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Applied nutritional investigation

Relationship between nutritional treatment compliance and nutritional status improvements in patients with gastrointestinal impairment taking an oral peptide–based supplement

José A. López-Medina MD, PHD [a], Cristóbal López-Rodriguez [b], María A. Estornell-Gualde MD [c], Laura Rey-Fernández [b], Silvia Gómez-Senent MD [d], Clara Joaquín-Ortiz MD [e], M. Luisa Fernández-Soto MD [f], Roberto Hurtado-García MD [g], Margarita Martín-Martín PHD [h], Ana Barrera-Martín MSc, MD [i], M. Teresa Vitales-Farrero [j], Antonio J. Martínez-Ortega MD, PHD [k], María Blanca-Martínez-Barbeito MD [l], Begoña Vázquez-Vizcaíno MD [m], Clara Tasende-Fernández MD, PHD [n], M. Ángeles Penacho-Lázaro MD [o], Esther Jordá-Sorolla MD [p], Rebeca Sánchez-Sánchez MD [m], Laura Díaz-Gómez MD [q], Sergio Baos-Fernández [r], Germán Guzmán-Rolo MD [s,*], María D. Ballesteros-Pomar MD, PHD [t]

[a] *Centro Médico San Juan de la Cruz, Málaga, Spain*
[b] *Hospital Costa del Sol, Marbella, Málaga, Spain*
[c] *Hospital de la Ribera, Alzira, Valencia, Spain*
[d] *Hospital La Paz, Madrid, Spain*
[e] *Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain*
[f] *Hospital Campus de la Salud (San Cecilio), Granada, Spain*
[g] *Hospital Vega Baja, San Bartolomé, Alicante, Spain*
[h] *Hospital Ramón y Cajal, Madrid, Spain*
[i] *Hospital U Reina Sofia, Córdoba, Spain*
[j] *Hospital U de Vic, Vic, Barcelona, Spain*
[k] *Hospital Virgen del Rocío, Sevilla, Spain*
[l] *Hospital Rey Juan Carlos, Móstoles, Madrid, Spain*
[m] *Hospital U Cruces, Barakaldo, Bizkaia, Spain*
[n] *Hospital U Príncipe de Asturias, Meco, Madrid, Spain*
[o] *Hospital El Bierzo, Fuentesnuevas (Ponferrada), León, Spain*
[p] *Hospital Clínico U de Valencia, Valencia, Spain*
[q] *Hospital de Jerez, Jerez de la Frontera, Cádiz, Spain*
[r] *Biomedicine, Madrid, Spain*
[s] *Scientific and Medical Affairs, Abbott Nutrition, Madrid, Spain*
[t] *Complejo Asistencial Universitario de León, León, Spain*

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ABSTRACT

Objectives: Compliance in outpatients with gastrointestinal (GI) malabsorption is key in nutritional treatment. The objective of this study was to assess compliance in patients with GI impairment and malnutrition taking a high-calorie, high-protein, peptide-based oral nutritional supplement (ONS-PBD).
Methods: A prospective, multicenter, observational study was conducted in 19 medical sites in Spain where ONS-PBD were prescribed as standard of care. Patients consumed ONS-PBD daily for 12 wk. Compliance was calculated as the percentage consumed of the prescribed amount of ONS per day.
Results: A total of 90 adult patients were included in the study, of whom 64 completed the 12-wk regimine. Mean compliance was 78.8% ± 24.5%. Risk of malnutrition decreased in 56.3% of patients at 12 wk, as measured with the malnutrition universal screening tool. A reduction in abdominal pain was observed and stool

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*Corresponding author. Tel.: +34 681017342.
E-mail address: german.guzman1@abbott.com (G. Guzmán-Rolo).

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Peptide-based formulas
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consistency improved, with a mean of 54.7% and 27.5%, respectively. Improvements in quality of life and a decrease in percentage of patients with severe functional impairment were observed.
Conclusions: These data show that ONS-PBD compliance in malnourished patients with GI symptoms is high, reducing GI symptoms and improving patients' nutritional status.

