TÜBİTAK

Original Article

Turk J Med Sci
2012; 42 (Sup.2): 1414-1422

E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1204-64

Effects of long-acting beta-2 agonist treatment on daily energy balance and body composition in patients with chronic obstructive pulmonary disease

Abdurrahman GENÇ[1], Kağan ÜÇOK[1], Ersin GÜNAY[2], Yücel GÖNÜL[3], Hatice KARABACAK[1], Ümit ŞENER[1], Serkan NURAL[2], Mehmet ÜNLÜ[2]

Aim: The aim of this study was to investigate the effects of long-acting beta-2 agonist (formoterol) treatment on the resting metabolic rate (RMR), daily physical activity, body composition and anthropometry, nutritional status, and quality of life of patients with chronic obstructive pulmonary disease (COPD).

Materials and methods: A total of 30 male patients who were diagnosed with COPD participated in the study. The RMR was determined using an indirect calorimeter, daily physical activity was measured with an accelerometer, and body composition was established by bioelectric impedance analysis. Body circumference and skinfold thickness measurements were carried out. Pulmonary function tests were performed with a spirometer. The 36-item short-form health survey (SF-36) quality of life questionnaire and dietary intake records were obtained from the participants. Following the initial measurements, the patients received a 12-μg formoterol inhaler twice daily for 3 months. At the end of the 3 months, all of the measurements and questionnaires were collected once again.

Results: Although the RMR, daily physical activity, body mass index, body fat percentage and fat distribution measurements, dietary intake record, and quality of life questionnaire scores were not statistically different before and after treatment in the patients with COPD, an increase in pulmonary function tests (forced expiratory volume in 1 s and peak expiratory flow) was recorded.

Conclusion: Our results suggest that 3-month long-acting beta-2 agonist treatment does not change the daily energy balance and body composition in male COPD patients.

Key words: Chronic obstructive pulmonary disease, beta-2 agonist, resting metabolic rate, daily physical activity, body fat, anthropometry

Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem. Worldwide, COPD is in the spotlight because its high prevalence, morbidity, and mortality create formidable challenges for healthcare systems (1). COPD is a severe disease that leads to a nonreversible obstruction of the small airways.

COPD is largely the result of smoking, and the consequences of this habit generally become clinically apparent during the late productive period of life. Tobacco smoking represents the most important risk factor for respiratory diseases and it is the primary risk factor for COPD (2). Age of starting smoking, total pack years smoked, and current smoking status are all predictive of COPD

Received: 13.04.2012 – Accepted: 30.05.2012
[1] Department of Physiology, Faculty of Medicine, Afyon Kocatepe University, Afyonkarahisar – TURKEY
[2] Department of Pulmonary Medicine, Faculty of Medicine, Afyon Kocatepe University, Afyonkarahisar – TURKEY
[3] Department of Anatomy, Faculty of Medicine, Afyon Kocatepe University, Afyonkarahisar – TURKEY
Correspondence: *Abdurrahman GENÇ, Department of Physiology, Faculty of Medicine, Afyon Kocatepe University, Afyonkarahisar – TURKEY*
E-mail: dragenc@hotmail.com

mortality (3). Nevertheless, smoking cessation is recognized as essential to the treatment of COPD. In addition to smoking intervention, pharmacological treatment remains a key to therapy for patients with COPD (4).

COPD is known to be both pathophysiologically and clinically heterogeneous, with highly variable rates of progression (5). It appears that patients with respiratory symptoms tend to have a more accelerated progression of airflow obstruction, while those who are asymptomatic are less likely to have progressive disease (6). A functional assessment is the use of subjective and objective data, often from diagnostic tools, to obtain a description of an individual's functional status or ability to participate in everyday activities by quantifying the effects of the disease severity on physical and psychological function (7). Dyspnea is a major contributor to decreased exercise capacity and functional status in this population (8). Moreover, body weight loss, often observed in patients with COPD, is related to a lack of appetite.

Formoterol is a rapidly acting, well-tolerated, effective beta-2-adrenergic receptor agonist that can be regularly used as a long-acting bronchodilator for patients with moderate to severe COPD, as per recommendations of the current treatment guidelines (9). Inhaled formoterol reduces symptoms and improves lung function and the general health status in patients with COPD.

The COPD management program emphasizes the importance of early detection and intervention to prevent and reduce the long-term consequences of disease progression (4). It is also essential for physicians to understand and evaluate all of the aspects of COPD patients, including their physiological parameters.

