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PROBIOTICS IMPROVE BOWEL MOVEMENTS IN HOSPITALIZED ELDERLY PATIENTS -THE PROAGE STUDY

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Abstract: *Objective:* To determine the impact of probiotics on the prevention of problems with bowel movements malnutrition and infection. *Design:* A randomized, double-blind, placebo-controlled trial. *Setting:* Peripheral Geriatric Hospital. Participants: 243 elderly patients age≥65y who were hospitalized in a Geriatric Orthopedic Rehabilitation Department. Intervention: Participants were randomized into treatment or control groups (daily probiotics or placebo for 45 consecutive days, respectively). *Measurements:* The main outcomes were: number of days of constipation or diarrhea and the number of days of laxative use. Secondary measures were nutritional status and blood measurements. *Results:* Of 599 patients admitted to the Geriatric Rehabilitation ward, 345 were eligible and agreed to participate. During a 7-day pre-trial period, 102 patients dropped out (45 and 57 in the probiotic and placebo groups respectively). Out of the 243 patients who entered the study, 28 dropped out during the study (11.5%), leaving 215 patients. Throughout the 45 days of follow-up, the incidence of diarrhea was significantly lower among the study group (HR=0.42, p=0.04) with a more pronounced difference among participants aged ≥ 80y (HR=0.32, p=0.026). Laxative use (as an indicator of constipation severity) was significantly lower in the study group compared with the control group (HR=0.74, p=0.032). Serum albumin, prealbumin and protein increased significantly more in the treatment group compared with the control group among participants age≥80y (P=0.047, p=0.07, p=0.03 respectively) but not in the younger age group. *Conclusion:* We showed that probiotic supplements may have a positive effect on bowel movements among orthopedic rehabilitation elderly patients.

Key words: Probiotics, elderly, constipation, diarrhea, nutrition.

Introduction

Hospitalized elderly patients are prone to develop bowel movement problems in the form of constipation (50% to 80%) and diarrhea [14.2% (1, 2)]. Severe constipation and diarrhea are thought to contribute to nutritional deficiency in this population (3,4) Studies of this population suggested that age-related changes in the equilibrium of the gastrointestinal bacteria may be responsible in part for these changes (5,6). Therefore, modulation of the gut microbiota is of special interest in the elderly population.

Probiotics are mostly lactic acid bacteria presented in high concentrations in some foodstuffs and are generally recognized as safe micro-organisms (7).

Among their health promoting effects, probiotic supplements have been shown to be especially effective in preventing antibiotic induced diarrhea (8-10). The impact of probiotics on constipation is not well established and needs better evidence (11). Nevertheless, recent studies have shown that probiotics can enhance colonic transit time (12). Several studies have also examined the effect of a variety of probiotic supplements on immunity including CRP levels (13-15) and on nutritional status (16, 17). However only a few studies have been conducted among the old and very old elderly and even fewer were performed among hospitalized elderly (18). Hospitalization is a critical juncture for older persons because it can be a period of exacerbation of multiple diseases. Hospitalized elderly patients are at risk for medical complications as well as nutritional deterioration (19, 20) diarrhea (21) and constipation (1).

The aim of the current study was to evaluate the impact of probiotics supplements on bowel movements as well as on nutritional status and CRP levels among hospitalized elderly.

Methods

The study is a randomized, double-blind, placebo-controlled trial.

Study sample

All elderly patients hospitalized in the Department of Geriatric Orthopedic Rehabilitation at the Harzfeld Geriatric Center, in Gedera, Israel, between February 2004 and January 2005 were screened for eligibility for the current study. The orthopedic rehabilitation patients were selected because they represent a relatively homogeneous population, with almost an equal length of stay. Usually about 50% of the patients are after elective knee and hip replacement and 50% after hip fracture.

A week before their enrollment, potential participants were evaluated by a geriatric qualified physician regarding their health status and cognitive ability to participate in the study and

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to sign an informed consent. Exclusion criteria included: (a). known or suspected allergy to any probiotics; (b) neutropenia; (c) inability to sign an informed consent. (d) life expectancy of less than six months.

Ethics approval

The study protocol was reviewed and approved by the Ethics Committee of the Kaplan-Harzfeld Medical Center and registered at NIH.gov NCT00794924.

