BALNEO RESEARCH JOURNAL
English Edition
eISSN 2069-7619 pISSN 2069-7597 ROMANIAN ASSOCIATION OF BALNEOLOGY

Impact of pulmonary rehabilitation programs in improving health status in COPD patients

TUDORACHE Emanuela[1], MOTOC Nicoleta Stefania[2], PESCARU Camelia[1], CRISAN Alexandru[1], CIUMARNEAN Lorena[2]

Corresponding author: **Nicoleta Stefania MOTOC**, E-mail: motoc_nicoleta@yahoo.com

Balneo Research Journal DOI: http://dx.doi.org/10.12680/balneo.2019.284 Vol.10, No.4, December 2019 p: 472–477

[1]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[2]„Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj Napoca, Romania

Abstract

Pulmonary rehabilitation programme (PRP) have a positive impact on multiple outcomes of COPD, such as decreasing symptoms, increasing exercise tolerance and improving general health status. The aim of this study is to evaluate exercise tolerance impairment and to assess the impact of PRP in improving health status in patients diagnosed with COPD. It was conducted a prospective parallel group study in the Pulmonary Rehabilitation Department of the Clinical Hospital "V. Babes", Timisoara, from 2007 to 2010. The subjects included in the study were patients diagnosed with COPD stages I-IV GOLD, initially evaluated and started a PRP, then re-evaluated after 3 weeks and 6 months. The study group included 168 patients, 158 men, mean age 61.73 years. The initial evaluation revealed higher values of dyspnea scores using mMRC scale in advanced COPD stages (3.69±0.77 in patients with COPD stage IV, vs 0.88±0.5 in patients with COPD stage, $p<0.05$), decreased Forced expiratory volume in 1 second (FEV1), PImax and PEmax, and 6 minutes walking distance values corresponding with COPD severity stages. Re-evaluation at 3 weeks and 6 months after the pulmonary rehabilitation programme was applied showed significant improved dyspnea scores and exercise tolerance. The results of this study reconfirmed the positive and persistent impact of pulmonary rehabilitation programme on muscle dysfunction, dyspnea, and quality of life in COPD patients, regardless of severity.

Key words: *COPD, pulmonary rehabilitation programme, 6 minutes walking test, pedometry,*

Introduction

In Romania, in the last 10 years, the tuberculosis endemia has decreased progressively (1,2), but the neoplastic and bronchial obstructive pathology mainly determined by risk behaviours such as smoking, and prolonged exposure to occupational or environmental respiratory pollution has gradually increased (3-6). Chronic obstructive pulmonary disease (COPD) remained one of the most common causes of hospitalization in the pulmonology departments, despite the general concern in health education, especially related to the strategies smoking cessation (7-12). COPD is an important cause of decreased quality of life due to chronic disabling symptoms and exercise intolerance, which worsens over time. Airflow limitation and muscle deconditioning lead to the gradual decrease of physical activity from the early stages of the disease (13). Physical activity level is a predictor of the risk of exacerbation and increased mortality in COPD (14,15). Randomised and observational studies, supported by common clinical practice have confirmed the positive impact of pulmonary rehabilitation programme (PRP) on multiple outcomes of COPD (16-18), and also in other chronic respiratory diseases, such as pulmonary fibrosis, sleep apnea syndrome, asthma (19-23). Often, patients with these disabling diseases are young (24-26) and require different types of interventions, including smoking cessation strategies, pharmacological therapy and PRP (27-30). The training of the peripheral musculature was established as an essential component of the PRP that aimed to prevent sedentary lifestyle, to improve the symptoms (especially the dyspnea), and to increase exercise tolerance (17). This study aims to identify the presence of skeletal muscular dysfunction and exercise tolerance impairment in patients diagnosed with COPD, and to assess the benefits of PRP when it is associated with specific pharmacological therapy.

Materials and methods

A prospective parallel group study was conducted in order to evaluate the muscular dysfunction in COPD patients and the impact of pulmonary rehabilitation programs on symptoms, respiratory function and exercise tolerance.

The study was conducted in the Pulmonary Rehabilitation Department of the Clinical Hospital "V. Babes", Timisoara, from 2007 to 2010, according to Good Clinical Practice criteria. All patients were initially evaluated and started a PRP, then re-evaluated after 3 weeks and 6 months. The subjects included in the study were patients diagnosed with COPD stages I-IV GOLD, without signs of acute exacerbation or clinically manifested respiratory failure and without significant associated pathology.

