratory, placebo-controlled, randomized study, aimed at evaluating the activity of a nutritional supplement containing highly purified whey proteins (ProLYOtin; see supplementary material available online) in colorectal cancer patients undergoing 5-fluorouracil-based chemotherapy. This study has been approved by the Institutional Ethical Committee (Approval Number 166 SA_2017) and conducted according to the Declaration of Helsinki guidelines.

Methods

Study Design

As discussed earlier,[10] this is a multicenter study on eligible patients (age ≥18 years; written informed consent obtained; European Cooperative Oncology Group [ECOG] Performance Status 0-1; histological neoadiagnosis of stage II, III, or IV colorectal cancer; candidates for a 5-fluorouracil-based adjuvant chemotherapy; without metabolic disorders [diabetes, dyslipidemia], infectious diseases, or other organ dysfunctions). Patients were single-blind randomized with 1:1 ratio to receive either the active product (A), ProLYOtin, a nutritional supplement, containing 13.5 g of highly purified whey protein (Italian Ministry of Health registration Number 71005), 1 packet per day from the start to the end of chemotherapy (6 months), or placebo (B), an isocaloric control product, consisting of a mix of inulin and potato starch without any protein or micronutrients.

The randomization was computer generated by a statistician not involved in data collection, who was called by phone at the time of assignment.

After written informed consent was obtained, and before starting chemotherapy, all patients performed a pretreatment computed tomography (CT) scan for both postsurgical staging and sarcopenia evaluation. CT scans were repeated after 3 and 6 months. Furthermore, in all patients, quality of life using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 instrument, nutritional risk screening (Malnutrition Universal Screening Tool [MUST]), and nutritional state (Mini Nutritional Assessment [MNA]) were assessed at baseline (T1), and repeated twice: first after 3 months (T2) and the second after 6 months (T3) during chemotherapy. Patients were screened for clinical condition and frailty at baseline, after 3 and 6 months and were categorized by the ECOG and Karnofsky performance status (PS) assessments. Physico-nutritional examination and blood analysis were also monitored in the same time frame. Moreover, the following clinicopathological parameters were recorded and analyzed: age, sex, comorbidities and concomitant treatment, dietary practices, baseline tumor characteristics, chemotherapy regimen, ECOG PS and Karnofsky PS, and maximum toxicity, especially hematological and gastrointestinal, evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE v 4.0). Compliance to the study protocol has been assessed by telephone contact and dietary diary review. The patient's food diary was completed for 1 week as an example of their daily lifestyle and analyzed by the MetaDieta Software, which is constantly updated and implemented with the values of the main Italian official database. In both treatment groups, patients reported an intake of proteins that ranged between 0.8 and 1.0 g/kg/day by their diet. From their food diary, we have determined that the ProLYOtin group patients reach a total daily protein intake of 1.2 g protein/kg body weight/day as reported in the European Society for Parenteral and Enteral Nutrition guidelines.

Sarcopenia (herein defined as the sole reduction of muscle mass) was evaluated by the skeletal muscle mass, cross-sectional area (cm^2) calculation, and using CT images. The level of the third lumbar vertebra (L3) was chosen as a standard landmark for a multiplanar reconstruction, considering the following muscles: psoas, paraspinal, abdominal transverse rectum, internal and external obliques. The CT images were analyzed by using the Slice-O-Matic software, version 5.0 (Tomovision, Montreal, Canada). The skeletal muscles were identified and marked by the Hounsfield units thresholds from −29 to +150.17, and the total cross-sectional area was computed for each patient. The L3 Skeletal Muscle Index (L3 SMI) was calculated as skeletal muscle mass area in cm^2 divided by height in m^2 and reported in units of cm^2/m^2. Sarcopenia was defined using cutoff points for lumbar SMI of ≤38.5 cm^2/m^2 and ≤52.5 cm^2/m^2 for women and men, respectively, according to previous studies.[3,4] To asses body mass composition, we have also conducted a tetrapolar single frequency bioelectrical impedance analysis (BIA), performed by passing current between 2 surface electrodes placed on the right hand and right foot.[11] All BIAs were performed by the same dietitian using an impedance plethysmograph that emits an 800-A, 50-kHz alternating current (BIALight, DS Medica, Milan, Italy). Unfortunately, a specific, well-defined procedure for performing routine BIA measurements is not practiced for cancer patients. However, to standardize the procedure, we have recommended fasting at least 2 hours before the analysis, avoiding physical activity the day before and the day of the procedure, and avoiding a dinner rich in carbohydrates. All randomized patients had received treatments and were evaluated during the time (T1,