Randomization and intervention

Eligible patients were randomly assigned in a 1:1 ratio to receive either probiotics or placebo with the use of centralized randomization in blocks of four. The study group received one sachet per day of a commercially available probiotic preparation (VSL#3, VSL Pharmaceuticals Inc, Towson MD). Each sachet contained 450 billion viable lyophilized bacteria consisting of four strains of Lactobacillus (L. plantarum, L. paracasei, L. bulgaricus, L. acidophilus), three strains of Bifidobacterium (B. breve, B. longum, B. infantis), and one strain of Streptococcus (S. thermophilus). The control group received a placebo that looked exactly like that of the study group; both were manufactured by the same company. The investigators as well as the patients were blinded as to the type of supplement used. During the primary analysis of the results, the allocation was still concealed to the investigators. Each packet contained a powder form, miscible in dairy products or soluble in water.

Compliance

Compliance with the treatment (probiotics supplement or placebo) was monitored daily by a nurse, who evaluated the consumption of the probiotics together with all the other drugs administered to the patient. Patients refusing to take the probiotic twice were considered non-compliers.

End point ascertainment

During hospitalization, daily follow-up was performed including bowel movements and laxative use. Primary end points included the number of days the patient suffered from diarrhea or from constipation and the number of days in which laxatives were used. Secondary end points were nutritional assessment, blood tests, Clostridium difficile toxin and Helicobacter pylori prevalence at the beginning and at the end of the study, after 45 days. Patients who were discharged before the end of the study were followed-up at home. Side effects were reported by the medical staff on a special form.

Bowel movements assessment

We used criteria which were derived from the nursing records i.e. bowel movements and laxative use. In our hospital patients receive laxatives at their request. They are being asked every day if they suffer from constipation, not only stool frequency but also straining, and hard stools. Laxative use reflects suffering from constipation. Thus, bowel movements and laxative use together indicate constipation similar to the Rome III criteria for the diagnosis of constipation (22).

Monitoring the number of days the patient was constipated or had diarrhea, was used to evaluate both the existence of constipation or diarrhea. More than two days without a bowel movement was considered as constipation. Diarrhea was defined as two or more watery stools per day (23). Laxative use was measured by the number of laxatives taken. Bowel movements were assessed by the number of days a patient was constipated or had diarrhea and the number of laxatives used. As probiotic use has been associated with abdominal discomfort and flatulence, all patients answered a questionnaire about abdominal discomfort.

Nutritional status assessment

Nutritional status was assessed using two validated methods: 1. Mini Nutritional Assessment- Short Form (MNA-SF) screening tool, which was performed at baseline only (9); 2. Nutritional Risk Assessment (NRA), an assessment tool developed by the Canadian Dietetic Association for hospitalized elderly patients (10).

Health status assessment

Medical history, including medical diagnosis and use of medications were obtained from the patient's medical records. The risk for developing pressure ulcers was calculated using the Norton scale (24).

Laboratory tests

Peripheral blood samples were obtained from all the subjects. Blood tests included complete blood count (CBC) and routine chemistry blood tests, including renal function tests, electrolytes, lipid profile, albumin, prealbumin, thyroid stimulating hormone (TSH), vitamin B12, folic acid and C-reactive protein (CRP). Stool was examined for Clostridium Difficile toxin and for Helicobacter Pylori. All tests were performed at the certified laboratory of Kaplan Medical Center in Rehovot, Israel.

Complete blood count was measured by an automated analyzer (Technicon H*2, Technicon instruments Corp, Trrytown, NY). Glucose, urea, electrolytes, albumin, prealbumin and lipid profile were measured using the Olympus Analyzer System (Olympus, Tokyo, Japan). TSH and vitamin B12 were measured by immunochemilumiscence method, using Siemens Advia Centaur (Tyco, NJ, USA). CRP was measured by Propec-Nephalometry, Rehovot, Israel. Clostridium difficlle toxins A and B were measured in the stool by ELISA (Techlab Analyzer VA, USA). Helicobacter Pylori was measured in the stool by ELISA (Oxoid, Ely LTD, Cambridge, UK).

Statistical analysis

For univariate comparisons of demographic and anthropometric variables, the Student's t-test or χ^2 tests were used. The Mann-Whitney test was used for analysis of non-normal distributed variables (number of medical diagnoses and number of drugs used).

The total numbers of days with diarrhea as well as days of laxative use were recorded. More than one event was counted as positive. The recorded values were compared between the groups using χ^2 tests.