The inclusion criteria were: patients diagnosed with chronic obstructive respiratory disease who presented dyspnea, and/or limitation of effort capacity, with mild to severe functional limitation (Forced Expiratory Volume in 1 second less than 80%), with stable clinical condition on optimum bronchodilator therapy, non-smokers, former smokers or smokers included in a smoking cessation programme. The patients were also motivated and made able to understand and cooperate in the investigations and rehabilitation programme. Patients with neuromuscular or major locomotives deficits, alcoholics, patients with severe hypercapnic respiratory failure and those with acute, incontrollable cardiovascular disease or decompensated heart failure were excluded.

Pre and post rehabilitation program patient assessment included: measurement of respiratory functional capacity by spirometry using a Jaeger-type spirometer (Viasys, Germany), PImax and PEmax assessment, the 6-minute walking test (6MWT) exercise tolerance evaluation, comprehension force testing (in kg-force) at the level of the dominant upper limb using a Dynatest type dynamometer (Riester brand - Germany).

Pulmonary rehabilitation programs (PRP) included:

a. Training of the lower limbs muscles performed by walking on a rolling mat or on an ergometric bicycle, pedometer monitored lower extremities light aerobic gymnastics or walking-at-will. There was a gradual increase in the intensity and duration of the sessions, from 5 minutes initially with repeated breaks of 3-4 minutes, to an effective minimum of 20 minutes.

b. Training of upper limb muscles using ergometric levers, weights of different sizes, dynamometers, tubes / elastic bands.

c. Exercises to increase joint flexibility in order to increase the degree of suppleness of movements, especially in elderly patients who frequently have joint changes (arthrosis / arthritis). The exercises consisted of flexion movements - repetitive extensions, with extensive and complete muscular trips. The length of the program ranged from 3-12 weeks (minimum 3 weeks), 3-5 sessions per week, with a minimum duration of 20-30 minutes per day. The initial increase in the effort volume was achieved by increasing the frequency or duration of the trainings. When we reached 45 minutes of training / day, at a frequency of 5 days / week, the intensity of their training progressively increased.

Each training session consisted of the muscle heating period (10 minutes), the training session itself (fast walking, pedaling, rowing) and the relaxation session (10 minutes). In order to achieve a proper control of the intensity of the training, we used the pulse-oximeter, the blood-pressure monitor and the effort self-perception scale (Borg scale).

Results The study group included 168 patients, 158 men and 10 women, with COPD stages I-IV GOLD, who were proposed to follow the pulmonary rehabilitation programme. There were no deaths during the 6 months of monitoring. The initial comparative evaluation of patients is shown in table 1. The majority of patients were male (93%), in all GOLD stages groups. The average age increased gradually from COPD II to COPD IV, the average growth per stage being 3.22 years of age. Body mass index decreased as COPD severity was higher. As the waist did not change significantly between groups, body weight decreased steadily as the severity of the disease and age increased. Only 95 patients had BMI within normal limits, 28 were underweight, with an average value of 18.1kg/m^2 (BMI minimum value = 14.2kg/m^2), and 45 of them were overweight, with an average value of 32.3kg/m^2 (maximum BMI = 35.5kg/m^2).

Forced expiratory volume in 1 second varied with COPD severity stages, between 80.55±10.6% in stage I, respectively 64.21±9.5% in stage II, 39.50±5.86% in stage III, and 24.49±7.54% in stage IV. The PImax and PEmax measurement detected decreased values from the healthy control group to the COPD group IV: PImax from 7.20kPa to 4.18kPa (with an average decrease of 1.06kPa per stage), respectively PEmax from 8.56 to 7.37kPa (with an average decrease of 0.40kPa per stage). It was noted that the ratio between the average values of PImax and PEmax increased steadily in favor of PEmax from COPD II group to COPD IV group (respectively values of 1.18 in COPD II group, 1.40 in COPD III group and 1.76 in COPD group IV). In dynamics, the subsequent evaluations at 21 days and

at 6 months did not detect significant changes in the average values obtained within the study groups.