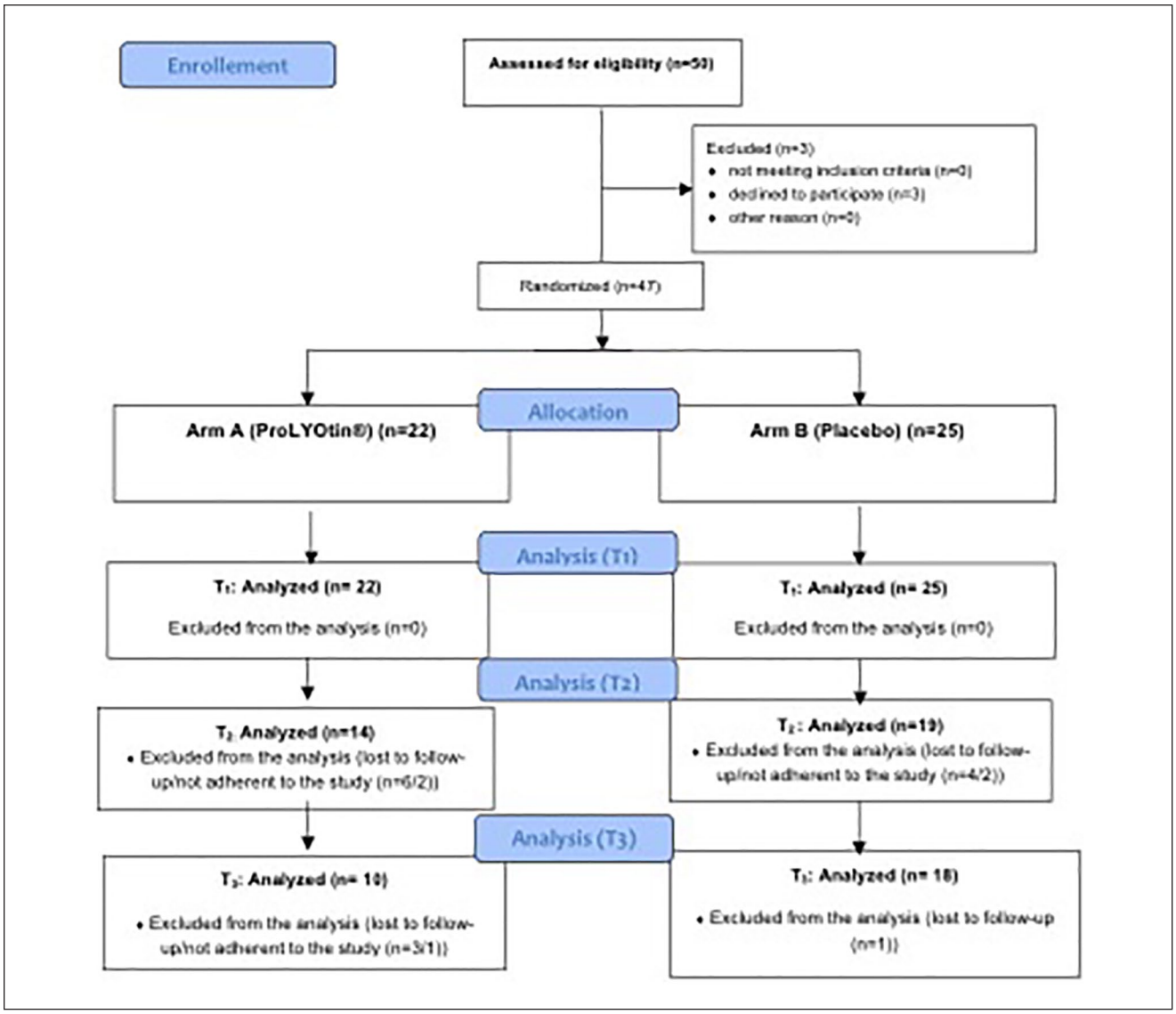

Figure 1. CONSORT flow chart.

T2, and T3) expected by the protocol by a specialist team of a nutritionist and medical oncologists. All patients could have interrupted the study protocol if one of the following criteria had occurred: (1) patient's choice; (2) grade 4 toxicity or any other impairment of a patient's health conditions; and (3) progression of disease.

Statistical Analysis

According to the aforementioned background, in order to provide an adequate sample size, assuming a 40% and 20% of malnutrition prevalence in placebo and experimental arms, respectively, a total of 220 (110 for each arm) patients will be randomized (calculated with an error of 10% and confidence interval [CI] of 95%). However, a feasibility study analysis was conducted on the first 50 cases enrolled, described in this publication. Descriptive analysis of clinicopathological parameters and differences between nutritional state and both hematological parameters and toxicities was analyzed by a univariate and multivariate logistic regression model. Clinicopathological differences between the 2 treatment arms were determined using a 2-sided paired *t* test. The statistical analysis was performed using SPSS software (v 24.0).

Results

Baseline (T1)

At baseline, we identified 50 eligible patients, but 3 of them refused to participate in the study, while the other 47 were

Table 1. Baseline Clinicopathological Characteristics of Enrolled Patients (N = 47).

	A: ProLYOtin (N = 22)	B: Placebo (N = 25)
Sex, n (%)		
Male	15 (68.2)	14 (56.0)
Female	7 (31.8)	11 (44.0)
Median age, years	68 (34-83)	67 (49-85)
Comorbidity, n (%)		
CV	7 (31.8)	10 (40.0)
EM	2 (9.1)	5 (20.0)
CV + EM	6 (27.3)	3 (12.0)
Tumor site, n (%)		
Right colon	10 (45.5)	9 (36.0)
Left colon	6 (27.3)	14 (56.0)
Rectum	6 (27.3)	2 (8.0)
Stage of disease, n (%)		
II	6 (27.3)	8 (32.0)
III	7 (31.8)	10 (40.0)
IV	9 (40.9)	7 (28.0)
Chemotherapy regimen		
Capecitabine	6 (27.3)	6 (24.0)
FOLFOX +/− biologic agent	13 (59.1)	15 (60.0)
XELOX	3 (13.6)	4 (16.0)
PS, ECOG, n (%)		
0	18 (81.8)	24 (96.0)
1	4 (18.2)	1 (4.0)
EORTC QLQC-30, median (range) %		
Quality of life scale	66 (33-100)	66 (0-100)
Function scale	82 (36-100)	81 (58-100)
Symptoms scale	18 (0-38)	18 (3-90)
MNA, n (%)		
24-30 (normal)	7 (31.8)	12 (48.0)
17-23.5 (at risk of malnutrition)	11 (50.0)	9 (36,0)
<17 (malnourished)	4 (18.2)	4 (16.0)
MUST, n (%)		
0	5 (22.7)	14 (56.0)
1	7 (31.8)	8 (32.0)
≥2	10 (45.5)	3 (12.0)
Body mass index, n (%)		
18.5-24.9 kg/m^2	12 (54.5)	13 (52.0)
25-30 kg/m^2	7 (31.8)	7 (28.0)
30.1-40 kg/m^2	3 (13.6)	5 (20.0)
<18.5 kg/m^2	0	0

Abbreviations: CV, cardiovascular; EM, endocrine-metabolic; PS, performance status; ECOG, European Cooperative Oncology Group; EORTC, European Organization for the Research and Treatment of Cancer; MNA, Mini Nutritional Assessment; MUST, Malnutrition Universal Screening Tool.

recruited (Figure 1). All randomized patients received treatments at a 1:1 ratio of either ProLYOtin (A) or Placebo (B), which were homogeneously distributed in the 2 groups at baseline by sex, median age, performance status (with a prevalence of patients with good PS), food intake, site and stage of disease, as well as scoring of the EORTC QLQ-C30 summaries (Table 1). The majority of patients were at risk of malnutrition according to the MNA score (50% in the group A and 36% in the group B), while malnourished patients were found in 18.2% and 16% of the cases, respectively. Similarly, the MUST test identified 31.8% of patients in the group at medium risk of malnutrition versus 32% in the placebo group. High risk of malnutrition was observed in 45.5% of patients in group A versus 12% in group B. Meanwhile, none were underweight, and half of the entire cohort study were overweight (31.8% vs 28%) or obese (13.6% vs 20%). BIA revealed an altered body composition with excess of fat in relation to LBM in both treatment