Cox proportional hazard models were used to test the association between treatment and diarrhea or laxative use. A composite score of both diarrhea or laxative use was also performed using Cox regression analysis stratified by Age (<80 or ≥80).

Over two events of diarrhea or laxative use were considered as the primary outcome measures, with follow-up time as the time variable in the model. The proportional hazard assumption was confirmed in all independent variables using log minus log (LML) survival plots and interactions with time (log transformed).

To evaluate the changes in blood measurements, a repeated measure model was used. The dependent variables in this model were the results of the blood tests. Due to the presence of age by time by treatment interaction in the full repeated measure model that appears also in the graphical presentation, the repeated measure model was used separately for each age category. This statistical model enables to test the difference over time by treatment. Changes in subject specific prevalence of Clostridium difficile toxin were compared using Wilcox sign rank test for changes from baseline in the presence of Clostridium difficile.

For all comparisons, $p<0.05$ was used as the significance level. Statistical analyses were performed using SPSS software (version 15) .

Results

Of 599 patients who were admitted to the Geriatric Rehabilitation ward during the study period and screened by a geriatric physician for their eligibility, 254 were excluded from the study. Patients included in the study were all admitted to the ward for rehabilitation after orthopedic surgery or bone fracture and were generally in good medical condition and able to withstand the physical efforts of rehabilitation. Participants were excluded mostly due to an inability to sign an informed consent (219 patients) or because they were in poor health (35 patients). The other 345 eligible participants went into a 7 day pre-trial period, 174 in the study group and 171 in the control group (Figure 1). The purpose of the 7 day pre-trial was to assess the ability of the patients to comply with the treatment protocol. During the 7 day pre-trial period, 45 in the study group and 57 in the control group, decided not to participate in the study. These patients were not included in the follow-up. 129 patients in the study group and 114 in the control group participated in the trial (altogether 243 patients). 28 patients dropped out during the study period (Figure 1).

Baseline data

The baseline characteristics of the patients are presented in Table 1. No differences were detected between the groups in demographic, medical or nutritional status, nor in their anthropometric characteristics or blood tests, except for a slight difference in the MNA score. The use of medications, including antibiotics was recorded and analyzed with no statistically significant differences between the groups.

Table 1
A comparison in baseline demographic, nutritional and medical characteristics between the study and the control group

Characteristics	Study group N = 114	Control group N = 101	P Value
Demographic			
Female, N (%)	83 (72.8%)	73 (72.3%)	0.93
Age (year) mean+SD	76.4+8.5	75.7+8.6	0.54
Age (year)			
65-80, N (%)	73 (64.0%)	72 (71.3%)	0.26
>80, N (%)	41 (35.9%)	29 (28.7%)	
Anthropometric			
Weight, kg, mean+SD	70.8±12.6	68.1±14.1	0.96
BMI, mean+SD	26.8±4.9	26.2±5.0	0.88
Common Diagnoses			
Heart disease, N (%)	39 (34.2%)	34 (33.7%)	0.93
Orthopedic problems N (%)	103 (90.3%)	84 (83.2%)	0.12
Diabetes, N (%)	29 (25.4%)	24 (23.8%)	0.87
Hypercholesterolemia, N (%)	22 (19.3%)	19 (18.8%)	0.93
B12 def. N (%)	5 (4.4%)	7 (6.9%)	0.42
No. of diseases, median (range)	2 (1-6)	3 (1-6)	0.49
No. of medications, mean (range)	8 (3-14)	8 (1-15)	0.43
Medication			
Antibiotic use	60(53.0%)	48(47.5)%	0.91
opiates	14 (12.3%)	20 (19.8)	0.139
Blood test			
Albumin gr/dl, mean+SD	3.4 ± 0.5	3.5 ± 0.5	0.17
Prealbumin mg/dl, mean+SD	16.2 ± 6.8	17.6 ± 6.3	0.15
Protein gr/dl, mean+SD	6.3 ± 0.77	6.4 ± 0.65	0.15
CRP Mg/L, mean+SD	72.0±55.2	69.8±64.9	0.83
Bowel movement assessment			
constipation	18(15.8%)	12 (11.8%)	0.22
diarrhea	3 (2.6%)	1 (0.99%)	0.10
Questionnaires			
Nutritional Risk Assessment (NRA) score, median (range)	7 (3-15) (N=86)	8 (2-17) (N=76)	0.77
Mini nutritional assessment (MNA) score, mean, range	18 (10-19) (N=106)	17 (4-18) (N=98)	0.04
Norton (score for developing pressure ulcer), mean+SD	16.5 ± 2.3	15.8 ± 2.9	0.11

