THE EFFECT OF PULMONARY REHABILITATION ASSOCIATED WITH NUTRITIONAL SUPPLEMENTATION ON PHYSICAL ACTIVITY IN PATIENTS WITH BRONCHIECTASIS: RANDOMIZED TRIAL

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Abstract

Introduction: physical activity is closely related to mortality and respiratory status for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF).Pulmonary rehabilitation (PR) programs have been shown to improve the level of physical activity in COPD patients.There are no specific studies on patients with bronchiectasis.

Objectives: study the effect of PR on physical activity over 12 weeks, in comparison with PR plus a hyperproteic supplement enriched in beta-hydroxy-beta-methylbutyrate (HMB) in patients with non-CF bronchiectasis.

Material and methods: prospective, randomized study in which a structured PR program is applied in bronchiectasis patients for three months.Additionally, one of the groups received a hyperproteic supplement with HMB.The degree of physical activity was evaluated at baseline and after three and six months using the wGT3X (ActiGraph) accelerometer and the IPAQ (International Physical Activity Questionnaire).Data was analyzed using a repeated measures ANOVA (intention to treat).

Results: 30 patients with non-CF bronchiectasis (15 in each group)were included, without differences in clinical variables between groups.After intervention, a significant percentage of patients in the supplement group increased their average physical activity according to the IPAQ after 3 and 6 months. Significant differences depending on type of intervention were not observed.A slight increase in average moderate intensity physical activity measured by accelerometer was observed at 3 and 6 months, but it did not reach statistical significance.

Conclusions: PR, along with nutritional supplements, in non-CF bronchiectasis patients increased the level of physical activity measured by the IPAQ (at 3 and 6 months).However, it did not reach statistical significance according to accelerometer measurements.Further studies are needed to evaluate the validity of the different measurement instruments.

Key words: bronchiectasis, pulmonary rehabilitation, physical activity, accelerometer, IPAQ.

EFECTO DE LA REHABILITACIÓN RESPIRATORIA ASOCIADA A SUPLEMENTACIÓN NUTRICIONAL SOBRE LA ACTIVIDAD FÍSICA EN PACIENTES CON BRONQUIECTASIAS: ESTUDIO ALEATORIZADO

Resumen

Introducción: la actividad física está fuertemente relacionada con la mortalidad y la situación respiratoria en patologías respiratorias como la enfermedad pulmonar obstructiva crónica (EPOC) y la fibrosis quística (FQ). Los programas de rehabilitación respiratoria (RR) han demostrado mejorar el grado de actividad física en pacientes con EPOC. No existen trabajos específicos en pacientes con bronquiectasias (BQ).

Objetivos: comparar el efecto sobre la actividad física de la RR durante 12 semanas, comparado con RR más un suplemento hiperproteico enriquecido en beta-hidroxi-beta-metilbutirato (HMB) en pacientes con BQ no debidas a FQ.

Material y métodos: estudio prospectivo aleatorizado, en el que se aplica un programa de RR estructurado a pacientes con BQ durante tres meses. A uno de los grupos, además, se le asoció un suplemento hiperproteico con HMB. Se valoró el grado de actividad física en situación basal, a los tres y seis meses mediante acelerómetro wGT3X (ActiGraph) y cuestionario IPAQ. Se analizaron los datos mediante una Anova de medidas repetidas (intención de tratar).

Resultados: se incluyeron 30 pacientes con BQ no debidas a FQ (15 en cada rama) sin diferencias en variables clínicas entre los grupos. Después de la intervención, un porcentaje significativo de pacientes incrementaron la actividad física medida mediante el cuestionario IPAQ en el grupo suplementado a los 3 y 6 meses. No se observaron diferencias significativas en función del tipo de intervención. En ambos grupos se observó un discreto aumento de la actividad física de intensidad moderada medida por acelerómetro, a los 3 y 6 meses, pero no alcanzó significación estadística.

Conclusiones: la RR, unida a suplementación nutricional en pacientes con BQ no debidas a FQ, aumentó el nivel de actividad física medida mediante el cuestionario IPAQ (a los 3 y 6 meses). Sin embargo, no alcanzó la significación estadística mediante acelerómetro. Son necesarios más estudios que evalúen la validez de los diferentes instrumentos de medida.

Palabras clave: Bronquiectasias, Rehabilitación Respiratoria, Actividad física, Acelerómetro, IPAQ.