The aims of this study were to investigate the effect of long-acting beta-2 agonist treatment (formoterol inhaler) on the resting metabolic rate (RMR), daily physical activity, body fat percentage, lean body mass and body fat distribution, nutritional status, and quality of life of patients with COPD.

Materials and methods

Patients

The study protocol was approved by the local ethical committee of clinical research, and all of the patients participated voluntarily with written informed consent. Inclusion criteria were as follows: patients who were diagnosed with COPD and who planned to receive formoterol. A total of 30 COPD patients, between 43 and 67 years of age, were enrolled in the study. Classification of disease severity was made using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations (10). There was an indication for receiving long-acting beta-2 agonist treatment in the COPD patients. Exclusion criteria were as follows: asthma; atopy; acute infection; metabolic, cardiovascular, or other systemic diseases; and use of drugs affecting basal metabolism. A total of 30 male patients who were diagnosed with COPD participated in the study. First, all of the measurements were taken and the questionnaires were administered in the sports physiology laboratory. Following the measurements, the patients received a 12-μg formoterol inhaler twice daily for 3 months. At the end of the 3 months, all of the measurements and questionnaires were collected once again.

Resting metabolic rate

RMR was measured using an indirect calorimeter (Quark b^2, Cosmed, Rome, Italy) with a computerized metabolic card, which analyzed the oxygen consumption and carbon dioxide production (11). The device was calibrated prior to each test. The subjects were instructed to avoid food intake for 12 h and to not perform exercise for 24 h before the test. The tests were performed at the same time (0830–1030 hours) of the day. After resting for 15 min, the measurements were taken for all of the subjects in a silent, lightless laboratory at room temperature. The subjects were asked to put on a face mask, lie in a supine position, and not move their arms or legs during the test.

Daily physical activity

Daily physical activity was measured using an accelerometer (RT3, Stayhealthy Inc., Monrovia, CA, USA). The accelerometer measures acceleration in each anatomical axis with vertical

(x), anterioposterior (y), and mediolateral (z) measurements. The accelerometer was attached to a belt, using its integral belt clip, and worn on the right hip of the patients. The epoch interval was set at 1 min and output was expressed as mean counts per minute for each activity (12). The accelerometer periodically measures acceleration and converts it to a digital representation, which is then processed to obtain an 'activity count' that is stored in the memory. Participants were monitored with an accelerometer for 12 h (0800–2000 hours) per day for 3 days. The mean value of the 3 days was calculated (kcal/12 h).

Body composition

The body fat and lean body mass of the patients were determined using a bioelectrical impedance analysis system (Bodystat 1500, Bodystat Ltd., Douglas, Isle of Man, UK). Metal accessories (belts, cell phones, etc.) were removed from the body (13). Heavy physical exercise was restricted for 24 h before the test. Impedance was measured between the right wrist and right ankle using a tetrapolar electrode system. The subjects lay supine, with the arms separated from the body and the legs not touching each other. Signal electrodes were positioned in the middle of the dorsal surface of the hands and feet, proximal to the metacarpophalangeal and metatarsophalangeal joints. Detecting electrodes were more proximally positioned at the ankle and the wrist. An excitation current of 500 μA at 50 kHz was applied to the distal electrodes, and the voltage was detected by proximal electrodes. The data were analyzed using the manufacturer's software, and the body fat percentage, total body fat, and lean body mass were determined for each patient. Exclusion criteria were conditions that change the body fluid–electrolyte balance, such as dehydration.

Anthropometric measurements

Skinfold thickness measurements were taken using a skinfold caliper (Holtain Ltd., Crosswell, Wales, UK). The skin was picked up between the thumb and index finger, and the caliper was applied about 1 cm from the fingers (14). The measurements were either taken in rotation through measurement sites or a period of time was allowed for the skin to regain normal texture and thickness. Standardized sites were used for skinfold thickness measurements as follows (15): biceps, triceps, subscapular, midaxillary, chest (pectoral), abdominal, suprailiac, thigh, and medial calf skinfold.

Circumference measurements were taken at standing-straight but relaxed positions with a measuring tape. The tape was held parallel to the ground and completely surrounded the part of the body, but it did not compress the subcutaneous fat tissue. Duplicate measurements were taken at each site and retests were done if duplicate measurements were not within 7 mm. The standardized sites used for circumference measurements were as follows (15): waist circumference was measured at the narrowest part of the torso at the end of the expiration, hip circumference was measured at the widest part over the buttocks, and abdomen circumference was measured horizontally at the level of greatest anterior protuberance of the abdomen (usually at the umbilicus) at the end of the expiration. The waist-to-hip ratio was calculated.