Dyspnea assessment using mMRC and Borg scales revealed higher values in advanced COPD stages. Thus, the mean values obtained for the mMRC scale started from 0.03 in the healthy control group and reached 3.69 in the COPD IV group, and on Borg scale reached 4.85 units from 2.18. After the completion of the PRP, statistically significant improvements ($p < 0.05$) of dyspnea scores were detected on both scales, both after 21 days and after 6 months. Thus, the average decrease in the degree of dyspnea on mMRC scale was -0.39 units, and the average difference was -0.76 units on Borg scale.

The 6-minute effort test (6MTW) initially showed a decrease in effort tolerance as lung function decreased, but PRP had a significant impact on exercise capacity, the distance travelled after 21 days and after 6 months was significantly greater than the initial one (table 2). The average distance travelled by patients according to the stage of COPD, before and after the PRP is shown in figure 1.

Table 2. Comparative statistical analysis of the distance travelled at 6MWT between the COPD groups II-IV, pre and post rehabilitation (Two-way ANOVA test and Bonferroni post-tests)

COPD II vs COPD III				
Time	*COPD II*	COPD III	Difference	95% CI of diff.
Initial	*472.5*	415.0	-57.47	-145.5 to 30.54
21 days	*540.6*	482.4	-58.20	-146.2 to 29.81
6 months	*524.6*	456.3	-68.27	-156.3 to 19.74
Time	*Difference*	t	P value	Summary
Initial	*-57.47*	1.829	P > 0.05	ns
21 days	*-58.20*	1.853	P > 0.05	ns
6 months	*-68.27*	2.173	P > 0.05	ns

COPD II vs COPD IV				
Time	*BPOC II*	BPOC IV	Difference	95% CI of diff.
Initial	*472.5*	350.2	-122.3	-208.7 to -35.87
21 days	*540.6*	400.6	-140.0	-226.4 to -53.55
6 months	*524.6*	387.9	-136.7	-223.1 to -50.25
Time	*Difference*	t	P value	Summary
Initial	*-122.3*	3.964	P<0.001	***
21 days	*-140.0*	4.537	P<0.001	***
6 months	*-136.7*	4.430	P<0.001	***

COPD III vs COPD IV				
Time	*BPOC III*	BPOC IV	Difference	95% CI of diff.
Initial	*415.0*	350.2	-64.83	-130.1 to 0.4298
21 days	*482.4*	400.6	-81.78	-147.0 to -16.52
6 months	*456.3*	387.9	-68.41	-133.7 to -3.150
Time	*Difference*	t	P value	Summary
Initial	*-64.83*	2.783	P < 0.05	*
21 days	*-81.78*	3511	P<0.01	**
6 months	*-68.41*	2.937	P < 0.05	*

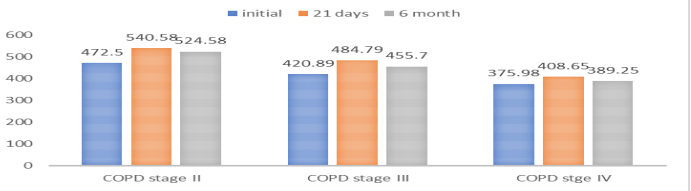

Fig 1. 6MWD (m) in stage II to IV COPD patients

For patients taking outdoor walks, there was a progressive improvement in the walking distance per day highlighted on the pedometer, with a daily average values shown in table 3. The minimum average value was registered in the COPD group IV (2476 steps / 24 hours), but with the highest increase at 6 months after PRP (+636 steps / 24 hours). In COPD group III, the daily activity increase was + 597 steps / 24 hours after 6 months, and COPD group II registered the lowest increase of +540 steps / 24 hours (probably because the patients in this group performed the best preserved physical activity).

The evaluation of the muscular force by dynamometry (the force of comprehension at the level of the dominant arm) revealed the decrease of the average values from the healthy control group to COPD stage IV, respectively from 0.865kg-force to 0.675kg-force.