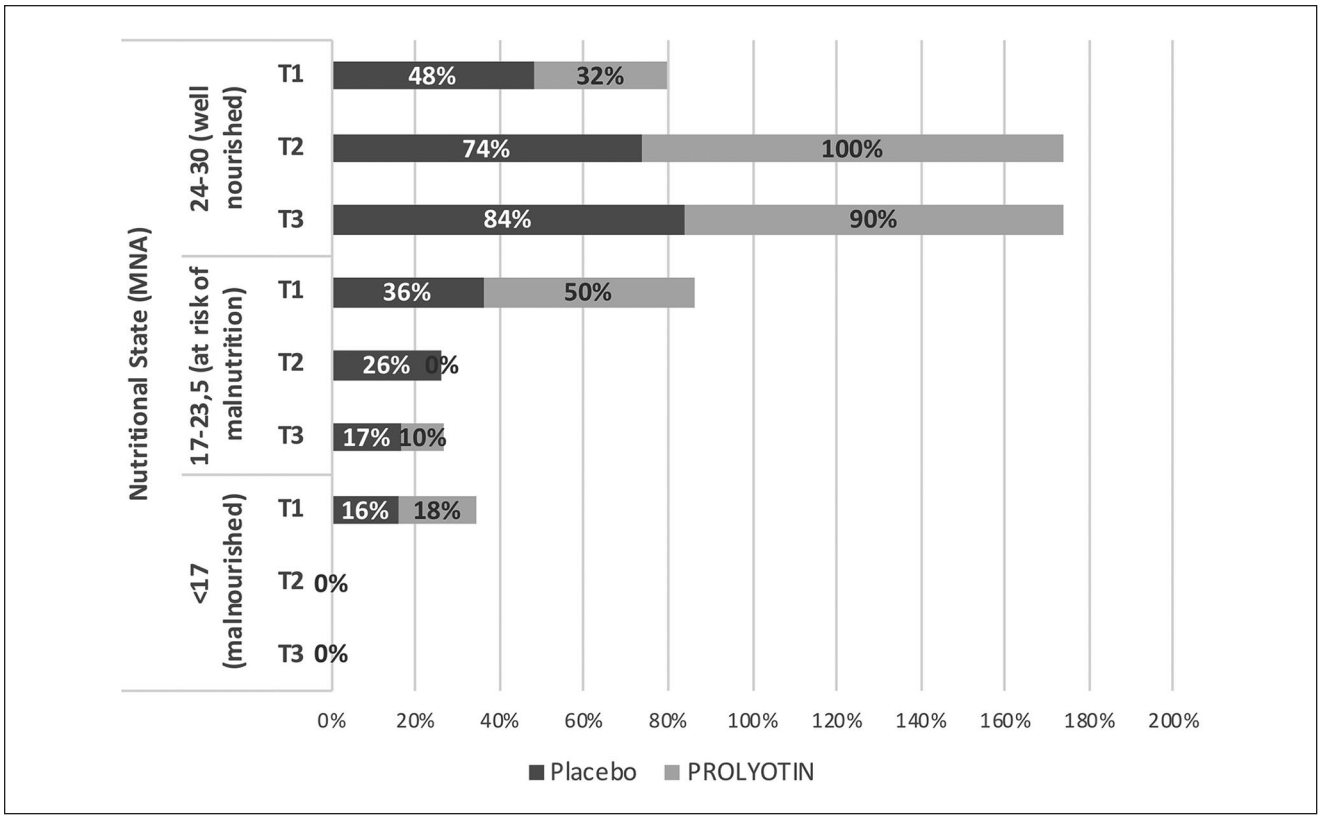

Figure 2. Mini Nutritional Assessment (MNA) differences between 2 treatment arms at baseline (T1), and after 3 (T2) and 6 (T3) months.

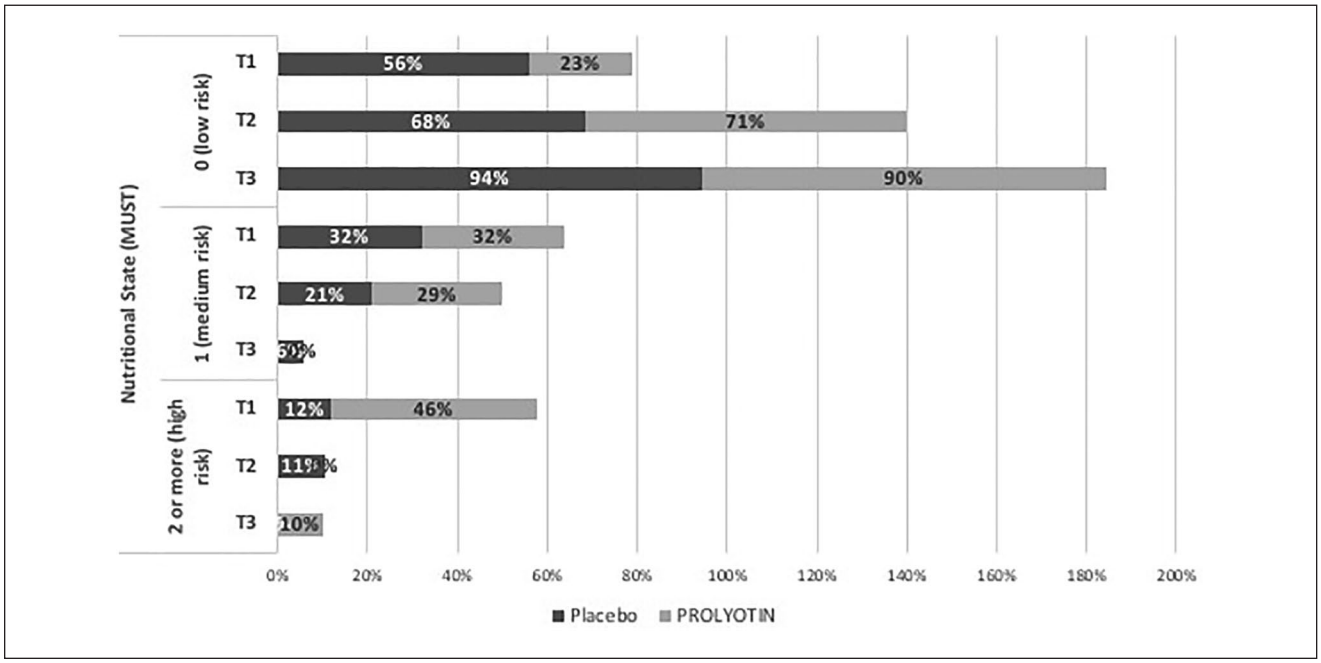

Figure 3. Malnutrition Universal Screening Tool (MUST) differences between 2 treatment arms at baseline (T1) and after 3 (T2) and 6 (T3) months.

groups, as well as in male and female patients. Moreover, about 50% of patients showed low body water.