Height was measured using an inflexible steel meter while the subjects stood with heels, back, and shoulders against a wall, with feet together and head on the Frankfort plane (16). The body weight measurements were taken with the subjects' outerwear and shoes removed, using calibrated measurement devices (17). Body mass index (BMI) was calculated as the body weight divided by the square of the height (kg/m^2). The BMI is mostly used as a reference parameter for the assessment of obesity (18).

Pulmonary function tests

Pulmonary function tests were performed twice with a spirometer (Quark b^2, Cosmed). The tests were performed at room temperature (19). Acceptability criteria were applied to all of the participants (20). The tests were explained to the patients prior to each measurement and a test was performed for adaptation. The procedure required the patient to wear a nose clip and perform a forced expiratory maneuver. Before the mouthpiece was placed into the patient's mouth, the patient was instructed to inhale completely and then make as deep and rapid of an expiration as possible. The forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), forced expiratory flow at 25%–75% vital capacity ($FEF_{25–75}$), and peak expiratory flow (PEF) were measured, and the FEV_1/FVC ratio was calculated.

The maximal voluntary ventilation (MVV) was measured using another spirometry maneuver. The patient's expired maximal volume during 12 s of forced breathing into the spirometer was measured and MVV was calculated for 1 min.

Short-form health survey (SF-36)

The SF-36 is a multipurpose health survey with only 36 questions. A validity and reliability study of the SF-36 was conducted in Turkey (21). The SF-36 has been useful in comparing general and specific populations, comparing the relative burden of diseases, differentiating the health benefits produced by a wide range of different treatments, and screening individual patients (22). It yields an 8-scale profile of scores, as well as physical and mental health summary measures (23):

-Physical health: physical functioning, role–physical, bodily pain, and general health.

-Mental health: vitality, social functioning, role–emotional, and mental health.

Responses from the SF-36 are summed and then transformed to give 8 scores with a 0–100 scale, where higher scores indicate better functioning in that dimension (24).

Dietary intake record

The record form is a newly developed estimated dietary record form for use in home settings and is designed to be self-explanatory. The record form includes all meals, snacks between meals, and a list of measures of nutrients (e.g., number, slice, a soap plate, a tablespoon, a dessert spoon, a water glass) for 3 days. The participants recorded their dietary intake on the form using the measurement of nutrients for 3 days (25). The calories of all of the nutrients were calculated for each day. The mean value for a day was determined from 3 days of data.

Statistical analysis

The data were analyzed using SPSS 18.0 (SPSS, Chicago, IL, USA). All of the parametric results were expressed as mean ± standard deviation for each group. Distribution of the group was analyzed with the Kolmogorov–Smirnov test. Differences between means were analyzed with Student's t-test or the Mann–Whitney U test according to the distribution of the data. The significance level was determined at $P \leq 0.05$.

Results

The mean age of the COPD patients was 57.9 ± 10.2 years. The mean values of the RMR, daily physical activity, dietary intake record, and body composition values before and after treatment are shown in Table 1. There was no significant difference in the RMR, daily physical activity, dietary intake record, and body composition values before and after treatment.

The mean height of the COPD patients was 169.4 ± 6.6 cm. Table 2 shows the body weight, BMI, circumference measurements, and waist-to-hip ratio values in patients with COPD. There was no significant difference in the body weight, BMI, circumference measurements, and waist-to-hip ratio values before and after treatment.

Table 1. RMR, daily physical activity, dietary intake records, and body composition values before and after treatment.

	Before treatment (n = 30)	After treatment (n = 30)	P-value
RMR (kcal/day)	1881.0 ± 430.0	1806.3 ± 483.2	0.621
Physical activity (kcal/12 h)	628.4 ± 238.9	640.3 ± 264.6	0.896
Dietary intake (kcal/day)	2496.8 ± 570.5	2507.4 ± 658.4	0.952
Body fat (%)	29.2 ± 6.2	30.0 ± 7.1	0.876
Total body fat (kg)	23.5 ± 6.5	24.1 ± 7.7	0.954
Lean body mass (kg)	56.2 ± 8.7	55.8 ± 8.2	0.795

RMR: Resting metabolic rate.