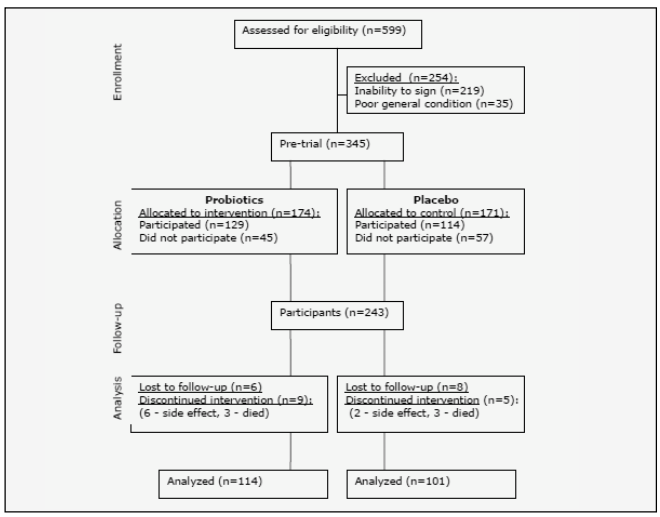
Primary endpoints

No difference was detected in the prevalence of diarrhea (2.1% vs. 0.9%) or constipation (17.8% vs. 18.3%) at baseline between the study and control groups, respectively.

The prevalence of Clostridium difficile toxin in the stool decreased from 6.1% to 4.1% in the study group and increased from 2.2% to 6.6% in the control group ($P<0.04$).

In both age groups, probiotics treatment was associated with a trend of reduced antibiotics use (HR=0.85, P=0.06 for age<80 and HR=0.89, P=0.09 for age>80).

Figure 1
Participant Enrollment, Randomization and Followup



A significant difference in bowel movements between the two groups was found (p<0.001). The percentage of days with diarrhea out of the total days of follow-up is presented in figure 2a. As shown, the percentage was significantly lower in the treatment group compared with the control and was more prominent in patients aged ≥80. The Cox regression model analyses, enhances this finding (Table 2).

Figure 2a
Histogram of percent days with diarrhea more than 1 day out of the follow-up days by group

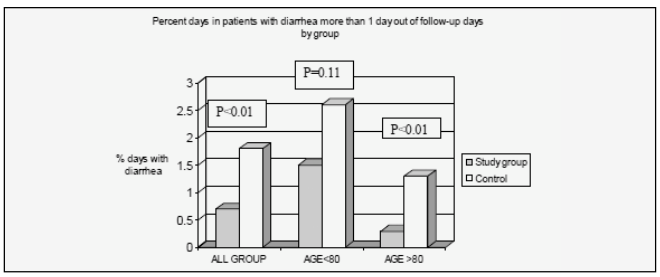


Figure 2b
Histogram of percent laxative use more than 1 day out of the follow-up days by group

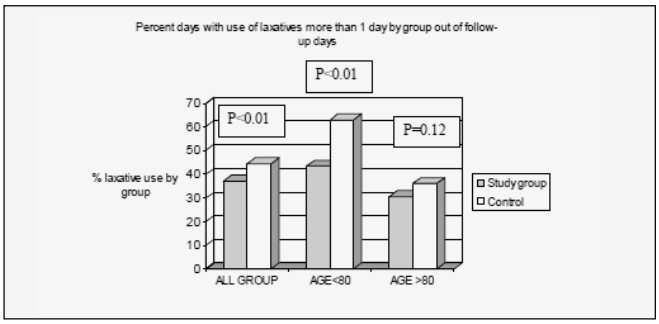


Figure 2b presents the percentage of days with more than one laxative use. As shown, the use of laxatives was lower in the treatment group with a stronger effect in patients under age 80. The Cox regression model analysis of the days of laxative use is shown in Table 2. The composite score of improvement in either diarrhea or laxative use shows better results than each parameter separately (Table 2).

There was no significant reduction in constipation in the study group compared to the control group. The prevalence of constipation was aggravated in both groups during the hospitalization stay, which was statistically significant for the total group (p<0.001). Patients with constipation had a longer length of stay in hospital (p = 0.04).