Table 3. The values obtained at pre and post rehabilitation pedometry

BPOC stage	**Initial Pedometry**	**Pedometry after 6 months**	**Difference in metres**	**P**
BPOC II	**8724**	**9264**	+540	<0.05
BPOC III	**5528**	**6125**	+ 597	<0.05
BPOC IV	**2476**	**3112**	+ 636	<0.01

Discussion

In the present study, the results of the initial evaluation of COPD patients demonstrated the presence of muscle deconditioning and decreased exercise tolerance, decreased motivation, with negative repercussions on patients' lives in most cases. This study confirms the importance of introducing pulmonary rehabilitation programs in the treatment of symptomatic COPD patients. The PRP main goals are to decrease the level of dyspnea, increase effort tolerance and improve the quality of life (18,31).

Our results were also confirmed by a large study involving 647 patients from 9 rehabilitation centres in California, who registered significant improvements in symptoms and quality of life after rehabilitation, at 3-, 6-, 12-, and 18-month. The study confirmed also significant reductions in all measures of healthcare utilization. Over 18 months, benefits gradually declined, but levels remained above baseline values (32). In another cohort that included 76 patients with COPD, Mahler et al. described the TDI decline with - 0.7 (SD ± 2.9) at 2 years (33). Also, dyspnoea has been shown to be a predictor of survival in COPD patients. In a prospective, multicenter trial conducted by Nishimura and his colleagues on 227 patients with

COPD, survival was not significantly associated with COPD GOLD staging, and dyspnoea assessed by the MRC questionnaire was a better predictor of survival ($p < 0.05$) (34). Exercise capacity assessed by 6MWT showed a gradual decrease in physical performance as COPD severity increased. The recorded values gradually decreased compared to the normal values predicted from the healthy control group to the COPD stage IV group.

Patients with COPD have an annual decrease in distance walked in 6 minutes (6MWD) of approximately 25 meters, which is 5 times greater than in the healthy subject (35,36). Pinto-Plata and colleagues evaluated patients with COPD for 2 years, and they observed that the decline of 6MWD was 26 (SD ± 37) meters / year, while for healthy persons of similar age the distance decreased by 12 (SD ± 25) meters / year. In our study, after the implementation of PRP, the reassessment of patients at both 21 days and 6 months showed statistically significant increases (with high significance, $p < 0.001$) of the average values of 6MWD in all COPD stages groups (36). The highest increase was recorded on all groups at 21 days, with the average value of + 61.94 m (respectively + 68.8m in the COPD II group, + 67.34m in the COPD III group and + 50.40m in the COPD group IV). The 6MWD was maintained after 6 months compared to the initial test, but smaller than at 21 days. Thus, at 6 months the average growth on all groups was + 42.25m (respectively + 52.08m in the group COPD II, + 41.28m in the group COPD III and + 33.4m in the group COPD IV). This study reconfirmed the clinical relevance of 6MWT, as 6MWT is known as a predictor of survival. It has been shown that the absolute value of 6MWT is a better predictor of mortality in COPD patients compared with FEV1 and BMI. The value of 6MWD lower than 350 meters is has been demonstrated to be associated with an unfavourable prognosis of the disease (35-39). In this study, the improvement obtained in average values was over 40 meters (respectively 61.94m at 21 days and + 42.25m at 6 months), which corresponds to the proven favourable clinical response threshold. Clinical studies reported that pulmonary rehabilitation increases the 6MWS by 15-20% (36,37), situation in which the current results were also included.

Pedometry has shown an increase in the daily activity of COPD patients (39,40). The use of pedometers proved to be a very good motivation for patients to increase their daily physical activity, but the values recorded were very varied within each subject, depending on the clinical status, the weather, the days of the week and certain current problems of the patients, the duration and the type of physical training sessions, aso. It is possible that the simple wearing of the pedometer, with the patients' awareness that they were being "watched" caused them an increasing in their physical activity on the days when they were evaluated. However, we noticed the attractiveness of these pedometers for patients, regarded as motivating, cheap and easy-to-handle "personal toys", which made some patients buy them.

Multiple evidences indicate that COPD is a systemic disease that may severely affect muscle function in patients diagnosed with this condition (13,41). Decreased muscle strength is independently associated with poorer exercise capacity and lower extremity functioning in COPD patients, and this is the main reason for targeting improved exercise capacity through pulmonary rehabilitation (39). In our study, after the completion of the PRP, the values recorded by dynamometry retesting were improved compared to the initial testing both at 21 days and at 6 months. In the COPD stage II group, an increase with 0.031kg-force at 21 days and 0.021kg-force at 6 months was calculated, in the COPD stage III group the improvement was 0.030kg-force, respectively 0.018kg-force. The highest improvement was obtained in COPD stage IV group, namely 0.037kg-force at 21 days and 0.024kg-force at 6 months. All patients received also pharmacological treatment respecting the GOLD guideline (42,43).