Table 2. Body weight, BMI, waist-to-hip ratio, and circumference measurement values before and after treatment.

	Before treatment (n = 30)	After treatment (n = 30)	P-value
Body weight (kg)	79.6 ± 12.5	79.8 ± 11.9	0.839
BMI (kg/m^2)	27.9 ± 3.6	28.0 ± 3.7	0.628
Waist circumference (cm)	93.9 ± 8.1	94.7 ± 8.6	0.764
Abdomen circumference (cm)	99.4 ± 9.2	99.6 ± 9.6	0.945
Hip circumference (cm)	97.4 ± 6.8	97.6 ± 7.1	0.929
Waist-to-hip ratio	0.96 ± 0.06	0.97 ± 0.06	0.738

BMI: Body mass index

Table 3 lists the skinfold measurement values before and after treatment in patients with COPD. There was no significant difference in the skinfold measurement values before and after treatment. The skinfold and circumference measurements and the waist-to-hip ratio reflect the body fat distribution (e.g., central obesity, upper or lower body fatness) in the patients.

The mean values of the pulmonary function tests and smoking before and after treatment in patients with COPD are shown in Table 4. We found that the FEV_1 and PEF values were significantly higher after treatment than before treatment in patients with COPD. There were no significant differences in the other pulmonary function tests and smoking values before and after treatment.

Table 5 shows the quality of life questionnaire (SF-36) scores before and after treatment in patients with COPD. There was no significant difference in the SF-36 scores before and after treatment.

Table 3. Skinfold measurement values before and after treatment.

	Before treatment (n = 30)	After treatment (n = 30)	P-value
Triceps (mm)	12.7 ± 4.8	12.3 ± 4.1	0.779
Biceps (mm)	6.1 ± 2.1	6.6 ± 1.9	0.459
Subscapular (mm)	18.1 ± 4.5	18.8 ± 5.1	0.635
Midaxillary (mm)	16.1 ± 5.1	17.1 ± 5.0	0.542
Pectoral (chest) (mm)	18.0 ± 5.7	18.5 ± 5.6	0.761
Abdominal (mm)	29.8 ± 9.2	30.9 ± 8.9	0.702
Suprailiac (mm)	16.9 ± 6.8	16.6 ± 6.5	0.879
Thigh (mm)	16.1 ± 5.9	16.3 ± 6.0	0.923
Medial calf (mm)	11.7 ± 3.8	11.9 ± 4.0	0.834

Table 4. Pulmonary function test results and cigarette consumption before and after treatment.

	Before treatment (n = 30)	After treatment (n = 30)	P-value
FVC (L)	3.4 ± 0.9	3.7 ± 0.9	0.196
FEV_1 (L)	2.3 ± 0.6	2.7 ± 0.6	0.041
FEV_1/FVC (%)	67.3 ± 7.7	70.6 ± 8.1	0.111
PEF (L)	4.9 ± 1.6	6.2 ± 1.9	0.035
$FEF_{25–75}$ (L)	1.6 ± 0.6	1.9 ± 0.6	0.066
MVV (L)	91.5 ± 31.4	102.1 ± 32.9	0.204
Smoking (pack-years)	43.0 ± 20.3	43.0 ± 20.3	1.000

FVC (forced vital capacity), FEV_1 (forced expiratory volume in 1 second), PEF (peak expiratory flow), FEF_{25-75} (forced expiratory flow at 25% to 75% vital capacity), MVV (maximal voluntary ventilation)

Table 5. Quality of life questionnaire (SF-36) scores before and after treatment.

	Before treatment (n = 30)	After treatment (n = 30)	P-value
Physical health score	81.5 ± 13.5	85.3 ± 10.2	0.321
PF score	85.5 ± 15.9	89.7 ± 17.2	0.342
RP score	88.7 ± 17.2	88.8 ± 15.5	0.990
BP score	77.3 ± 20.8	85.2 ± 19.5	0.229
GH score	76.2 ± 19.0	79.2 ± 15.5	0.599
Mental health score	89.1 ± 6.7	90.5 ± 7.9	0.536
VT score	81.8 ± 9.9	85.8 ± 10.3	0.241
SF score	96.0 ± 8.8	96.8 ± 8.2	0.760
RE score	96.6 ± 0.5	94.7 ± 12.4	0.578
MH score	91.0 ± 8.2	91.4 ± 8.6	0.881
Total score	83.9 ± 9.5	86.9 ± 7.5	0.288

PF: physical functioning, RP: role–physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role–emotional, MH: mental health.