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INTRODUCTION

Bronchiectasis is a condition characterized by abnormal and irreversible dilatations of the bronchus with changes in the cilated epithelium. It is a chronic disease, with frequent infectious flare-ups which cause a progressive deterioration in lung function and health-related quality of life (HRQoL)[1, 2].

Pulmonary rehabilitation (PR) has become a basic element in treating chronic respiratory diseases. There is ample scientific evidence showing its utility in improving dyspnea, exercise tolerance and HRQoL in chronic obstructive pulmonary disease (COPD)[3, 4]. There are no specific established PR programs for non-CF bronchiectasis[5] and there is limited evidence of the advantages of physical training. It is assumed that the results may be comparable to those obtained for other respiratory diseases[6–12].

Bronchiectasis patients are at risk of malnutrition, progressive deterioration in lung function and effort capacity[7, 13]. In these patients, the depletion of lean mass can be high, although there is a very slight prevalence of weight loss[14], directly relating to the decrease in parameters for lung function. In any case, it has been proposed as a predictor of morbidity and mortality in patients with chronic respiratory diseases (including bronchiectasis), regardless of the degree of lung impairment[15, 16].

In COPD patients, PR combined with nutritional supplements improves effort capacity and nutritional status[17–19]. Dietary supplements with the amino acid leucine, whose main metabolite is beta-hydroxy-beta-methylbutyrate (HMB), in combination with resistance exercises, have proven to prevent muscular damage resulting from exercise, increase lean mass and functionality and, in combination with exercise, facilitate the loss of fat mass[20, 21]. There are no existing studies in bronchiectasis patients that have evaluated PR along with nutritional supplements.

International recommendations for health promotion and maintenance for the entire population suggest a minimum of 150 minutes of moderate physical activity per week and avoiding a sedentary lifestyle[22]. An adequate amount of physical activity brings health benefits and reduces mortality in both the healthy and sick population[22, 23]. There are no specific studies on physical exercise in bronchiectasis patients. However, it is closely related to mortality and respiratory status in other respiratory diseases like COPD and CF[24–26].

The main objective of this preliminary study is to evaluate the effect on physical activity of PR alone or associated with a hyperproteic supplement enriched in HMB in bronchiectasis patients.

MATERIAL AND METHODS

This is a prospective, randomized study of two parallel groups recruited from the specialized bronchiectasis unit at the Hospital Regional Universitario de Málaga from September 2013 through September 2014.

Subjects of the study: those patients diagnosed with bronchiectasis through high resolution computerized tomography (HRCT) according to Naidich's criteria[24] who met the inclusion criteria, did not meet exclusion criteria, and who signed the informed consent.

- Inclusion criteria: patients with non-CF bronchiectasis, well-nourished (body mass index -BMI- above 18.5 kg/m^2 in patients under 65 years old and above 20 kg/m^2 in patients above 65), aged between 18 and 80.

- Exclusion criteria: oral steroid treatment; respiratory flare-up or oral ingestion of nutritional supplements at the time of randomization; traumatological, neurological or cardiovascular diseases that impeded completion of PR programs; life-threatening hemoptysis in the year prior to the study; previous diagnosis of cancer or major surgery in the three months prior to the study; acute intestinal disease; severe liver or kidney failure; gastrectomy; gastroparesis or other alterations in gastric emptying; enteral feeding; drug or alcohol abuse and patients on an active transplant waiting list.

After signing the informed consent, patients were randomly assigned to the PR or PR plus nutritional supplementation (PR + S) group at a 1:1 ratio using a table of random numbers.

This study was approved by the Málaga Nordeste Research Ethics Committee on April 29, 2013 and was registered as clinical trial NCT02048397 on the web page http://clinicaltrials.gov.

Intervention:

- Rehabilitation program (PR group): both groups attended a 60-minute exercise program at the hospital twice a week for 12 weeks and a weekly at-home session.

- In-hospital sessions were individual and consisted of a 5-minute warm up, a central aerobic exercise phase lasting 25-30 minutes, global resistance exercises targeting a muscle group (shoulders, arms, abdomen, back, hips and legs) including 8-10 repetitions for 10 minutes, 15 minutes of respiratory muscle exercises with ORYGEN-Dual Valve® (training device for respiratory musculature which allows simultaneous work with the expiratory and inspiratory musculature) and a final 5 minutes of cool down and final stretching. The maximum intensity of training sessions was 75 - 80% of the maximum consumption (VO2) reached in the previous cardiopulmonary effort test. Pulse oximetry was used during exercise to confirm that arterial blood oxygen concentration was always above 90%. Exercise intensity was progressively increased each week according to patient symptom qualifications, as is done in training for COPD patients.