Sarcopenia occurred in more than half of the population (85% of patients in arm A vs 83% in arm B) in agreement with the data described with the BIA, in both treatment groups, regardless of gender. In terms of age no difference was found between sarcopenic and non-sarcopenic patients (median age: 68 vs 63 years, respectively, $P = .16$). However, 89.5% and 75.0% of patients older than 65 years were sarcopenic and non-sarcopenic, respectively, but this difference was not statistically significant.

No significant differences were found in blood tests between the 2 arms, nor any relevant alterations of the analyzed inflammatory indexes. The level of vitamin D was found to be insufficient, with values markedly lower than the normal reference limits, both in the active group and in the placebo group (16.8 and 16.1 ng/mL, respectively).

T2 Evaluation

At the 3-month (T2) evaluation during chemotherapy, 33 patients were reevaluated, 14 from arm A and 19 from arm B. Some patients were lost to follow-up (2 patients changed center, 1 died from an ischemic attack, and 7 patients were enrolled <3 months ago and have not done the T2 evaluation visit yet). Some patients did not adhere to treatment (2 patients randomized to ProLYOtin and 2 patients to placebo, because of nonspecific symptoms like sense of excessive gastric fullness, nausea, abdominal bloating, and alteration of taste).

The majority of patients in both groups (71.4% of A arm vs 73.7% of B arm) showed a PS of ECOG = 0, although 1 patient in placebo group showed PS of ECOG = 2. Therefore, the PS score of patients in the A arm did not show significant modifications compared with the baseline evaluations. Meanwhile, in the B arm there was a slight worsening of clinical conditions. However, this difference was not statistically significant.

After 3 months of treatment, a statistically significant difference between the 2 groups was registered in nutritional conditions evaluated with the MNA score (Figure 2). All patients taking ProLYOtin were found normally nourished according to their MNA score, while 26.3% of patients receiving placebo were found at risk of malnutrition (relative risk [RR] = 0.5, 95% CI = 0.34-0.72, $P = .05$); however, no malnutrition was reported in either group.

The MUST score showed similar distribution between the 2 groups (Figure 3): normal MUST was observed in 71.4% of patients in A arm and 68.4% in B arm; 28.6% of patients in group A versus 21.1% in group B proved to be at risk of malnutrition. The condition of severe malnutrition was registered only among patients in the placebo group (10.5%). However, this difference was not statistically significant.

With regard to body mass index (BMI), none of patients presented a BMI <18.5 kg/m^2; in both groups, cases of overweight or obese subjects are described, but the majority of normal-weight subjects are those taking ProLYOtin (42.9% vs 26.3% in groups A and B, respectively; Figure 4).

There were no significant differences of body weight between the 2 treatment groups.

The BIA measurements performed on 32/33 patients (1 patient has a pacemaker) showed a different body weight distribution in the 2 groups (Figure 5), with the percentage of median lean mass higher in the female patients of the A arm (64.7%) compared with the B arm (58%) and among the males (72.4% of arm A vs 67.2% of arm B). Overall, there was in improvement in the LBM of group A, from 68.5% to 71.2%, Z score (T2 > T1) = −2.48, $P = .01$, in comparison with group B, whose LBM from baseline to 3-month evaluation remained stable (68.7% to 66.3%, Z score = −1.43, $P = .15$).

In the TC-L3 evaluation, the overall percentage of sarcopenic patients was reduced, although sarcopenia remained a prevalent condition in both groups (Figure 6). However, the percentage of non-sarcopenic patients was higher in the ProLYOtin group (46%) compared with the placebo group (24%).

No significant differences were found from laboratory measurement, although the vitamin D values were increased compared with baseline assessments in the arm A (18.0 vs 16.8 ng/mL at T2 vs T1, respectively).

Finally, no difference was reported in terms of quality of life between the 2 groups.

T3 Evaluation

The T3 evaluation, at 6 months from the start of treatment, was done on 28 patients (10 and 18 in arms A and B, respectively): 3 patients of arm A and 1 of arm B were enrolled <6 months ago, and therefore, at the time of the analysis they were considered lost to the follow-up; while 1 patient in the A arm was excluded from the last analysis for poor adherence to the protocol. With regard to nutritional conditions, no further significant changes were found in terms of MNA (Figure 2), MUST (Figure 3), and BMI (Figure 4) compared with T2 evaluation.

At T3 evaluation in both treatment groups, the patients were well fed, with a good PS, and a variable BMI as in previous evaluations. However, patients in the ProLYOtin group reached a further improvement in the representation of LBM compared with the patients in the placebo group, in particular among females (73.2% vs 67.1% median of lean mass percentage between groups A vs B, respectively, $P = .07$; Figure 5). Even the 6-month sarcopenia evaluation was not particularly different between the 2 arms, although a higher percentage distribution of sarcopenia was maintained in the placebo group (63%) compared with the active group (40%; Figure 6).