Discussion

COPD is defined as a preventable and treatable disease characterized by airflow limitation that is not fully reversible (4). With regard to respiratory function, it must be pointed out that smokers are at a higher risk of decreased FEV_1, with an excess annual FEV_1 decline ranging from 7 mL/year to 33 mL/year (26). Chhabra et al. (27) applied single doses of formoterol (12 μg) to 44 stable patients with COPD and found that the formoterol resulted in an immediate improvement in lung function. Aalbers et al. (28) treated 692 COPD patients with formoterol (4.5, 9, or 18 μg, 2 times a day) or a placebo via Turbuhaler for 12 weeks. They found that the FEV_1 improved significantly after all 3 doses of formoterol. Similar to these studies, we found that the pulmonary functions (FEV_1 and PEF) increased significantly

after 3 months of formoterol treatment (Table 4). The bronchodilatory effect of long-acting beta-2 agonists seemed to be fairly stable after regular treatment with bronchodilators in patients with COPD (29).

Bronchodilators could have 2 opposite effects on energy expenditure in patients with airway obstruction: first, an increase in energy expenditure due to a direct thermogenic effect, and second, a decrease in energy expenditure due to diminished work of breathing because of bronchodilation (30). In this study, we found that there was no significant difference in RMR, daily physical activity, or dietary intake before and after treatment (Table 1). Cazzola et al. (31) found that formoterol was not able to reduce energy expenditure during 6-min walking tests in COPD patients. They hypothesized that the reduction in pulmonary hyperinflation was not enough to induce a reduction in energy expenditure. Moreover, it is well known that continuous long-term exposure to beta adrenergic agonists results in the downregulation of mRNA and receptor protein with the rapid onset of tolerance to their effects (32). Therefore, the thermogenic effect of formoterol would be expected to be transient in nature and it is likely that the regular use of this drug does not affect the energy expenditure in COPD patients (31).

Patients with COPD often have limited daily physical activity. However, the level, type, and intensity of daily physical activity are not known, nor is there clear insight into the contributing factors (33). Dyspnea leads to inactivity, which leads to physical deconditioning, and a vicious circle ensues. It was found that using inhaled formoterol is effective in ameliorating exercise intolerance in patients with COPD (34–36). However, Aalbers et al. (28) found no differences between groups using formoterol and a placebo in walking distance in a shuttle walking test. Moreover, Wadbo et al. (37) found that formoterol improved the airway function and symptoms, without significant improvements in the shuttle walking test and quality of life. In the current study, it was found that there was no significant difference in the daily physical activity before and after treatment (Table 1). A study using the SF-36 reported that the physical subscale of the health status questionnaire was positively correlated with daily physical activity ($r = 0.40$, $P < 0.001$), whereas correlation with the mental subscale was not ($r = 0.15$, not significant) (38). Regular treatment of patients with COPD with long-acting beta-2 agonists can induce an improvement in the respiratory function and certain aspects of quality of life (29). We found that there was no significant difference in the SF-36 scores and smoking (pack year) values before and after treatment (Tables 4 and 5). The lack of effect on quality of life of the treatment might at least partially be explained by the severity of COPD, with little or no reversibility in these patients (37). We believe that because of active cigarette smoking and the progressive characteristic of COPD, daily physical activity and quality of life were not significantly improved with long-acting beta-2 agonist treatment in patients with COPD. Smoking cessation is the mainstay of the management of COPD because it reduces the decline in pulmonary function, improves the prognosis, and enhances quality of life (39,40).

Malnutrition is a common and often underrecognized problem in patients with COPD. Malnutrition in COPD, with the increased secretion of inflammatory mediators, the increased metabolic rate due to the ventilatory effort, and the therapeutic use of sympathomimetic drugs, together with a lack of appetite that results in decreased caloric intake and weight loss, is multifactorial (41). BMI has been shown to be a predictor of functional ability in people with COPD and a reduction in BMI adversely affects the clinical outcomes in COPD (8). With the development of COPD, peripheral muscles may undergo compositional changes with a loss of peripheral muscle mass, despite the patient having a normal BMI (7). Peripheral muscle composition is recognized as an important factor in assessing functional ability and exercise capacity. We measured the lean body mass, which includes the body muscle mass, of the patients. The present study demonstrates that there was no significant difference in the BMI, body composition (body fat %, total body fat, and lean body mass), and body fat distribution (skinfold and circumference measurements and waist-to-hip ratio) values before and after treatment in patients with COPD. Because of the energy balance between the energy intake and expenditure, the body composition and body fat distribution parameters may not be changed with long-acting beta-2 agonist treatment in patients with COPD.