- At-home sessions consisted of walking for 30 minutes, 15 minutes of strength training in the upper and lower extremities and 15 minutes of respiratory training with the ORYGEN-Dual Valve®. During the intervention, the non-supplement group was instructed on general recommendations for a Mediterranean-style healthy diet, to maintain a level of physical activity and to continue using the ORYGEN-Dual Valve® twice a week during the monitoring period. Session attendance was recorded.

- Hyperproteic supplement group (PR + S): along with the previously mentioned PR program, patients received a 220 ml Ensure Plus Advance® supplement for 12 weeks, which provided 330 kcal (1.5 kcal/ml), 18 g of protein, 1.5 g of HMB and 1.7 g of prebiotic fiber (FOS). Patients were advised to take the supplement at least 60 minutes before undergoing PR. Given that the patients were well-nourished, they were informed about reducing consumption of natural foods by 200 kcal/day to compensate for the increased calories provided by the supplement, especially focusing on those with a BMI above 25 kg/m^2.

- Adherence to the program was recorded in a journal and controlled by researchers at the PR sessions, in planned visits or through monthly phone inquiries.

Variables: data was collected for:

- Demographics such as age, sex and anthropometric data like baseline weight, height and BMI.

- Criteria for chronic colonization, defined as the presence of 3 positive samples for the same pathogen in 6 months with a minimum of 1 month between samples, regardless of persistence in the baseline for the study[3].

- Structural damage was evaluated at baseline with the Bhalla scoring system for chest HRCT (the lower the final score, the poorer the radiological status)[27]. This defines the extension of bronchiectasis and the presence of cystic bronchiectasis.

- Baseline score for bronchiectasis from the FACED multi-dimensional prognostic scale[28]. This system takes into account patient age, the number of affected lobes, if chronic Pseudomonas aeruginosa colonization is present, the severity of dyspnea and lung function.

- Baseline lung function, defined as forced spirometry values obtained by the JAEGER (OXICOM®) pneumotachograph following the indications of the SEPAR standard[29].

- The level of physical activity was evaluated at baseline and at three and six months using the short version of the IPAQ30 and the wGT3X (ActiGraph®) accelerometer. The IPAQ allows us to evaluate physical activity as a continuous variable by calculating weekly and absolute "Metabolic Equivalent" units (MET), classifying subjects according to whether they show low, moderate or high levels of physical activity. Evolution of physical activity level was evaluated as going from a low

to moderate or high level, or by the increase in the number of METs per week. In previous studies, said questionnaire has shown good validity and reliability in the general population[30]. The wGT3X device along with ActiLife analysis software® version 6.6.1. measures physical activity over 24 hours as well as wake/sleep times31. It was worn by patients for 7 days at three different times: the week before and after intervention, and six months after the start of the study. It was set to record 10-second periods and was not taken off to sleep, only to bathe or shower. The device analyzing a minimum of 5 days out of 7 in the complete study was considered valid.

Data analysis: analysis was done using the R Statistical software. The distribution of quantitative variables was examined using the Kolmogorov-Smirnov test. Quantitative variables were expressed as the average ± standard deviation. Comparison with qualitative variables was done using the chi-square test, using Fischer's exact test when necessary and McNemar's test. The quantitative variable hypothesis contrast was analyzed with the student's t-test and non-parametric tests (Mann-Whitney or Wilcoxon) were used when the variables to be analyzed did not follow a normal distribution. Associations between variables were made by estimating the Pearson or Spearman correlation coefficient. To compare the parameters that varied over time and depending on assigned intervention group, a repeated measures ANOVA was used. All contrast was done following the "intention to treat" principle. Only two subjects were unable to complete evaluation of study variables at six months (see reasons in Results section), for whom data was completed using the last registered observation (last observation carried forward, LOCF). A p probability lower than 0.05 was considered significant for calculations for both groups.