There was no difference between the study and the control groups in the prevalence of abdominal pain during the study period or length of hospitalization (p=0.53, p=0.78 respectively).

Secondary analyses

Serum albumin, prealbumin and total protein increased over time in both groups but more in the probiotics group (Figure 3a-3c) . The differences between the treatment and the control group were more profound among those over age 80. The levels of CRP decreased during hospitalization in all patients, including both the study and the control groups but more in the study group. The treatment appeared to have a stronger effect

Table 2
Hazard ratios (95% confidence interval (CI)) for the use of laxatives (over 1 laxative=1), days with diarrhea (over 1 event =1) and a composite score of both using Cox regression stratified by Age (<80 ≥80)

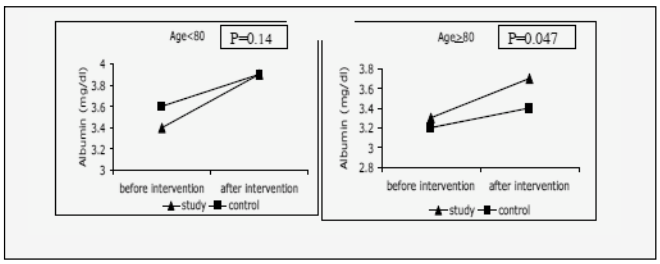
	ALL GROUP			AGE<80			AGE >80		
Measurement	**HR**	**95% CI**	**P - Value**	**HR**	**95% CI**	**P - Value**	**HR**	**95% CI**	**P - Value**
				Dependent variable: over 1 laxative use					
Group (treatment vs. control)	0.96	0.84-1.10	0.57	0.70	0.35-0.96	0.04	0.80	0.42-1.21	0.09
Treatment*age	0.66	0.58-0.77	<0.01						
				Dependent variable: over 1 day with diarrhea					
Group (treatment vs. control)	0.72	0.37-1.40	0.33	0.53	0.32-1.33	0.19	0.32	0.08-0.65	0.026
Treatment*age	0.25	0.10-0.81	0.009						
				Dependent variable: over 1 day with diarrhea or over 1 laxative (a composite score)					
Group (treatment vs. control)	0.97	0.85-1.11	0.64	0.46	0.39-0.54	<0.01	0.86	0.85-1.10	0.08
Treatment*age	0.64	0.56-0.74	<0.01						

on CRP levels among older patients (age>80),compared with the placebo group (p =0.054). Diabetic patients were analyzed separately. In both groups, CRP levels decreased during hospitalization. The decrease was more prominent in the diabetics on probiotics than in the diabetic control group (p=0.06). No statistically significant difference was found between the treatment and the control groups in other tests, including helicobacter pylori, vitamin B12 levels, renal function tests and lipid profile.

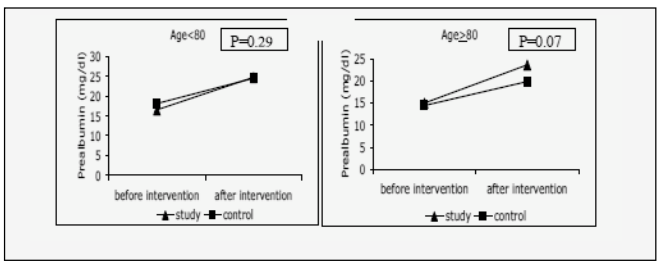
Figures 3a-3c

A comparison in the changes in serum albumin, prealbumin, and total protein over 45 days

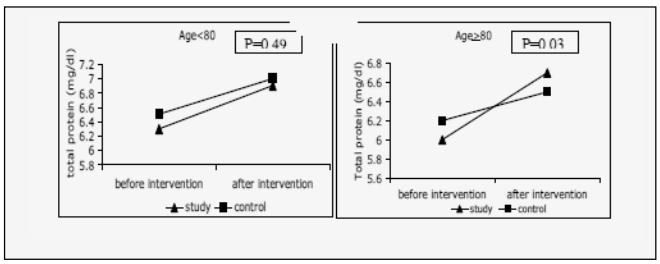
3a- A comparison in the changes in serum albumin



3b- A comparison in the changes in serum prealbumin



3c- A comparison in the changes in serum total protein



Follow up

During the follow-up period, 14 patients (4%) were lost to follow-up and 8 (2.3%) discontinued due to side effects, 4 patients in the study group had nausea or abdominal pain and another 4 patients, 2 in the probiotic group and 2 in the control group, had an allergic reaction or diarrhea.

