Evaluation of thyroid hormone levels and somatomedin-C (IGF-1) in patients with chronic obstructive pulmonary disease (COPD) and relation with the severity of the disease

Funda COŞKUN, Ercüment EGE, Esra UZASLAN, Dane EDİGER, Mehmet KARADAĞ, Oktay GÖZÜ

Uludağ Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Bursa.

ÖZET

Kronik obstrüktif akciğer hastalığı (KOAH) olan olgularda tiroid hormon ve somatomedin-C (IGF-1) düzeylerinin değerlendirilmesi ve hastalığın ağırlık derecesi ile ilişkisi

Kronik obstrüktif akciğer hastalığı (KOAH), yaygınlığından dolayı günümüzde önemli bir mortalite ve morbidite nedenidir. Araştırmamızda KOAH'lı olgularda serumda tiroid hormonlarının ve somatomedin-C [insülin benzeri büyüme faktörü (IGF-1)] düzeylerinin hastalığın ağırlık derecesi ile ilişkisini incelemeyi amaçladık. Çalışmaya 61 KOAH olgusu alındı. Kontrol grubunu; herhangi bir hastalığı bulunmayan 20 sağlıklı olgu oluşturdu. Olguların aynı gün içinde arteryel kan gazları ve hormon düzeyleri için kanları alınarak, solunum fonksiyon testleri yapıldı. Ölçülen hormon düzeyleri hasta grup (grup 1) ile kontrol grubu (grup 2) arasında karşılaştırıldı. Grup 1 ve grup 2 arasında tiroid hormon değerlerinden tiroid stimüle edici hormon ve serbest T3 düzeylerinde anlamlı fark bulunmazken, çalışma grubunda serbest T4 düzeyi istatistiksel olarak anlamlı yüksek saptandı (p< 0.01). IGF-1 ortalama değerleri grup 1'de istatistiksel olarak anlamlı düşük saptandı (p< 0.05). "Global Initiative for Chronic Obstructive Lung Disease (GOLD)" kriterlerine göre olgular üç gruba ayrılarak (hafif-orta, ağır, çok ağır) karşılaştırıldığında hafif-orta derecede KOAH'lı olgularla, çok ağır KOAH'lı olgular arasında serbest T3 ve IGF-1 düzeyleri arasında istatistiksel olarak anlamlı farklılık bulundu (p< 0.05). KOAH'lı olgularda hastalığın ağırlık derecesine göre hormon düzeylerinde değişiklikler olmaktadır. Gelecekte hormon replasman tedavilerinin KOAH'lı olguların tedavisinde yer alabileceği düşünülebilir. Bunu saptamak için daha geniş hasta gruplarının olduğu çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *KOAH, tiroid hormonları, IGF.*

Yazışma Adresi (Address for Correspondence):

Dr. Funda COŞKUN, Uludağ Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı 16050

BURSA - TURKEY

e-mail: fundacoskun@gmail.com

SUMMARY

Evaluation of thyroid hormone levels and somatomedin-C (IGF-1) in patients with chronic obstructive pulmonary disease (COPD) and relation with the severity of the disease

Funda COŞKUN, Ercüment EGE, Esra UZASLAN, Dane EDİGER, Mehmet KARADAĞ, Oktay GÖZÜ

Department of Chest Disease, Faculty of Medicine, Uludag University, Bursa, Turkey.

Chronic obstructive pulmonary disease (COPD) has recently become a significant cause of mortality and morbidity. In the present study, we aimed to investigate the relationship between the severity of the disease and levels of serum thyroid hormones and somatomedin-C [Insulin-Like Growth Factor (IGF-1)]. Sixty one COPD cases (group 1) were enrolled. Control group (group 2) consisted of 20 healthy individuals. Blood samples were obtained for the analysis of arterial blood gases and hormone levels and respiratory function tests were performed on the same day. Measured hormone levels were compared between group 1 and group 2. Among thyroid hormone levels, there was no significant difference in thyroid stimulating hormone and free T3 between group 1 and 2 whereas free T4 levels were significantly higher in group 1 (p< 0.01). Additionally, mean IGF-1 levels were significantly lower in group 1 (p< 0.005). When three groups, classified according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, were compared, significant differences were observed between mild-moderate COPD cases and severe patients with respect to free T3 and IGF-1 levels (p< 0.05). Hormone levels in COPD patients change depending on the severity of the disease. In the future hormone therapies can use for the COPD treatments. Further studies with larger sample sizes are required to confirm our conclusions.