Introduction

Malnutrition is a condition affecting between 5% and 15% of the adult population worldwide [1], and leads to disorders in body composition and cellular function. This cellular alteration leads to reduced physical and mental function, as well as impacting health outcomes [1]. Another kind of malnutrition is disease-related malnutrition (DRM), which is caused by a concomitant disease with or without inflammation, or arises in a clinical situation in which there is a risk due to metabolic stress, oncology processes and their associated treatments, or even major surgical procedures [1]. DRM is prevalent in hospitals, and is estimated to affect 20% to 50% of patients [2,3]. DRM was significantly associated with a markedly higher risk for complications, increased health care system utilization, increased length of hospital stay, and mortality risk [4,5].

To address DRM management, the European Society for Clinical Nutrition and Metabolism recommends the establishment of a plan that includes nutritional therapy in patients who are identified by means of a validated screening tool as being at nutritional risk [3]. According to these guidelines, a nutritional assessment should be conducted in patients to diagnose the degree of malnutrition, identify underlying diseases or conditions causing malnutrition, and determine patients' nutritional requirements based on their clinical situation [3,6]. If dietary modifications fail to meet patients' nutritional needs, prescriptions for oral nutritional supplements (ONS) are recommended [4,6,7]. ONS provide energy and nutrient-dense solutions to malnourished patients, and their clinical effects [7–10] and cost-effectiveness [11,12] are well-established. To obtain maximum benefits from ONS, patient compliance is important, although reported compliance rates vary according to health care setting (80% in hospital setting vs. only 50% in outpatients) [13,14].

ONSs specially formulated for gastrointestinal (GI) impairment utilize ingredients that may be advantageous in patients with critical illness or significant GI malabsorption [15–17]. Special formulas, including peptide-based protein systems that are more rapidly and efficiently absorbed compared with intact protein, may help reduce the symptoms of GI impairment [18]. Additionally, formulations containing medium-chain triacylglycerols (MCTs) may provide a more readily absorbable lipid source compared with long-chain triacylglycerols for patients with GI disorders, including fat malabsorption [15,19-22]. However, to the best of our knowledge, the scientific literature provides scarce information on outpatient compliance with this type of enteral nutrition. In this context, the main objective of this study was to determine compliance in patients taking a high-calorie, high-protein peptide-based ONS containing 100% hydrolyzed proteins and MCTs over 3 mo, with or at-risk of malnutrition and with impaired GI tolerance, living in nursing homes or as outpatients.

Methods

Study design and subjects

This was a 12-wk, prospective, single-arm (i.e., no comparator), multicenter, observational study in which an ONS was prescribed according to routine clinical practice. The study recruited patients age ≥18 y with a GI impairment from 19 medical sites in Spain. GI impairment was defined as compromised tolerance by at least one of the following main symptoms: diarrhea, nausea, vomiting, satiety, or bloating. The inclusion criteria as follows: patients who live at home or in geriatric centers; considered by the health care provider as malnourished or at risk of suffering malnutrition according to the Malnutrition Universal Screening Tool (MUST) [23] (score ≥2) and GI disorders for which a high-calorie, high-protein, peptide-based oral nutritional supplement diet (ONS-PBD) would be beneficial; and under medical supervision owing to malnutrition with a prescription for two ONS servings per day in the 7 d before study inclusion (Vital Peptido 1.5, Abbott Laboratories S.A). The main exclusion criteria were patients who, from a medical perspective, would not be able to participate owing to their nutritional status or personal condition or if the patient could not safely take the nutritional supplement for GI tolerance and comorbidities (e.g., kidney or liver disease [glomerular filtration rate <60 mL/min or aspartate and alanine aminotransferase at × 3 normal]), and diabetes.

The study included a total of three visits every 6 wk (±7 d). At the time of the baseline visit (V1), all patients received dietary counseling, and were asked to consume an ONS (one bottle twice a day in the morning and afternoon) for 12 wk. The ONS was a high-calorie, high-protein, peptide-based formula containing 100% hydrolyzed proteins and MCTs (Vital Peptido 1.5, Abbott Laboratories S.A.; 200 mL, 13.6 g protein/200 mL bottle; 1.5 kcal/mL).

The study protocol was approved by the ethical clinical research committee of Leon, Spain, and conducted according to the International Conference of Harmonization guidelines. The trial is registered with clinicaltrials.gov (NCT02698540).

Outcome measures

Patients' sociodemographic characteristics (age, sex) and medical diagnoses (primary and secondary diagnoses) were collected at the time of V1. The primary endpoint of the study was compliance with ONS-PBD intake, which was calculated using self-completed patient or caregiver intake diary cards with the percentage of consumed products scored (0%, 25%, 50%, 75%, abd 100%). Subsequently, the mean value of the feedings at weeks 6 and 12 was calculated.