For maximum benefit, peripheral muscle training should combine several types of exercises: strength, endurance, flexibility, both in the lower and upper limbs muscles. Our findings supports the fact that earlier attention to skeletal muscle strength and/or endurance training of skeletal muscles could represent important components of disability prevention.

Conclusion

The results of this study demonstrated a favourable impact of pulmonary rehabilitation programme on muscle dysfunction, dyspnea, and quality of life in COPD patients, regardless of severity, with statistically significant and persistent improvements (6 months after PRP completion).

Declaration of conflict of interests

There is no conflict of interest for any of the authors regarding this paper.

Informed consent

An informed consent was obtained from the patients included in this study.

Table 1. Initial comparative assessment of patients according to GOLD stage

Parameter	Control group (healthy) n=32	COPD stage I n=27	COPD stage II n=43	COPD stage III n=45	COPD stage IV n=53
Gender Male/female	29/3	26/1	41/2	42/3	49/4
Urban/rural	17/15	14/13	22/21	24/21	27/26
Age, years mean-DS	55.65±15.58	56.66±10.35	62.93±11.2	63.15±10.19	64.20±8.31
Smokers/non-smokers	14/18	15/12	28/15	33/12	40/13
FVC%	96.54±11.0	89.12±11.2	72.63±13.7	57.04±10.37	37.50±11.77
FEV1%	96.2±9.8	80.55±10.6	64.21±9.5	39.50±5.86	24.49±7.54
FEV1/FVC	101.65±11.1	69.38±11.8	65.92±12.3	63.21±15.65	59.57±19.43
PI predicted, l	10.57±3,6	10.53±0,14	10.50±0,07	10.49±0,17	10.45±0,17
PI test, l	7.86±1.5	7.92±2.4	6.49±2.4	5.32±2.5	4.43±2.02
PI max%	71.67±25.0	75.2±21.9	59.36±23.13	49.67±23.15	40.83±18.39
PE predicted, l	13.30±2.9	12.74±2.3	13.51±0.17	12.72±2.12	13.04±1.46
PE test, l	9.59±0.26	9.70±2.03	8.480±3.28	8.39±2.98	7.76±3.32
Weight, kg	79.40±18.4	74.33±17.9	74.23±14.6	72.57±16.23	71.05±18.72
Waist, m	169.18±8.7	168.33±5.4	169.60±8.8	168.4±7.69	168±8.94
BMI, kg/m2	27.55±4.7	26.1±5.7	25.96±5.6	25.58±5.4	25.10±6.34
6 MWT, m	561.81±110.2	515.5±78.05	467.14±123.78	421.84±117.36	394.57±104.31
Dynamometry, kgf	0.865±0.07	0.846±0.06	0.823±0.03	0.82±0.16	0.67±0.03
Dyspnea BORG scale	2.18±0.9	2.44±0.97	3.64±2.13	3.77±1.39	4.85±2.11
Dyspnea MRC scale	0.03±0.01	0.88±0.5	1.21±0.47	2.86±0.79	3.69±0.77

References:

1. Arghir OC, Dantes E, Otelea M, Rascu A, Borgazi E, Cambrea SC. Eight-year survey of tuberculosis in-hospital mortality in the south eastern part of Romania. Rom J Leg Med 2018; 26(2):183-187.
2. Fildan AP, Toma CL, Tofolean D, Arghir OC, Dantes E. TB Risk in Patients with Biological Therapy for Psoriasis. Chest. 2016;150(4_S):201A.
3. Alexescu TG, Tarmure S, Negrean V, Cosnarovici M, Ruta VM, Popovici I, Para I, Perne MG, Orasan OH, Todea DA. Nanoparticles in the treatment of chronic lung diseases. J Mind Med Sci. 2019; 6(2): 224-231.
4. Dantes E, Fildan AP, Toma CL, Voicu GH, Oancea C. Respiratory impact in workers exposed to air pollutants from petroleum refinery. J Environ Prot Ecol, 2016; 17(2):523-531.
5. Todea D, Cosma C, Dicu T, Roşca L, Cucoş Dinu A, Rişteiu M, Iancu D, Papuc I, Rădulescu D. Lung cancer risk induced by residential radon in CLUJ and Alba Counties, ROMANIA. Environmental Engineering and Management Journal. 2013; 12(6):1281 -1285
6. Dantes E, Lilios G, Fildan AP. Environmental smoke exposure – an independent risk factor for lung cancer? J Environ Prot Ecol, 2015;16(4):1620-1626.
7. Alexescu TG, Maierean A, Ciumarnean L, Budin C, Dogaru G, Todea AD. Rehabilitation therapies in stable chronic obstructive pulmonary disease. Balneo Research Journal. 2019; 10(1):37-44.
8. Jorenby DE. Smoking cessation strategies for the 21st century. Circulation 2001; 104:51–52.
9. Jimborean G, Ianosi ES, Alpar C, Postolache P. Training the future trainers - Intensifying anti-smoking education for a better community health. Rev Chim 2017; 68(9):2129-2131.
10. Ianosi ES, Postolache P, Macovei LA, et al. Smoking cessation in COPD patients by a selective partial nicotinic agonist. Rev Chim 2018; 69(7):1766-1769.
11. Lotrean LM, Varga B, Popa M, Radu-Loghin C, Man MA, Trofor A. Opinions and practices regarding electronic cigarette use among Romanian high school students. Gac Sanit, 2016; 30(5):366-369.
12. Trofor A, Petris O, Trofor L, Man MA, Filipeanu D, Miron R. Biochemistry in assessing tobacco exposure -smokers versus non-smokers correlations with clinical practice. Rev Chim 2017; 68(5):1002-1006.
13. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med. 1996; 153:976–980.
14. Garcia-Aymerich J, Serra I, Gomez FP, Farrero E, Balcells E, Rodriguez DA, et al: Physical activity and clinical and functional status in COPD. Chest 2009, 136:62–70.
15. Budin CE, Maierean AD, Ianosi ES, Socaci A, Buzoianu AD, Alexescu TG, Olteanu M, Rusu E, Moldovan CA, Nemes RM. Nocturnal Hypoxemia, a Key Parameter in Overlap Syndrome. REV.CHIM.(Bucharest). 2019; 70 (2): 449-454.
16. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews. 2006;4.
17. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: Key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine. 2013;188:e13-e64 .
18. Spruit MA, Burtin C, De Boever P, et al. COPD and exercise: does it make a difference? Breathe (Sheff). 2016; 12(2):e38–e49 .
19. Dantes E, Man MA, Tudorache E. The role of pulmonary rehabilitation in patients with idiophatic pulmonary fibrosis. Available from https://www.intechopen.com/online-first/the-role-of-