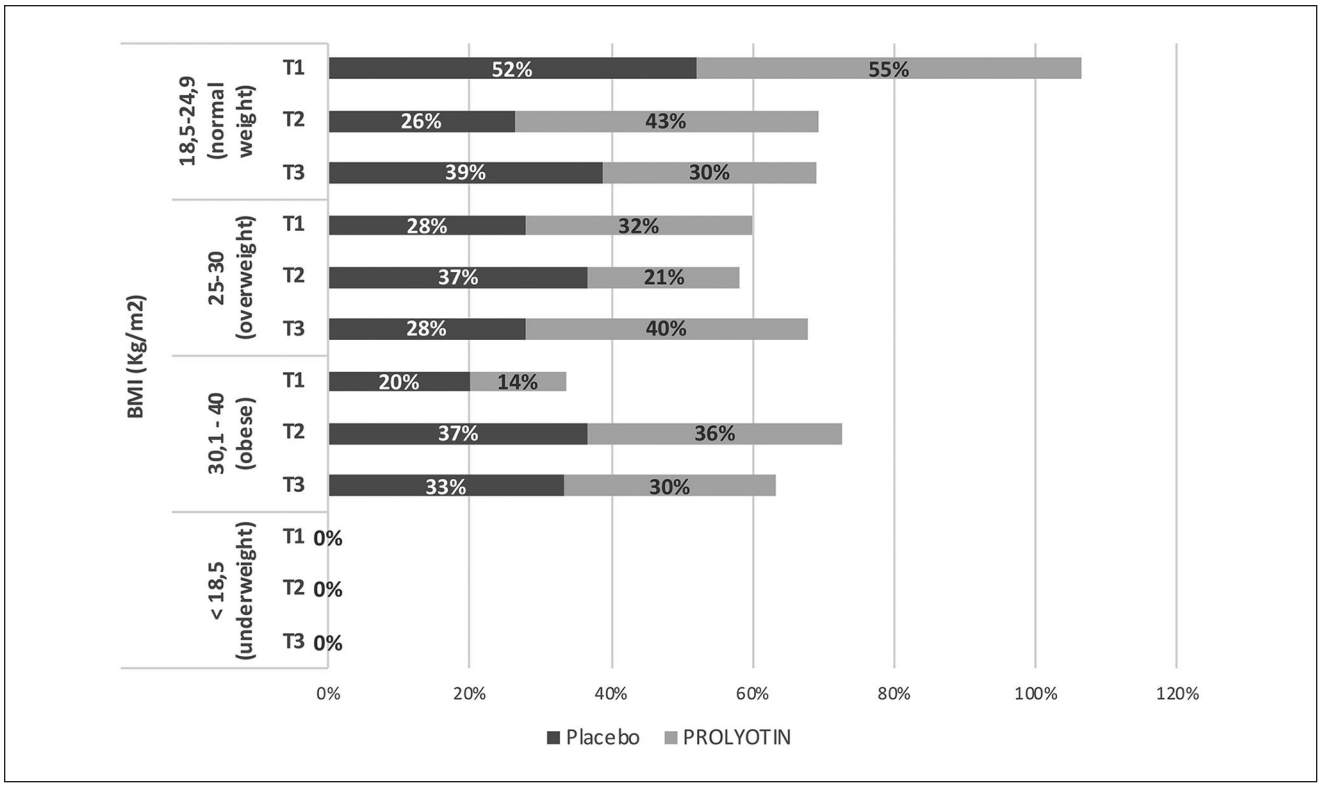

Figure 4. Body mass index differences between 2 treatment arms at baseline (T1) and after 3 (T2) and 6 (T3) months.

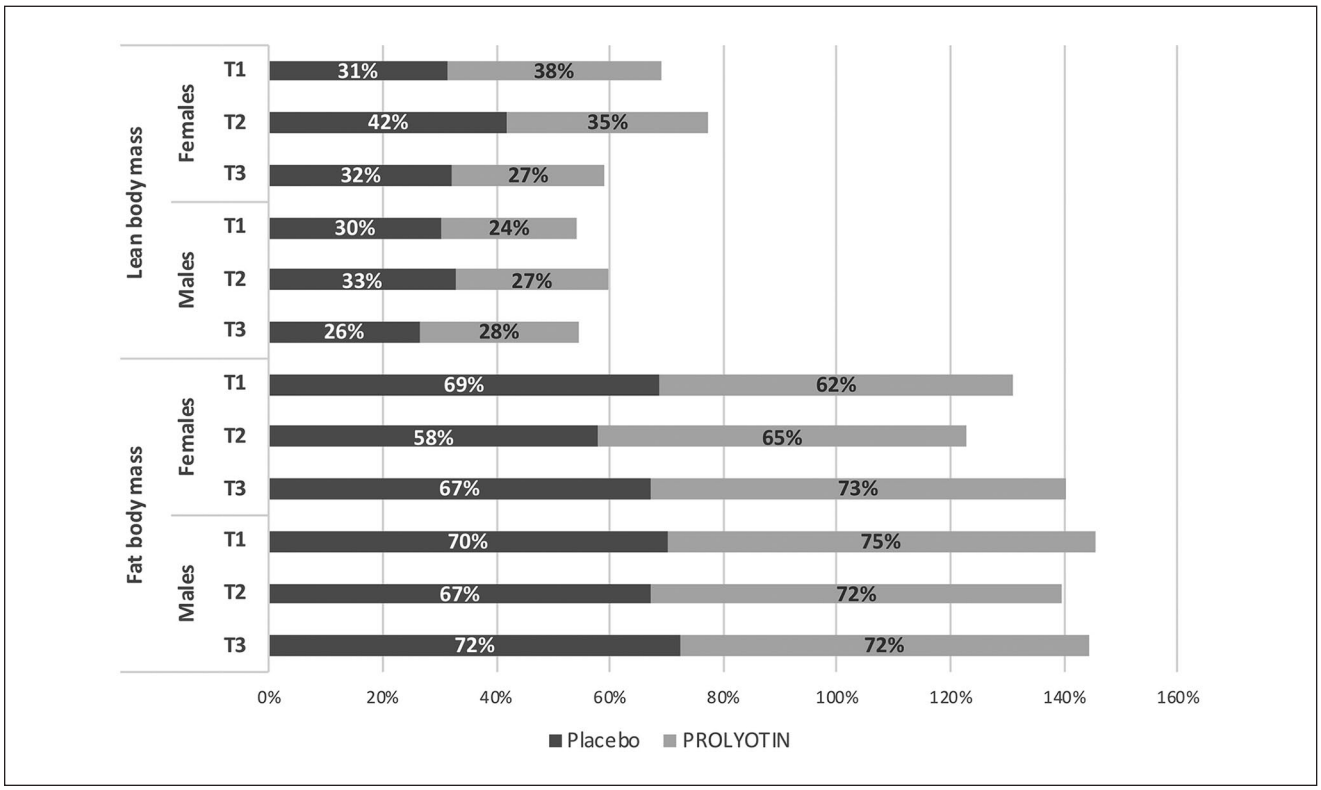

Figure 5. Bioelectrical impedance analysis differences between 2 treatment arms at baseline (T1) and after 3 (T2) and 6 (T3) months.