RESULTS

59 patients were evaluated, 29 of which were excluded for not meeting inclusion criteria or because they declined to participate in the trial. The final sample consisted of 30 patients, 15 randomized to the PR group and another 15 to the PR + S group. All of them completed the PR program. Two patients, one from each group, did not receive follow-up at 6 months due to illnesses not related to bronchiectasis (Figure 1).

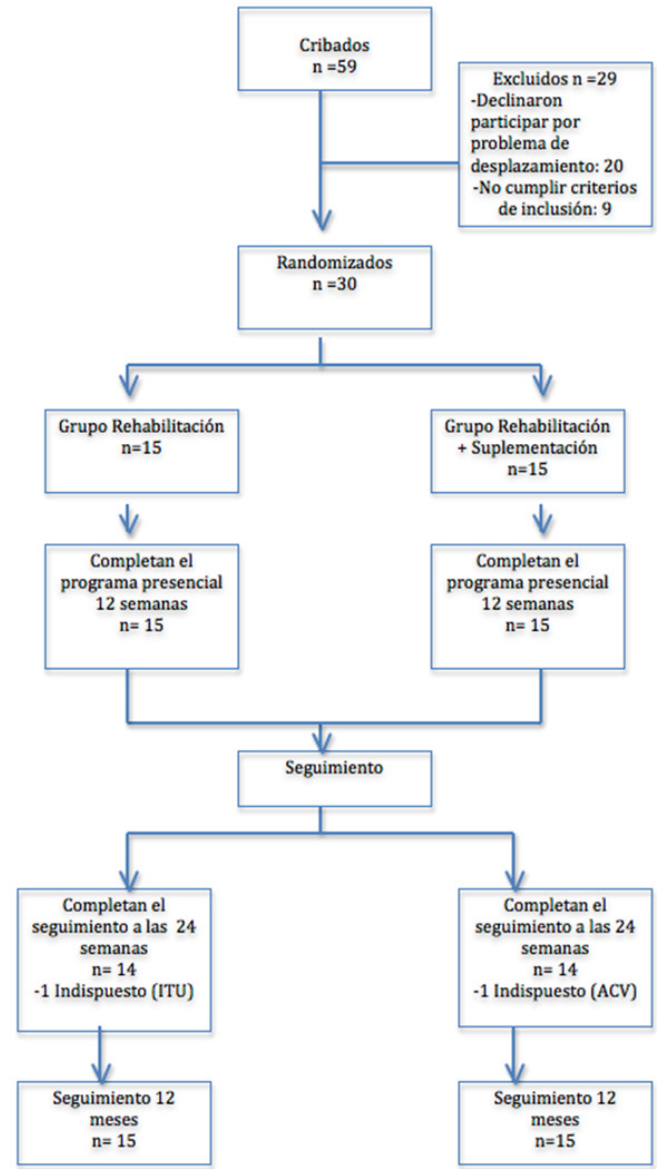

Figure 1. Inclusion diagram.
UTI: urinary tract infection, CVA: cerebrovascular accident.

The main characteristics of the population are shown in Table 1, without significant differences between the two groups.

Baseline physical activity levels and their evolution over time, estimated by the IPAQ and accelerometer, are reflected in Tables 2 and 3, respectively. There were not significant differences in baseline levels of average physical activity for both treatments. The evolution of physical activity data is shown in Tables 2 and 3. Significant differences depending on type of intervention were not observed. Although no significant differences were observed in average physical activity measured by accelerometer between groups (PR vs PR + S) at the three evaluations (baseline, 3 and 6 months), there were differences in the total group of patients and in the supplement group (PR + S) when evaluated with the IPAQ, showing a significant improvement in physical activity levels with respect to the baseline at 3 and 6 months.

No association was found between the level of baseline physical activity or its evolution and the presence of bronchial colonization, severity according to Bhalla or FACED scores or the degree of spirometry obstruction (data not shown).