The secondary endpoints included changes in body weight, body mass index (BMI), nutritional status (Subjective Global Assessment [SGA]) [24], health-related quality of life (HRQoL), GI pain and tolerance, and functional performance in activities of daily living (ADL). Body weight and height were measured in a standardized manner using scales and stadiometers, respectively. BMI was calculated as kg/m^2.

Nutritional screening and status were assessed by the physician, using MUST and SGA, respectively. MUST is a five-step screening tool to identify risk of malnutrition, estimating a risk as low, medium, or high [23]. The SGA tool provides a classification of malnutrition (A = well-nourished; B = mildly or moderately malnourished; C = severely malnourished) based on both medical history and clinician observations [24]. HRQoL was measured using the three-level version of the European Quality of Life−5 Dimensions (EQ-5D) [25], both as an index and a visual analogue scale between 0 and 100, with higher scores indicating better HRQoL [25].

GI tolerance was assessed with the Bristol stool scale [26] and Numeric Pain Rating Scale [27]. The Bristol stool scale is a visual chart designed to classify the form of human feces into seven groups [26], making an evaluation of intestinal transit time possible, because the shape of the stool is dependent on the time spent in the colon. Types 1 and 2 generally indicate constipation, types 3 and 4 are ideal stools and easier to pass, and types 5 to 7 are indicative of diarrhea and urgency [26]. The Numeric Pain Rating Scale was used to assess severity of pain in case of bloating, nausea, satiety, diarrhea, and vomiting within 7 d before each study visit (0 = no pain; 10 = worst pain) [27].

The Katz index of independence in ADL [28] was collected at every visit as a supporting variable. Functionality by Katz ADL was used to evaluate overall health status, where a score of 6 indicates full function or independence, 3 to 5 indicates moderate impairment, and ≤2 indicates severe functional impairment [28]. Moreover, dependence of ADL performance was collected at the time of all three visits.

Data collection

An electronic case report form was developed to register data at every visit. At V1, written consent was obtained, eligibility criteria were verified, and sociodemographic characteristics and medical diagnoses were recorded. At V2 and V3, ONS-PBD intake or consumption diary cards were collected by investigators, and the data were included in the electronic case report form. Secondary endpoints and supporting variables were collected at every visit (V1−V3).

Statistical analysis

The statistical analysis was based on all data of included patients who reported ONS-PBD consumption data. The study was observational in nature. Thus, no prespecified hypothesis about the statistical significance and the correlations was assumed, and no sample size to get a given power was calculated.

Descriptive analysis

In the descriptive analysis, absolute and relative frequencies were calculated to describe qualitative variables (sex, medical diagnosis, changes in body weight, nutritional status, and changes in MUST and SGA scores, GI pain, and EQ-5D domains), whereas measures of centrality and dispersion (mean and SD) were calculated to describe the quantitative variables (age, weight, height, BMI, compliance, number of GI impairment symptoms, and health status score). As an objective of compliance with the consumption of the product, specified by protocol as the primary endpoint of the study, 60% was chosen as the cutoff point, because (according to reviewed bibliography) average compliance varies between 37% and 100% depending on the selected environment, characteristics of patients and follow-up time, with the mean value in a hospital setting of 67% as a reference [14].

Compliance was measured at 6 and 12 wk and until discontinuation for all patients who consumed ONS-PBD >60%. Patients were deemed compliant if they achieved a mean intake of >60% of the ONS-PBD according to the score previously determined as clinically meaningful [14]. Changes in body weight were calculated at V2 and V3, and patients were classified according to their weight gain and maintenance (defined as gain or loss of no more that 1% of body weight from baseline) or their weight loss. Changes in MUST and SGA scores were calculated at V2 and V3, and patients were classified according to their nutritional status as improved, maintained optimal, or not improved.

Comparative analysis

A bivariate analysis of baseline variables (age [≤65 y, >65 y], sex, BMI category [≤ 18.4 kg/m^2, 18.5–24.9 kg/m^2, ≥25.0 kg/m^2], weight [mean], nutritional status [MUST: Percentage of patients with low, medium, and high risk of malnutrition; SGA: Percentage of patients classified as A, B, or C], health status score [mean] and presence of GI symptoms [bloating, nausea, satiety, diarrhea, and vomiting]) was performed according to the percentage of compliance at 12 wk (mean) and consumption of >60% of ONS-PBD (yes or no).