In conclusion, our results suggest that long-acting beta-2 agonist (formoterol) treatment does not change the daily energy balance parameters, which are RMR, daily physical activity, and dietary intake, as well as body composition parameters such as body fat and lean body mass in male COPD patients.

References

1. Soriano JB, Rodríguez-Roisin R. Chronic obstructive pulmonary disease overview: epidemiology, risk factors, and clinical presentation. Proc Am Thorac Soc 2011; 8: 363–7.
2. Viegi G, Scognamiglio A, Baldacci S, Pistelli F, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease (COPD). Respiration 2001; 68: 4–19.
3. Viegi G, Pistelli F, Sherrill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. Eur Respir J 2007; 30: 993–1013.
4. Ferguson GT. Maintenance pharmacotherapy of mild and moderate COPD: what is the evidence? Respir Med 2011; 105: 1268–74.
5. Raghavan N, Guenette JA, O'Donnell DE. The role of pharmacotherapy in mild to moderate chronic obstructive pulmonary disease. Ther Adv Respir Dis 2011; 5: 245–54.
6. de Marco R, Accordini S, Antò JM, Gislason T, Heinrich J, Janson C et al. Long-term outcomes in mild/moderate chronic obstructive pulmonary disease in the European Community Respiratory Health Survey. Am J Respir Crit Care Med 2009; 180: 956–63.
7. Downs CA. Functional assessment of chronic obstructive pulmonary disease. J Am Acad Nurse Pract 2011; 23: 161–7.
8. ATS/ERS. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. Am J Respir Crit Care Med 1999; 159: S1–40.
9. Berger WE, Nadel JA. Efficacy and safety of formoterol for the treatment of chronic obstructive pulmonary disease. Respir Med 2008; 102: 173–88.
10. Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2009 update. 2009. Available at www.goldcopd.com.
11. Cosar E, Köken G, Sahin FK, Akgün L, Üçok K, Genç A et al. Resting metabolic rate and exercise capacity in women with polycystic ovary syndrome. Int J Gynaecol Obstet 2008; 101: 31–4.
12. Rowlands AV, Thomas PW, Eston RG, Topping R. Validation of the RT3 triaxial accelerometer for the assessment of physical activity. Med Sci Sports Exerc 2004; 36: 518–24.
13. Unutmaz G, Tekin Koruk S, Sert C. Determination of changes in the basal metabolic rate and body composition of patients with chronic active and inactive hepatitis B infection using bioelectrical impedance analysis. Turk J Med Sci 2012; 42: 237–43.
14. Ucok K, Aycicek A, Sezer M, Genc A, Akkaya M, Caglar V et al. Aerobic and anaerobic exercise capacities in obstructive sleep apnea and associations with subcutaneous fat distributions. Lung 2009; 187: 29–36.
15. American College of Sports Medicine (ACSM). ACSM's guidelines for exercise testing and prescription. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p.59–62.
16. Gezmen Karadağ M, Aksoy M. The effect of omega-3 fatty acid supplementation on plasma orexin A, plasma fatty acids, and anthropometric measurements in patients with narcolepsy. Turk J Med Sci 2012; 42: 77–88.
17. Sevinç Ö, Bozkurt Aİ, Gündoğdu M, Baş Aslan Ü, Ağbuğa B, Aslan Ş et al. Evaluation of the effectiveness of an intervention program on preventing childhood obesity in Denizli, Turkey. Turk J Med Sci 2011; 41: 1097–105.
18. Aydın S, Gemalmaz A, Nayır T, Özkan S. Which predicts the cardiovascular risk best in elderly metabolic syndrome patients: ATP III or IDF? Turk J Med Sci 2011; 41: 125–9.
19. Üçok K, Dane Ş, Gökbel H, Akar S. Prevalence of exercise-induced bronchospasm in long distance runners trained in cold weather. Lung 2004; 182: 265–70.
20. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005; 26: 511–22.
21. Kocyiğit H, Aydemir Ö, Ölmez N, Memiş A. SF-36'nın Türkçe için güvenilirliği ve geçerliliği. Ege Fizik Tedavi ve Rehabilitasyon Derg 1999; 12: 102–6.
22. Shiely JC, Bayliss MS, Keller SD, Tsai C, Ware JE. SF-36 health survey annotated bibliography: first edition (1988–1995). Boston: The Health Institute, New England Medical Center; 1996.
23. Ware JE Jr. SF-36 health survey update. Spine (Phila Pa 1976) 2000; 25: 3130–9.
24. Paksoy Erbaydar N, Bilir N, Özcebe LH, Vaizoğlu S, Aslan D. Evaluation of health-related quality of life of women living in a city center in the east of Turkey. Turk J Med Sci 2011; 41: 307–16.
25. Thibault R, Le Gallic E, Picard-Kossovsky M, Darmaun D, Chambellan A. Assessment of nutritional status and body composition in patients with COPD: comparison of several methods. Rev Mal Respir 2010; 27: 693–702.