Table 1. Population characteristics

	Total (n)	RR	RR + S	p
Age (avg ± SD)	56.1 ± 13	53.7 ± 13.1	58.4 ± 12.9	NS
Sex n (%)				
Male	12 (40)	4 (26.7)	8 (53.3)	NS
Female	18 (60)	11 (73.3)	7 (46.7)	NS
Weight (kg)(avg ± SD)	70.5 ± 16.2	71 ± 20.0	70.1 ± 12	NS
Height (cm) (avg ± SD)	162.2 ± 8.2	160.3 ± 8.8	164.1 ± 7.4	NS
BMI (kg/m2) (avg ± SD)	26.6 ± 4.7	27.3 ± 5.8	25.9 ± 3.4	NS
Bhalla (score)(avg ± SD)	17.6 ± 2.1	18.3 ± 1.7	16.9 ± 2.3	NS
FACED (score) (avg ± SD)	1.90 ± 1.02	1.86 ± 1.18	1.93 ± 0.8	NS
FEV_1 (%) (avg ± SD)	66.1 ± 23.6	66.8 ± 28.1	65.5 ± 19	NS
Colonization n (%)				
S. aureus	8 (26.7)	3 (20.0)	5 (33.3)	NS
H. influenzae	17 (56.7)	9 (60.0)	8 (53.3)	NS
P. Aeruginosa	21 (70.0)	10 (66.7)	11 (73.3)	NS
Adherence (avg ± SD)	19.5 ± 5.7	18.8 ± 6.6	20.2 ± 4.8	NS

avg ± SD: average ± standard deviation. p: rehabilitation vs rehabilitation + supplementation comparison. NS: no significant statistical difference. BMI: body mass index.

Table 2. Evolution of average physical activity with the IPAQ

	Baseline	3 months	6 months
Total (n)			
Low activity n (%)	14 (46.7)	3 (10)	5 (16.6)
Moderate + high activity n (%)	16 (53.3)	27 (90) **	25 (83.3) **
PR			
Low activity n (%)	6 (40)	2 (13.3)	2 (13.3)
Moderate + high activity n (%)	9 (60)	13 (86.7)	13 (86.7)
PR + S			
Low activity n (%)	8 (53.3)	1 (6.7)	3 (20)
Moderate + high activity n (%)	7 (46.7)	14 (93.3)*	12 (80)*

*p <0.05; **: p <0.01 with respect to baseline

Table 3. Evolution of average physical activity with accelerometer

	Baseline (avg ±SD)	3 months (avg ±SD)	6 months (avg ±SD)
Kilocalories per day			
Total (n)	308 ± 167,6	371,5 ± 321,8	359,6 ± 169,7
RR	288,1 ± 101,6	346,3 ± 268,8	378 ± 200,4
PR + S	327,9 ± 216,8	396,7 ± 375,4	339,7 ± 134,4
Steps/week			
Total (n)	44681,1 ± 629,7	43228,2 ± 16606,9	42151,1 ± 13769,6
RR	45833,2 ± 20937,6	45166,6 ± 19369,7	42722,3 ± 16442,9
PR + S	43529 ± 14233,2	41289,8 ± 13712,8	41536 ± 10822
METs			
Total (n)	1,15 ± 0,10	1,17 ± 0,15	1,17 ± 0,09
RR	1,14 ± 0,09	1,15± 0,08	1,16 ± 0,1
PR + S	1,16 ± 0,12	1,2 ± 0,2	1,17 ± 0,09
METs/wk sedentary activity			
Total (n)	7282,3 ± 728,4	8105 ± 3660,7	6692,5 ± 2285
RR	7100,9 ± 785	8593,6 ± 4818,2	6843,9 ± 2595,8
PR + S	7463,7 ± 642,1	7616,5 ± 2008,1	6529,6 ± 1989,4

METs/wk daily and light activities			
Total (n)	2373.2 ± 599.7	2318.6 ± 950.3	2152.5 ± 1053.1
RR	2554 ± 582.5	2555.3 ± 954.7	2449.2 ± 1325.6
PR + S	2192.4 ±579.5	2081.9 ± 916	1832.9 ± 534.8
METs/wk moderate activity			
Total (n)	416.4 ± 258.1	454.4 ± 341.9	444.4 ± 380.5
RR	416.2± 274.3	478.2 ± 382.4	463.9 ± 514.3
PR + S	416.6± 250.5	430.6 ± 307.8	423.5 ± 162
METs/wk strenuous activity			
Total (n)	7.8 ± 16.8	6.12 ± 13	5.75 ± 15.1
PR	8.5 ± 17.3	3.17 ± 2.4	7.1 ± 20.5
PR + S	7 ± 16.8	9 ± 18.1	4.2 ± 6.1

avg ± SD: average ± standard deviation. MET: metabolic equivalent. METs/wk: METs per week.

DISCUSSION

This study shows that adding a supplement enriched in HMB to a PR program may improve results for physical activity level, at least when estimated with the IPAQ.