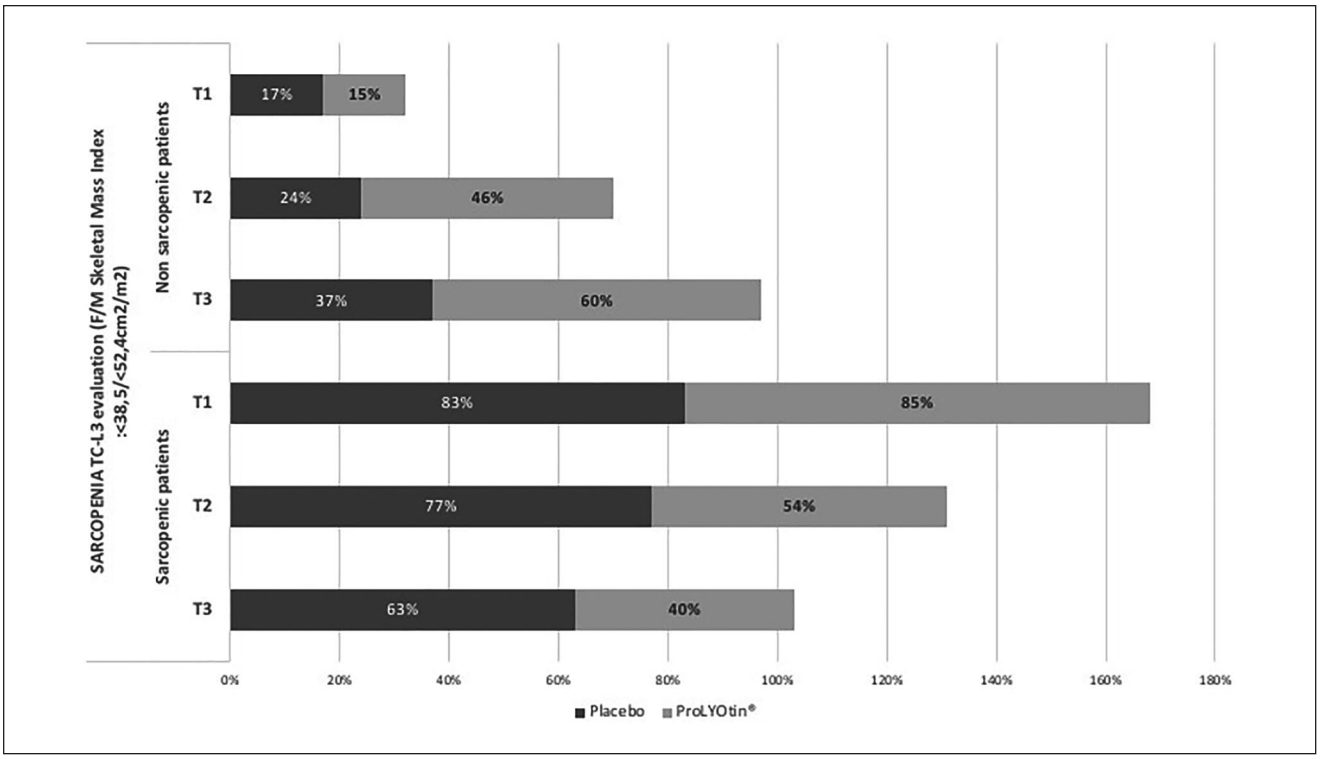

Figure 6. Sarcopenia evaluation by TC-L3 at baseline (T1) and after 3 (T2) and 6 (T3) months.

Vitamin D level always remained lower than normal values, although a slightly positive difference was observed in the active group compared with the control group (18.6 vs 17.8 ng/mL, respectively).

Even at the last evaluation, no differences between the 2 groups were reported in terms of quality of life.

Predictive Markers of Sarcopenia and Correlations to Clinical Outcome

No statistically significant correlation resulted between the analyzed clinicopathological parameters and the condition of both sarcopenia and malnutrition. However, we found data of important clinical impact with regard to the toxicities among the 2 treatment groups, and a correlation between toxicity onset and nutritional condition.

The assessment of toxicities resulting from chemotherapy as evaluated according to CTCAE v 4.0 after 3 months revealed significant variations between the 2 groups. In detail, almost all patients taking ProLYOtin did not report treatment toxicity, neither hematological (86% vs 29% between arms A and B, respectively) nor gastrointestinal (94% in arm A vs 29% in arm B). Instead, high toxicity (grade ≥2 CTCAE v4.0) was only reported in patients taking placebo (23% and 47% hematological and gastrointestinal, respectively). This difference was statistically significant for both hematological (P = .005) and gastrointestinal toxicity (P = .001; Figure 7a and b). No difference in hand-foot toxicity was found.

A statistically significant difference in the onset of toxicity among patients taking ProLYOtin compared with the placebo group was also confirmed at the 6-month evaluation: no adverse effect in 70% of patients in the ProLYOtin group versus 33.3% in the placebo group for hematological toxicity (P = .04) and 80% versus 27.8% for gastrointestinal toxicity (P = .02).

Moreover, a correlation between nutritional status and the onset of toxicity during therapy was found: patients at risk of malnutrition or malnourished after 3 months of chemotherapy have a significantly higher risk of developing any grade toxicities compared with patients in normal nutritional conditions, according to MNA (RR = 1.5, 95% CI = 1.0-2.02, P = .02, for gastrointestinal toxicity) and MUST (RR = 7.5, 95% CI = 1.3-44.1, P = .02, for hematological toxicity). Despite the fact that polychemotherapeutic regimens are usually burdened by higher toxicity when compared with monochemotherapy, no statistically significant differences have been found between the schedules of chemotherapy taken by our patients (P = .40 and P = .54 for correlation between chemotherapy and hematological or gastrointestinal toxicity, respectively).

We used binary logistic regression to identify which factor is more predictive of chemotherapy toxicity between the nutritional parameters considered (MNA, MUST, BMI,