Moreover, the primary diagnosis (percentage of patients with or without cancer diagnosis) was analyzed according to compliance (mean of compliance and consumption of >60% of ONS-PBD), patients who completed the study, change in body weight (gained or maintained), and nutritional status (improved or maintained optimal). The comparison of quantitative variables was performed using a one-way analysis of variance. The comparison of qualitative variables was performed using Fisher's exact test. A significance level of 0.05 was used for these analyses.

Results

Patient characteristics

At baseline, a total of 90 adult patients were eligible to participate in the study, with a mean age of 58.2 ± 18.3 y, and 57.8% of patients were men. With regard to the primary diagnosis, 44.3% of patients presented with moderate and severe GI disease, and 43.3% of patients had a cancer diagnosis. The baseline sociodemographic and clinical characteristics are shown in Table 1.

During the study period, there was variation in the number of patients in the different visits: V1 = 90, V2 = 81, and V3 = 64. Reasons for noncompletion of the study are described in Table 2.

Compliance

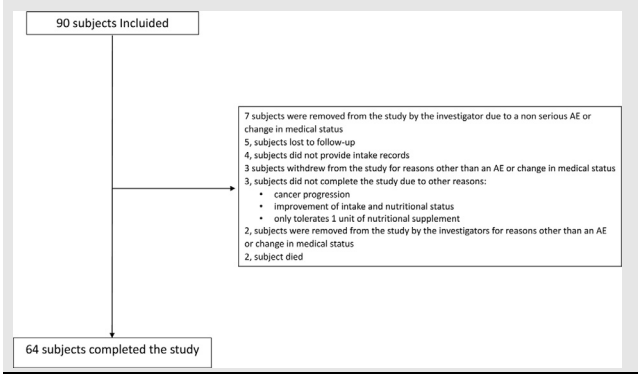
Mean compliance at 6 wk and 12 wk was similar, with 78.8% ± 25.1% and 78.8% ± 24.5%, respectively. The percentage of patients who consumed >60% of the prescribed ONS-PBD was 72.8% and 78.1%, respectively.

Table 1
Baseline sociodemographic and clinical characteristics of study population (n = 90)

Age, mean ± SD	58 ± 18.3
Sex, male, n (%)	52 (57.8)
Weight, kg, mean ± SD	59.0 ± 12.7
Height, cm, mean ± SD	165.2 ± 10.8
Primary diagnosis, n (%)	
Cancer, n (%)	39 (43.3)
Gastrointestinal functional disease*	17 (18.9)
Crohn's disease	11 (12.2)
Pancreatitis	3 (3.3)
Infectious disease	3 (3.3)
Ulcerative colitis	2 (2.2)
Short bowel syndrome	2 (2.2)
Diverticular disease	2 (2.2)
Others	11 (12.2)
Katz index, n (%)	
Complete independence (score 6)	50 (55.6)
Moderate impairment (score 3–5)	14 (15.6)
Severe functional impairment (score ≤2)	26 (28.9)

*Gastrointestinal functional disease integrates different conditions (celiac disease, chronic diarrhea, irritable bowel, idiopathic malabsorption)

Table 2
Flowchart of participants throughout the study



Weight and nutritional status

At 12 wk, 47 of 64 patients (73.4%) gained or maintained their body weight (Table 3). According to the MUST, risk of malnutrition decreased in 56.3% of patients, and the percentage of those with a high risk of malnutrition decreased by 44.5%. At 6 wk and 12 wk, 29.6% (n = 24) and 53.1% (n = 34) of patients showed a low risk of

Table 3
Anthropometric and nutritional variation

N	Visit 1 0	Visit 2 81	Visit 3 64
Weight, kg, mean ± SD	59.02 ± 12.66	59.10 ± 11.80	59.19 ± 11.85
Calculated body mass index (kg/m^2), mean ± SD	21.49 ± 3.65	21.49 ± 3.26	21.57 ± 3.10
Patients who gained/ maintained weight, n (%)		61 (75.3)	47 (73.4)
MUST score improved from baseline, n (%)			
Maintained optimal		10 (12.3)	8 (12.5)
Yes		31 (38.3)	36 (56.3)
SGA improved from baseline, n (%)			
Maintained optimal		8 (9.9)	6 (9.4)
Yes		21 (25.9)	30 (46.9)