Side-effects

The side effects were uncommon and mild with difficulty in assessing whether there was any association with the probiotics use. Nevertheless, the patients with suspected side effects were advised to discontinue the intervention (Figure 1).

Discussion

In the PROAGE study, probiotic supplements have shown beneficial effects in several areas, including decreased laxative and antibiotics use as well as CRP levels, and increase in albumin and prealbumin levels. Among participants over the age of 80 years, probiotics also decreased diarrhea.

We did not find a direct effect of probiotics on constipation, as has been found in previous studies in adults and in children (14). However, in our study population, prior use of laxatives was common. Participants who entered the rehabilitation facility were frequently using laxatives, with no structured attempt towards laxative withdrawal. Since patients were not forced to stop laxative use during the study, a decrease in laxative use likely indicates decreased constipation. The more prominent response among the younger age group might reflect a severe and prolonged constipation in the elderly, necessitating higher probiotic doses, or greater dependence on laxative use. Laxatives have a high risk of side effects (25, 26). These side effects include mainly abdominal pain, bloating and electrolyte disturbances. An alternative treatment with probiotics, conversely, has very few known side effects and if effective in treating constipation, may replace laxative use for some patients. These results express the benefit of probiotics on the prevention of both diarrhea and constipation.

Probiotics were also found to have had a significant effect on the reduction of diarrhea among patients over the age of 80 years. While diarrhea is less common than constipation in the elderly, it is common after antibiotic use especially as Clostridium difficile - associated diarrhea (CDAD), which increases with age. Since acute diarrhea increases morbidity and mortality in the elderly, prevention is therefore beneficial. A significant reduction of Clostridium difficile prevalence was found in the probiotic group, as has been shown in previous studies (7, 27).

No difference was found between the study and the control groups in the prevalence of H Pylori at the end of the study.

Malnutrition is associated with a higher incidence of acute and chronic diseases. Improvement in nutritional status could improve health status and quality of life in the elderly (28). We did not detect an improvement in the NRA associated with the treatment. However laboratory nutritional status as measured by serum albumin, prealbumin and total protein were all increased significantly after probiotic intake (Fig 3). This improvement was much more prominent in participants over the age of 80 years in the study group, probably due to their poorer health condition.

New antibiotic use was lower in patients who took probiotics. Both groups of participants, the study and the control groups, were hospitalized in the same department and treated by the same medical staff. Therefore, we assume that the reduction in new antibiotic use in the study group, may be due to an enhanced immune response, as has been shown in other studies (3, 29, 30). This theory is supported by the steeper

reduction in CRP levels at the end of the study in the probiotic group in comparison with the control group. This was significantly more prominent in patients over the age of 80 years P=0.054 then under the age of 80 P=0.95. Aging is associated with deregulated immune and inflammatory responses, characterized by declining T cell function (31).

A simple available way to measure chronic inflammation is by assessing the CRP level (32). Some studies in the elderly have found that probiotics could enhance immune response (13, 30, 32). Moreover, in a study of healthy elderly volunteers, it has been shown that those with the poorest immunological response had the best enhancement of immunity after probiotics intake.

The reduction in laxative use which reflects an improvement in constipation, as well as the decrease in the incidence of diarrhea, decrease in CRP levels and improvement in albumin levels, altogether demonstrate that many patients can gain from probiotic use. Since the study participants (orthopedic elderly patients) are generally in better health than chronic institutionalized elderly patients, a future study of patients with more comorbidity, especially internal medicine patients, may yield even more dramatic results.

Limitations

One limitation of this study is that constipation was diagnosed by the nurse's report of the frequency of bowel movements as well as of laxative use. This is only part of the Rome III criteria, which also includes strain, hard stools and incomplete evacuation. Our criteria were chosen due to their objective nature and medical staff dependence (33).

Another limitation is that all participants in the study were orthopedic rehabilitation patients. These are usually a healthier medical and nutritional status group than the average geriatric hospitalized patients. We assume that patients in worse condition would gain even more from probiotic treatment however this assumption needs to be evaluated in future studies.

Conclusion

The PROAGE study found a positive effect of probiotic supplement use on orthopedic elderly hospitalized patients, evidenced in bowel movements, in nutritional blood indicators and in CRP levels.

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