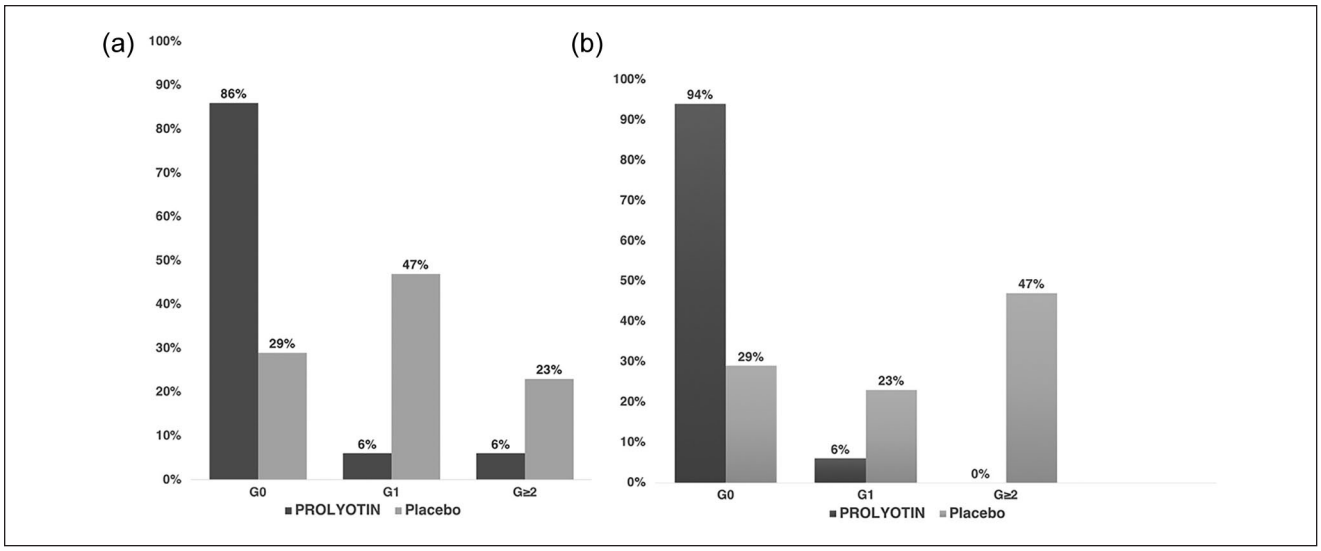

Figure 7. (a) Significant hematological toxicity differences between treatment arms. (b) Significant gastrointestinal toxicity differences between treatment arms.

lean mass after 3 months of therapy) and the use of protein support. From this univariate analysis, we report that a condition of risk or malnutrition according to MUST correlated with the occurrence of hematological toxicity ($P = .02$); a poor nutritional condition according to MNA correlated with a greater risk of gastrointestinal toxicity ($P = .02$); in both toxicities, there was a trend in favor of patients with normal or better LBM compared with baseline control ($P = .08$). However, the parameter that most significantly influenced the good tolerability of chemotherapy was the intake of whey protein supplements. Indeed, patients taking ProLYOtin presented a protection against the risk of developing any grade toxicity compared with placebo (hazard ratio = 0.12, 95% CI = 0.02-0.62, $P = .01$).

Discussion and Conclusion

According to literature data,[6] our study showed a high rate of sarcopenic and malnourished patients starting with the first oncological visit and the beginning of chemotherapy. Although often underestimated, such conditions may negatively affect the clinical outcome of cancer patients.[2-5] Therefore, an early diagnosis of malnutrition or the risk of malnutrition, and a therapeutic intervention for nutritional status appear very important in oncology.[7-10] As shown in our placebo-controlled, randomized clinical trial, nutritional support with highly purified whey protein could be an important therapeutic option to improve nutritional status, LBM, SMI, and particularly to prevent severe toxicity during chemotherapy. However, not all protein is created equal: some forms of proteins are better than others and whey protein is more than just a protein. Whey proteins are a mixture of proteins isolated from whey (the liquid part of milk) and contains many nutrients with beneficial biological effects. The important fact is that whey proteins can give the patients a high-quality protein supplementation and, at the same time, a good digestibility and excellent nutritional values.[12,13] Whey proteins contain a wide range of essential amino acids and they are quickly absorbed, but in general, they have a major flaw: their smell is nauseating and their taste is strange; this could be an important problem because it reduces the compliance of patients with taking the proteins. This is the reason why, in our study, we used the "highly purified whey proteins," which had been submitted to high technological processes that made whey proteins totally odorless and tasteless, with less than 2% of lactose and without casein (so people intolerant to milk can use it). They can be diluted in water or in other beverages at lukewarm temperatures.

Whey proteins have been historically used to improve athletic performance; moreover, they have been recently used in many clinical trials.[12,13] These studies demonstrate that the use of whey protein, in association to a healthy diet and a good physical activity, in a group of oncologic patients affected by sarcopenia (above all patients affected by colon cancer) can improve their PS and their muscular strength. In fact, they promote a redistribution of fat and muscle mass in the human body (which we have shown with the use of bioelectrical impedance).

Moreover, the latest studies reveal that whey proteins can also give patients (not only patients affected by neoplastic disease but also infective and metabolic conditions) an important antioxidant power; in fact their ingestion induces an increase in the levels of glutathione, the human body's most important defense against oxidative stress.[14,15] Glutathione is a tripeptide, it is ubiquitous in human cells, and it has a role in the expulsion of drugs from the body and

in the transport of amino acids through the cellular membranes. It is a cofactor in many chemical enzymatic reactions of human cell. Moreover, it prevents the oxidation of cells by its own oxidation. It is clear that the increase in the level of glutathione when the organism is exposed to toxicities (radiation or chemotherapies) can be an important defense for the body. The biological components of whey proteins have a large range of immune-enhancing properties and, moreover, there are some studies of their ability to act not only as an antioxidant, but also as an antihypertensive, antitumor, hypolipidemic, antiviral, antibacterial agent.[16] Whey proteins have an iron-binding capacity that may contribute to their anticancer potential because of the mutagenic action of iron that can cause oxidative damage to tissues.[17] Regarding immune function, immunoglobulins constitute approximately 10% to15% of whey proteins.[18] Some studies observed an increase in the percentage of immunoglobulin (Ig) G after whey protein supplementation; IgG contained in whey proteins has a potential immune modulatory effect in humans.[19] There are some bioactive components of whey (a-lactalbumin, b-lactoglobulin, and lactoferrin) that may offer protection against infections by enhancing immunity and this could be important to alleviate chemotherapy-related toxicity. One of the cytotoxic effects of cancer chemotherapy is mucositis, characterized by the alteration of absorptive capacity and gut barrier dysfunction; there is evidence that gut protein metabolism is also altered during mucositis (decreasing of protein synthesis and increasing of proteolysis).[20] Whey protein supplementations during chemotherapy should limit intestinal damage during the acute phase of mucositis by improving intestinal protein metabolism. The integration of diet with whey proteins may also increase the levels of secretory IgA, which plays a major role in intestinal barrier function.[21] Moreover, whey proteins can improve vitamin B_{12} and folate absorption and this should increase platelet count and therefore may reduce platelet depletion, which is one of the most common chemotherapy-related hematological side effects.[22] According to the aforementioned background, whey protein supplementation could increase glutathione levels in cancer patients, improving both their nutritional status and immunity during chemotherapy exposure.