MUST, Malnutrition Universal Screening Tool; SGA, Subjective Global Assessment

Fig. 1. Percentage of patients at risk for malnutrition and percentage of malnourished patients per visit according to the Malnutrition Universal Screening Tool and Subjective Global Assessment.

malnutrition. According to the SGA, 46.9% of patients showed improved nutritional status at 12 wk, and the percentage of malnourished patients (severely and mildly or moderately malnourished) decreased by 27.5%. At 6 wk and 12 wk, 23.5% (n = 19) and 37.5% (n = 24) of patients were well-nourished, respectively (Fig. 1).

Gastrointestinal tolerance

Pain level either improved or remained at an optimal level in 55 of 81 patients (68%) at week 6 and 48 of 64 patients (75%) at week 12. At V2 and V3, 46.9% and 54.7% of patients, respectively, reported a reduction in abdominal pain. The results from Bristol scale showed improvements in stool consistency at week 12 in types 3 and 4 (increased from 6.7% to 17.2% of patients, and from 22.2% to 42.2%, respectively) and types 6 and 7 (reduced incidence from 31.1% to 10.9%, respectively). During the overall study, improvement in mean value was 27.5%. As shown in Figure 2, the number of episodes of GI symptoms decreased during the study. Thus, at V3, episodes of diarrhea, bloating, nausea, and vomiting decreased by almost half.

Health-related quality of life and Katz index

At baseline, patients showed a high level of anxiety and depression (55.6%), impairments in usual daily activities (47.8%), and pain and discomfort (54.4%) in these domains of the EQ-5D. At V3, the percentage of patients with mild and severe problems was reduced in all domains, except for self-care. During the study period, improvements in mean health status scores were observed (day 1 = 62.4; at 6 wk = 70; at 12 wk = 71.4). Along with HRQoL improvements, a tendency to decrease the percentage of patients with severe functional impairment (Katz score $\leq$2) was observed. Domains with improvement during the study were continence, toileting, transferring, and feeding at V3, but no improvements were seen in dressing and bathing at V3 (Table 4).

Bivariate analysis

Significant differences in compliance and ONS-PBD intake were found by sex, SGA score, and health status score according to baseline patient characteristics (based on 64 patients), suggesting that these characteristics may affect patient compliance (Table 5). The

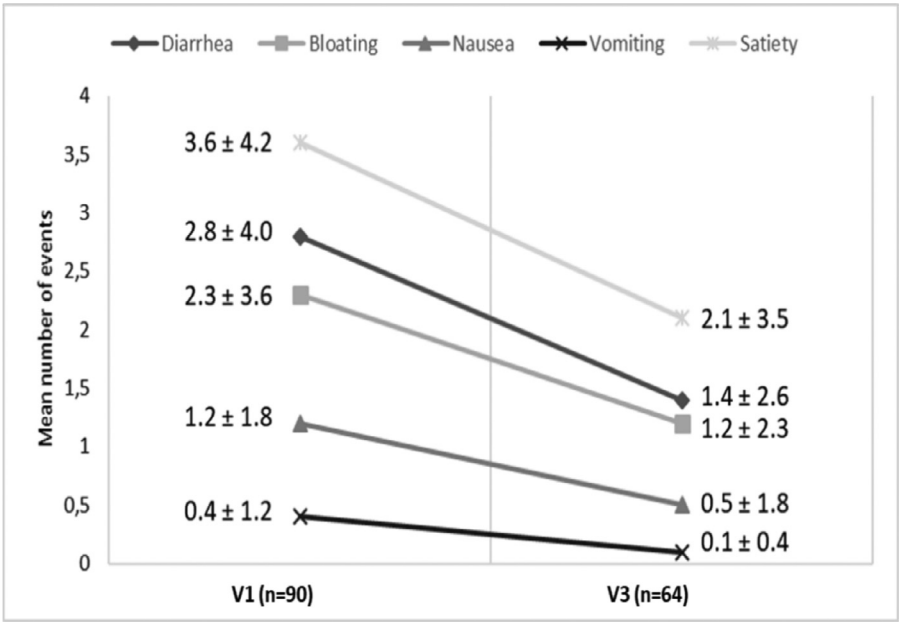


Fig. 2. Changes in mean number of episodes of gastrointestinal symptoms from baseline visit to 12 wk.