Key Words: *COPD, thyroid hormones, IGF.*

Hormones take part in respiratory control via peripheral chemoreceptors or by their local affects on the lungs and the airways (1). In chronic obstructive pulmonary disease (COPD) patients, respiratory muscles are required to work more efficiently than in normal individuals in order to establish a sufficient respiration. Changes in the serum hormone levels of COPD patients adversely affect functions of respiratory muscles (2). The management of COPD patients has particularly focused on primary organ dysfunction. However, decreased effort capacity in COPD patients affecting their life quality could not be explained solely by primary organ dysfunction. Several studies advocate that dysfunction of peripheral muscles is caused by dyspnea and markedly decreased effort capacity (3). Reduced muscle function is an obvious result of reduced muscle mass in COPD patients. An association has been proposed between increased systemic inflammatory response and fat-free muscle mass (4).

The exact relationship between thyroid hormones and anabolic hormones is yet to be identified. Decreased thyroid hormone levels have been associated with hypoventilation. Accompanying hypoventilation in addition to existing airway damage in COPD patients will increase the severity of the disease. Some studies reported decreased levels of growth hormone (GH) and insulin-like growth hormone (IGF-1) in COPD cases (5,6). This is thought to worsen the condition by further decreasing the respiratory muscle function.

In our study we aimed to compare the levels of thyroid hormones and IGF-1 levels of COPD patients with healthy controls. We also investigated the relation between the severity of COPD and hormone levels. The present study was designed based on the hypothesis that hormonal insufficiency in COPD patients would further increase the severity of the disease.

MATERIALS and METHODS

Sixty-one COPD cases (group 1) that were not receiving systemic steroid therapy and admitted to outpatient clinics or ward of lung diseases and tuberculosis department between October-July

2004 were enrolled. Patients with endocrinological disorder (a known thyroid disease or previous thyroid surgery, any other endocrine system disease), patients on systemic steroid therapy or displaying an infection profile (fever, leucocytosis, consolidation area on performed chest X-ray) and using long term oxygen therapy were excluded from the study. Group 2 consisted of 20 healthy individuals, whose written consents were obtained from themselves or relatives. The study was initiated after obtaining approval of the ethics committee.

Arterial blood gas measurements were taken on the same day with the respiratory function tests. Serum thyroid hormones in addition to the serum levels of IGF-1 were measured in Pharmacology Laboratory of Uludag University Faculty of Medicine. In all patients and control subjects, free T3, free T4, thyroid stimulating hormone (TSH) and IGF-1 measurements were obtained. Hormone measurements were made by 5 mL venous blood obtained during morning fasting. IGF-1 was measured using solid-phase enzyme linked chemiluminescent immunometric assay in IMMULITE Analizer® (USA). Other hormone levels were measured using enzyme immunoassay method in ADVİA Centaur® (USA) device.

Pulmonary function tests were performed by same technician using SpiroAnalyser ST 300 according to acceptable manoeuvre (7). In the same day, 2 mL arterial blood samples were drawn from the radial arteries using heparin injector. Arterial blood gas measurements were conducted within 15 minutes using Chiron Diagnostics (USA) device.

Disease severity of the patients were evaluated based on the criteria of Global Initiative for Chronic Obstructive Lung Disease (GOLD) according to respiratory function tests.

Statistical Analysis

Statistical analyses were performed using SPSS 11.0 package programme. Mann Whitney U test was used to compare the groups. Correlation analysis was also performed. A p value < 0.05 was considered significant. Values are expressed as mean ± SD.

RESULTS

Sixty-one cases of group 1 (46 male, 15 female) found eligible for the study protocol and 20 subjects as the group 2 (10 male, 10 female) were included in the study. Demographic characteristics of group 1 are presented in Table 1.

Age, gender and body mass index (BMI) were not found to be statistically different between two groups ($p > 0.05$).

TSH and T3 levels of group 1 and 2 were not found to be significantly different, however, T4 levels displayed a significant difference ($p < 0.01$) (Table 2, Figure 1). Mean IGF-1 levels of the groups were found to be statistically different ($p < 0.05$) (Table 3, Figure 2).