26. Tashkin DP, Detels R, Simmons M, Liu H, Coulson AH, Sayre J et al. The UCLA population studies of chronic obstructive respiratory disease. XI. Impact of air pollution and smoking on annual change in forced expiratory volume in one second. Am J Respir Crit Care Med 1994; 149: 1209–17.

27. Chhabra SK, Vijayan VK, Vasu T. Inhaled formoterol versus ipratropium bromide in chronic obstructive pulmonary disease. Indian J Chest Dis Allied Sci 2006; 48: 97–102.

28. Aalbers R, Ayres J, Backer V, Decramer M, Lier PA, Magyar P et al. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled, 3-month trial. Eur Respir J 2002; 19: 936–43.

29. Cazzola M, Donner CF. Long-acting beta2 agonists in the management of stable chronic obstructive pulmonary disease. Drugs 2000; 60: 307–20.

30. Burdet L, de Muralt B, Schutz Y, Fitting JW. Thermogenic effect of bronchodilators in patients with chronic obstructive pulmonary disease. Thorax 1997; 52: 130–5.

31. Cazzola M, Segreti A, Stirpe E, Appodia M, Senis L, Matera MG. Energy expenditure and impact of bronchodilators in COPD patients. Respir Med 2010; 104: 1490–4.

32. Newnham DM, Grove A, McDevitt DG, Lipworth BJ. Subsensitivity of bronchodilator and systemic b2 adrenoceptor responses after regular twice daily treatment with eformoterol dry powder in asthmatic patients. Thorax 1995; 50: 497–504.

33. Bossenbroek L, de Greef MH, Wempe JB, Krijnen WP, Ten Hacken NH. Daily physical activity in patients with chronic obstructive pulmonary disease: a systematic review. COPD 2011; 8: 306–19.

34. Cazzola M, Biscione GL, Pasqua F, Crigna G, Appodia M, Cardaci V et al. Use of 6-min and 12-min walking test for assessing the efficacy of formoterol in COPD. Respir Med 2008; 102: 1425–30.

35. Neder JA, Fuld JP, Overend T, Thirlwell J, Carter R, Stevenson R et al. Effects of formoterol on exercise tolerance in severely disabled patients with COPD. Respir Med 2007; 101: 2056–64.

36. Liesker JJ, Van De Velde V, Meysman M, Vincken W, Wollmer P, Hansson L et al. Effects of formoterol (Oxis Turbuhaler) and ipratropium on exercise capacity in patients with COPD. Respir Med 2002; 96: 559–66.

37. Wadbo M, Löfdahl CG, Larsson K, Skoogh BE, Tornling G, Arweström E et al. Effects of formoterol and ipratropium bromide in COPD: a 3-month placebo-controlled study. Eur Respir J 2002; 20: 1138–46.

38. Belza B, Steele BG, Hunziker J, Lakshminaryan S, Holt L, Buchner DM. Correlates of physical activity in chronic obstructive pulmonary disease. Nurs Res 2001; 50: 195–202.

39. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA 1994; 272: 1497–505.

40. Wilson D, Parsons J, Wakefield M. The health-related quality-of-life of never smokers, ex-smokers, and light, moderate, and heavy smokers. Prev Med 1999; 29: 139–44.

41. Raguso CA, Luthy C. Nutritional status in chronic obstructive pulmonary disease: role of hypoxia. Nutrition 2011; 27: 138–43.