Table 4
Health-related quality of life and functionality measurements

	Visit 1 (n = 90)	Visit 2 (n = 81)	Visit 3 (n = 64)
Domains European Quality of Life–5 Dimensions, n (%)*			
Mobility	34 (37.8)	22 (27.2)	19 (29.7)
Self-care	18 (20.0)	13 (16.0)	13 (20.3)
Usual activities	43 (47.8)	32 (39.5)	23 (35.9)
Pain/discomfort	49 (54.4)	41 (50.6)	26 (40.6)
Anxiety/depression	50 (55.6)	35 (43.2)	21 (32.8)
Health status score (European Quality of Life–3 Levels)			
Mean ± SD	62.4 ± 17.4	70.0 ± 16.3	71.4 ± 19.3
Katz index activities of daily living, n (%)†			
Bathing	28 (31.1)	27 (33.3)	22 (34.4)
Dressing	25 (27.8)	24 (29.6)	19 (29.7)
Toileting	29 (32.2)	24 (29.6)	17 (26.6)
Transferring	28 (31.1)	27 (33.3)	18 (28.1)
Continence	32 (35.6)	28 (34.6)	22 (34.4)
Feeding	25 (27.8)	23 (28.4)	17(26.6)
Katz index activities of daily living, total, n (%)			
Severe functional impairment (≤2)	26 (28.9)	22 (27.2)	16 (25.0)
Moderate impairment (3–5)	14 (15.6)	13 (16.0)	15 (23.4)

*Results in patients with mild or severe problems
†Results of patients who are unable to perform the activities

data show that male patients had significantly higher ONS-PBD compliance compared with their female counterparts (85.0% ± 3.9% vs. 70.3% ± 4.5%; $P = 0.0167$; values are least squares means ± standard error of the mean). Initial SGA score also affected ONS compliance. Severely malnourished patients showed a better percentage of compliance (89.3% ± 5.1%) than well-nourished patients (56.1% ± 9.4%; $P = 0.0087$) using a stepdown Bonferroni (Holm) adjustment for multiple comparisons.

According to the SGA scores and as established in the protocol, there was a significant difference in compliance among these three SGA categories ($P = 0.0074$ from Fisher's exact test; Table 6). The percentage of patients with cancer who gained or maintained their body weight or improved their SGA score at V3 was lower than patients without cancer (Table 7).

Discussion

The purpose of this study was to establish the prevalence of ONS-PBD compliance in patients with impaired GI tolerance and malnutrition or risk of malnutrition. These kinds of formulas are well known for their worse palatability versus standard formulas. Palatability among other factors, such as age, volume, nutritional composition, and primary diagnosis, could affect compliance [29,30,31]. In this study, the compliance percentage was 78.8% ± 24.5%, which may indicate good ONS-PBD compliance. These results are similar to the those reported by Hubbard et al. [14] in a systematic review with a mean compliance of 78.2% ± 15%. However, this review evaluated different types of ONSs.

With regard to the primary diagnosis, several studies have shown that patients with cancer have inadequate compliance. De van der Schueren et al. [32] conducted a systematic review and meta-analysis of the use of high-energy ONS in patients with cancer, and showed low compliance. Wan et al. [33] conducted a 12-wk longitudinal study to evaluate oral nutritional supplement compliance in 122 patients after gastric cancer surgery and the

Table 5
Variables with significant differences in high-calorie, high-protein, peptide-based oral nutritional supplement compliance of baseline variables

Variable	Level	Least squares mean ± SEM %	*P*-value
Sex	*Male*	*85.0 ± 3.9*	*0.0167*
	Female	*70.3 ± 4.5*	
Subjective Global Assessment rating	*Severely malnourished*	*89.3 ± 5.1*	*0.0087 (vs. well nourished)*
	Well nourished	*56.1 ± 9.4*	
	Mildly/moderately malnourished	*76.8 ± 3.7*	*Not significant (0.0894 vs. severely malnourished and well nourished)*

Table 6
Variables with significant differences in Subjective Global Assessment rating from patients with >60% compliance