Although there are limits to preliminary results, we report relevant data in the field of nutritional oncology where data about the role of nutritional support during chemotherapy are still missing. Our study showed how an early nutritional intervention and nutritional counseling may prevent the onset of sarcopenia and malnutrition, as well as improve patients' tolerance to chemotherapy. We did not measure the concentration of glutathione in our study, but as reported above, increase of glutathione levels induced by whey proteins, could be the key to explaining the lower chemotherapy toxicity in the ProLYOtin group versus the placebo group. Accordingly, recent studies underline the important role of supplementation with antioxidant molecules in order to reduce the neurological[23] and cardiac[24] chemotherapy-related toxicities.

Further studies are awaited to better understand the effects of whey protein against chemotherapy toxicity and by selecting more accurately those patients who may benefit from preventive whey protein support. Our future perspective will be in fact to widen the study population, to assess the effects of exercise and physical activity on chemotherapy tolerability, to consider intestinal microbiota variations related to protein supplementation, and to evaluate the oxide-reductive stress of each patients from both a genotypic and phenotypic standpoint.

Authors' Note

Paolo Marchett is also affiliated to Oncology Unit, IDI-IRCCS of Rome, Italy.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

References

1. Argilés JM, Busquets S, Felipe A, López-Soriano FJ. Muscle wasting in cancer and ageing: cachexia versus sarcopenia. *Adv Gerontol*. 2006;18:39-54.
2. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. *Clin Cancer Res*. 2009;15:2920-2926. doi:10.1158/1078-0432.CCR-08-2242
3. Prado CM, Baracos VE, McCargar LJ, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res*. 2007;13:3264-3268. doi:10.1158/1078-0432.CCR-06-3067
4. Arrieta O, De la Torre-Vallejo M, López-Macías D, et al. Nutritional status, body surface, and low lean body mass/body mass index are related to dose reduction and severe gastrointestinal toxicity induced by afatinib in patients with non-small cell lung cancer. *Oncologist*. 2015;20:967-974. doi:10.1634/theoncologist.2015-0058
5. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients

undergoing resection of colorectal liver metastases. *Br J Surg*. 2012;99:550-557. doi:10.1002/bjs.7823
6. Muscaritoli M, Lucia S, Farcomeni A, et al. Prevalence of malnutrition in patients at first medical oncology visit: the PreMiO study. *Oncotarget*. 2017;8:79884-79896. doi:10.18632/oncotarget.20168
7. Burke DG, Chilibeck PD, Davidson KS, Candow DG, Farthing J, Smith-Palmer T. The effect of whey protein supplementation with and without creatine monohydrate combined with resistance training on lean tissue mass and muscle strength. *Int J Sport Nutr Exerc Metab*. 2001;11:349-364.
8. Frestedt JL, Zenk JL, Kuskowski MA, Ward LS, Bastian ED. A whey-protein supplement increases fat loss and spares lean muscle in obese subjects: a randomized human clinical study. *Nutr Metab (Lond)*. 2008;5:8. doi:10.1186/1743-7075-5-8
9. Patel S. Emerging trends in nutraceutical applications of whey protein and its derivatives. *J Food Sci Technol*. 2015;52:6847-6858. doi:10.1007/s13197-015-1894-0
10. Mazzuca F, Roberto M, Botticelli A, et al. Effect of nutritional support with highly purified, whey proteins for malnutrition and sarcopenia in patients affected with stage II-III colorectal or breast cancer: a blind, placebo controlled, randomized clinical trial. *J Clin Oncol*. 2018;36:(15 suppl):TPS10129.
11. Cotogni P, Monge T, Fadda M, De Francesco A. Bioelectrical impedance analysis for monitoring cancer patients receiving chemotherapy and home parenteral nutrition. *BMC Cancer*. 2018;18:990.
12. Huang WC, Chang YC, Chen YM, et al. Whey protein improves marathon-induced injury and exercise performance in elite track runners. *Int J Med Sci*. 2017;14:648-654.
13. Englud DA, Kirn DR, Koochek A, et al. Nutritional supplementation with physical activity improves muscle composition in mobility-limited older adults, the VIVE2 study: a randomized, double-blind, placebo-controlled trial. *J Gerontol A Biol Sci Med Sci*. 2017;73:95-101.
14. Micke P, Beeh KM, Schlaak JF, Buhl R. Oral supplementation with whey proteins increases plasma glutathione levels of HIV-infected patients. *Eur J Clin Invest*. 2001;31:171-178.
15. Devlin TM. *Biochimica con aspetti clinic-farmaceutici*. Napoli, Italy: EdiSES; 2013.
16. Kadam B, Ambadkar R, Rathod K, Landge S. Health benefits of whey—a brief review. *Int J Livestock Res*. 2018;8:31-49. doi:10.5455/ijlr.20170411022323
17. Weinberg ED. The role of iron in cancer. *Eur J. Cancer Prev*. 1996;5:19-36.
18. Gupta C. Whey proteins: a novel source of bioceuticals. *Middle-East J Sci Res*. 2012;12:365-375.
19. Bumrungpert A, Pavadhgul P, Nunthanawanich P, Sirikanchanarod A, Adulbhan A. Whey protein supplementation improves nutritional status, glutathione levels, and immune function in cancer patients: a randomized, double-blind controlled trial. *J Med Food*. 2018;21:612-616.
20. Leblond J, Le Pessot F, Hubert-Buron A, et al. Chemotherapy-induced mucositis is associated with changes in proteolytic pathways. *Exper Biol Med (Maywood)*. 2008;233:219-228.
21. Boukhettala N, Ibrahim A, Aziz M, et al. A diet containing whey protein, free glutamine, and transforming growth factor-β ameliorates nutritional outcome and intestinal mucositis during repeated chemotherapeutic challenges in rats. *J Nutr*. 2010;140:799-805.
22. Eslami S, Karandish M, Marandi SM, Zand-Moghaddam A. Effects of whey protein supplementation on hematological parameters in healthy young resistance male athletes. *J Appl Sci*. 2010;10:991-995.
23. Li SD, Shi JH, Li XJ. Preventive effect of mecobalamin combined with glutathione on neurotoxicity induced by FOLFOX4 chemotherapy [in Chinese]. *Zhonghua Zhong Lui Za Zhi*. 2016;38:632-635.
24. Omole JG, Ayoka OA, Alabi QK, et al. Protective effect of kolaviron on cyclophosphamide-induced cardiac toxicity in rats. *J Evid Based Integr Med*. 2018;23:2156587218757649. doi:101177/2156587218757649