pulmonary-rehabilitation-in-patients-with-idiopathic-pulmonary-fibrosis.
20. Rusu A, Nita C, Todea D, Rosca L, Bala C, Hancu N. Correlation of the daytime sleepiness with respiratory sleep parameters in patients with sleep apnea and type 2 diabetes. Acta Endocrinologica (Buc); 2011:VII(2):163-171.
21. Rusu A, Todea D, Rosca L, Nita C, Bala C. The development of a sleep apnea screening program in Romania type 2 diabetic patients: a pilot study. Acta Diabetologica. 2012; 49(2): 105-109 .
22. Todea D, Herescu A, Rosca L. Obstructive Sleep Apnea Syndrome - a matter of public health. Transylvanian Review Of Administrative Sciences. 2012; 37E: 186 - 201 ..
23. Maierean A, Ciumarnean L, Alexescu TG, Domokos B, Rajnoveanu R, Arghir O, Todea DA, Buzoianu AD, Dogaru G, Bordea RI. Complementary therapeutic approaches in asthma. Balneo Research Journal 2019. 10(3): 204–212.
24. Toma CL, Dantes E, Oancea C, Fildan AP. Respiratory bronchiolitis - associated interstitial lung disease - an unexpected form of idiopathic interstitial pneumonia in a young male. Rom J Morphol Embryol 2017, 58(1):261–265.
25. Jimborean G, Postolache P, Ianosi ES, Arghir OC. Clinical consideration and lung function in different groups of patients (smokers, ex-smokers, nonsmokers). Eur Respir J, 2017; 50: PA2991 .
26. Fildan AP, Toma CL, Tofolean D, Balteanu M, Dantes E. Overlapping tuberculosis in a patient with pulmonary alveolar proteinosis. Acta Medica Mediterranea. 2016, 32:1021-1025.
27. Paone G, Serpilli M, Girardi E, Conti V, Principe R, Puglisi G, De Marchis L, Schmid G. The combination of a smoking cessation programme with rehabilitation increases stop-smoking rate. J Rehabil Med, 2008; 40:672–677.
28. Budin CE, Alexescu TG, Bordea IA, Gherginescu MC, Aluas M, Grigorescu BL, Biro L, Buzoianu AD, Nemes RM, Tantu MM, Todea DA. Nicotine Addiction: Objective in Educational Programs for Smoking Prevention in Young People. REV.CHIM.(Bucharest). 2019;70(6): 2168-2172.
29. Budin CE, Marginean C, Bordea IR, Enache LS, Enache EL, Grigorescu BL, Biro L, Rusu E, Nemes RM, Todea DA. The Influence of Smoking on Nicotine Exposure Biomarkers and Inflammatory Profile Among Foster Care Teenagers, Romania. Rev.CHIM.(Bucharest). 2018; 69(12):3659-63.
30. Vremaroiu-Coman A, Alexescu TG, Negrean V, Milaciu MV, Buzoianu AD, Ciumarnean L, Todea DA. Ethical aspects of smoking cessation among the population from Transylvania. Balneo Research Jornal. 2018; 9(3): 254-259.
31. Hopkinson N. Pulmonary Rehabilitation for COPD. Tanaffos. 2017; 16(Suppl 1):S7–S8.
32. California Pulmonary Rehabilitation Collaborative Group. Effects of pulmonary rehabilitation on dyspnea, quality of life, and healthcare costs in California. J Cardiopulm Rehabil. 2004; 24(1):52-62.
33. Mahler DA, Fierro-Carion G, Mejia-Alfaro R, Ward J, Baird JC: Responsiveness of continuous ratings of dyspnea during exercise in patients with COPD. Med Sci Sports Exerc. 2005; 37:529–535.
34. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest. 2002;121(5):1434-40.
35. Zeng GS, Chen LC, Fan HZ, Wu LL, Wu XP, et al. The relationship between steps of 6MWT and COPD severity: a cross-sectional study. Int J Chron Obstruct Pulmon Dis. 2019; 14:141-148.
36. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J. 2004; 23:28-33 .
37. Dajczman E, Wardini R, Kasymjanova G, Préfontaine D, Baltzan MA, Wolkove N. Six-minute walk distance is a predictor of survival in patients with chronic obstructive pulmonary disease undergoing pulmonary rehabilitation. Can Respir J. 2015; 22(4):225–229.
38. Enfield K, Gammon S, Floyd J, Falt C, Patrie J, et al. Six-minute walk distance in patients with severe end-stage COPD: association with survival after inpatient pulmonary rehabilitation. J Cardiopulm Rehabil Prev. 2010; 30(3):195-202.
39. Mendoza L, Horta P, Espinoza J, et al. Pedometers to enhance physical activity in COPD: a randomised controlled trial. Eur Respir J. 2015;45(2):347–354 .
40. Moy ML, Martinez CH, Kadri R, et al. Long-Term Effects of an Internet-Mediated Pedometer-Based Walking Program for Chronic Obstructive Pulmonary Disease: Randomized Controlled Trial. J Med Internet Res. 2016;18(8):e215.
41. Singer J, Yelin EH, Katz PP, et al. Respiratory and skeletal muscle strength in chronic obstructive pulmonary disease: impact on exercise capacity and lower extremity function. J Cardiopulm Rehabil Prev. 2011; 31(2):111–119 .
42. Rajnoveanu RM, Antoniu S, Ulmeanu R. Combined long-acting bronchodilator single therapy for COPD. Expert Opin Pharmacother. 2014; 15(1):139-42 .
43. Ariel A, Altraja A, Belevskiy A, et al. Inhaled therapies in patients with moderate COPD in clinical practice: current thinking. Int J Chron Obstruct Pulmon Dis. 2017;13:45–56 .