Variable	Level	Least squares mean ± SEM, %	*P*-value
Subjective Global Assessment rating−Baseline	*Severely malnourished*	*95.0*	*0.0074*
	Well nourished	*33.3*	
	Mildly/moderately malnourished	*76.3*	

Age, primary diagnosis of cancer, body mass index category, weight, height, Malnutrition Universal Screening Tool category, and gastrointestinal symptoms did not significantly affect compliance (all $P > 0.05$; data not shown)

Table 7
Variables with significant differences between patients with and without cancer

Variable	*Level*	*% gain/ maintain weight*	*P-value*
Primary diagnosis	*Cancer*	*54.2*	*0.0096*
	No cancer	*85.0*	
Variable	*Level*	*% maintain optimal/improve Subjective Global Assessment rating*	*P value*
Primary diagnosis	*Cancer*	*33.3*	*0.0085*
	No cancer	*70.0*	

factors that affected their compliance. The average overall compliance rate of ONS over 12 wk was 30.59%. Another recent publication by Faccio et al. [34] reported a 53% average intake of the prescribed ONS dose in patients under chemo or chemoradiation treatment.

In the same vein, as shown by Enrique-Fernandez et al. [35], compliance with ONSs among oncologic patients is considered a challenge owing to taste, fatigue, lack of flavor variety, and changes in palate. In a prospective analysis exploring potential barriers to compliance after an esophagectomy and gastrectomy, 35.9% of participants reported consuming all prescribed supplements. Bloating, early satiety, flavor or texture dislike, and diarrhea were the main barriers to oral nutritional supplement compliance [36]. In our study, no significant difference in ONS-PBD compliance was found between patients with and without cancer. Our results may indicate that patients with cancer who received ONS-PBD had higher compliance than what has otherwise been reported in the literature [32−36].

The bivariate analysis showed that patients with a poorer nutritional status by SGA score at baseline presented with better compliance, possibly because they were the most in need of an ONS. Therefore, these data point out the importance of early nutrition screening, assessment, and intervention through specialized nutrition. As shown in a previous study, the risk of malnutrition in patients with GI impairment is high and negatively affects clinical outcomes [37]. Our study results suggest that the use of an ONS-PBD for 12 wk contributes to maintenance or improvements in weight and nutritional status in most patients. Thus, a reduction in the number of patients at a high risk of malnutrition measured by MUST was observed from baseline to 12 wk. The same improvement trend was observed with SGA scores.

GI symptoms trend toward reduction with the use of the ONS-PBD, which is especially important in patients with GI symptoms. A recent study showed that ONS-PBDs were well tolerated and resulted in significant improvements in symptoms of GI distress when started in patients at risk for malabsorption due to GI surgery, pancreatitis, or previous pancreatic surgery versus standard polymeric formulas [38]. In intensive care unit patients, the use of a peptide-based formula has been associated with a statistically significant reduction in total days with GI adverse events (mainly constipation and abdominal distension) compared with a standard formula [15]. These results are aligned with our research where a reduction in GI symptoms, such as nausea, vomiting, bloating, and improvement in stool consistency were observed.

This study has several limitations. First, the European Society for Clinical Nutrition and Metabolism guidelines recommend a nutritional care plan that includes both regular diet counseling and the use of ONSs when the nutritional needs of patients are not being met [39]. In this study, data on the patients' regular diet was not collected. Although a regular diet could influence compliance and GI tolerance, this study was conducted in the context of a real clinical practice, with a goal of seeking to assess additional contributions of ONS-PBD to the diet. Further, the patient population was heterogeneous. Patients with different diseases related to GI impairment and patients with cancer, without specifying the type, were included. This could have influenced compliance and nutritional status between patients. A high dropout rate from the first to the last visit is also a limitation of the study. Finally, the study design (single arm) did not include a nonpeptide-based comparator.

Despite these limitations, this study had the distinction of providing insight into nutritional intervention as studied under routine clinical practice conditions, rather than a clinical trial with full control in an environment where clinicians manage patients with a large variety of diseases. These findings may be of interest to clinicians who may encounter situations as described in daily clinical practice. Additionally, this study shows promising results in a range of different clinical conditions, but further research is necessary to establish how these results might influence long-term clinical practice and patient outcomes.

Conclusions

The data presented in this study suggest a high level of ONS-PBD compliance in malnourished patients with GI symptoms that leads to a reduction of these symptoms, combined with an improvement in patients' nutritional status.

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