The IPAQ evaluates physical activity through a wide set of domains, which include free time activity, activities of daily life, and work and transport-related activity. The short version of the questionnaire measures 3 levels for specific activities, completed within the four previously mentioned domains[32]: walking, moderate and intense physical activity. The IPAQ has been used in patients with respiratory diseases like COPD where it has been compared with accelerometer measurements[33]. In these patients, a correlation was observed between steps/day and the score obtained in the short version of the IPAQ.

Inactivity has been linked to decreased survival, lower quality of life and increased medical care for COPD patients[34, 35]. After the PR programs, an increase in physical activity has been observed, although little is known about the translation to clinical variables that influence the morbidity and mortality prognosis[16] or if the improvement with these programs is maintained over the long term. In our study, when evaluating with the IPAQ, a significant percentage of patients were seen to move up to a higher level of physical activity after intervention and the effect was maintained 12 weeks after completing the program. On the other hand, when evaluating with accelerometer, although statistical significance was not reached, a slight increase in moderate intensity physical activity was observed in both groups, which was somewhat higher in the PR + S group. The effect was also maintained 12 weeks after completing the intervention.

Training with supervised exercise can cause a small but statistically significant effect on the level of physical activity in COPD patients[36, 37]. However, another study in COPD patients using accelerometer did not find an increase in physical activity in the short or long term[38]. A recent publication by Bradley et al.[39], which measured the physical activity of 63 bronchiectasis patients with an accelerometer, showed that the majority of patients led a sedentary lifestyle, scarcely complying with the recommendations on daily physical activity. In the publication, exercise capacity measured by the incremental shuttle walk test showed a strong correlation between physical activity and the dimensions of the QOL-B questionnaire. There was no correlation between the predicted FEV_1% nor disease severity and physical activity or inactivity, as seen in our work.

It is not entirely clear which are the best instruments to evaluate physical activity[40,41]. Some studies recommend the use of accelerometers over questionnaires to estimate levels of physical activity[42-44]. In the study done by Bradley et al.[39], similar to in our study, they decided to use the ActiGraph® activity monitor, one of the most studied activity monitors, with proven reliability and validated in the respiratory disease population[45]. Van Remoortel et al. have proposed that, in order to provide adequate evaluation, it is necessary to consider the time dedicated to different physical activity intensities, energy use and the number of steps.[41] In addition to these dimensions, the ActiGraph® activity monitor also registers the time spent on sedentary activity.

Previous studies have shown that sedentary activity has an important role in patients' clinical progression[46]. According to some authors, COPD patients tend to underestimate the time they spend on sedentary activity. Pitta et al. noted discrepancies between the data provided by the patients through a questionnaire and objective physical activity measured by an accelerometer and video sensors[34].

A recent study by Curry et al. in United Kingdom women compared physical activity with an accelerometer and the IPAQ[47]. It showed that

the questionnaire may not precisely measure physical activity due to problems with interpretation[47]. This argument would, in some way, justify the differences found in our study in the evolutionary evaluation of physical activity from the IPAQ versus the accelerometer. In any case, the validity of accelerometers in measuring physical activity must also be evaluated in different physiological and pathological situations[33, 48]. For example, in a systematic review of the use of accelerometers in relation to cardiovascular risk, total sedentary activity was shown to correlate with lower sensitivity to insulin, even when adjusting it to length of physical activity[48].

To date, there are no studies evaluating the effect of nutritional supplements associated with PR programs for bronchiectasis. It is possible that the improvement in physical activity seen in our study may be related to the increase in lean mass values or the muscular strength of our patients after administering the nutritional supplement[49].

According to our criteria, the study has several strengths. The first is its design, a prospective, randomized study of intervention with a structured program and extended follow-up to show the durability of the changes. The second is novelty, with a lack of studies that evaluate physical activity in non-CF bronchiectasis patients after PR programs with and without nutritional supplement.

On the other hand, limitations in showing the increased power of the conclusions presented would be the small sample size and the practical impossibility of making the study double blind as it is very difficult to assign a supplement with similar characteristics but without nutrients.

In conclusion, that data provided by this study can help support the fact that PR programs combined with nutritional supplements can slightly improve medium-term physical activity. In any case, further studies are needed to evaluate physical activity and the different instruments to measure said activity in the short and long term.

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https://clinicaltrials.gov/ct2/show/NCT02048397

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