Cases were divided into three groups according to GOLD criteria and the association between the severity of disease and hormone levels was investigated. In comparison of three groups formed according to GOLD criteria, free T3 and IGF-1 levels were found to be significantly different between mild-to-moderate and very severe COPD (Figure 3,4; Table 4). Pulmonary function tests of group 1 are presented Table 5.

Table 1. Demographic characteristics of groups.

	Group 1 (mean ± SE)	Group 2 (mean ± SE)
Age (year)	63.4 ± 1.04	61.2 ± 1.2
Sex (M/F)	46/15	10/10
BMI (kg/m^2)	27.9 ± 0.5	26.3 ± 0.7
Duration of illness (year)	11.9 ± 1.3	
Smoking duration (year)	31.7 ± 1.9	

BMI: Body mass index.

Table 2. Tyhroid hormone levels (mean ± SE).

	Group 1	Group 2
TSH (IU/mL)	1.02 ± 0.11	1.0 ± 0.0
Free T3 (pg/mL)	3.2 ± 0.1	3.2 ± 0.08
Free T4 (ng/dL)	1.2 ± 0.03*	1.07 ± 0.06*

* $p < 0.01$

TSH: Thyroid stimulating hormone.

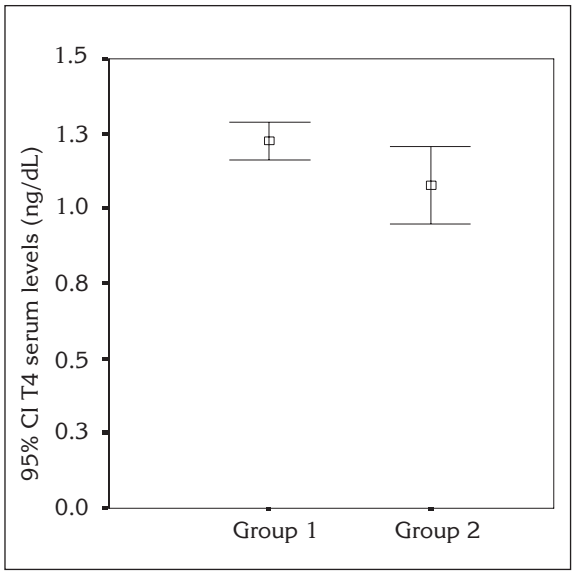

Figure 1. Free T4 levels of COPD patients and controls.

Table 3. IGF-1 levels (mean ± SE).

	Group 1	Group 2
IGF-1 (ng/mL)	117.2 ± 5.5*	191.3 ± 22.5*

* p< 0.01

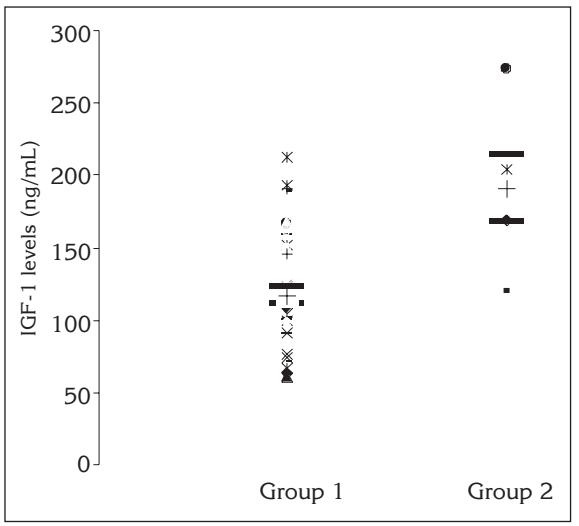

Figure 2. IGF-1 levels of COPD patients and controls.

We found positive correlation between PaO_2 and free testosterone in group 1. Also hypoxemic patients (PaO_2< 50 mmHg) has lower serum levels of IGF-1 than the other patients in group 1. We found negative correlation between forced expiratory volume in 1 second (FEV_1) and free T4.

DISCUSSION

Accompanying hypoventilation in addition to existing airway damage in COPD patients will increase the severity of the disease. Some studies reported decreased levels of GH, IGF-1 in COPD cases (5,6). This is thought to worsen the condition by further decreasing the respiratory muscle function.

In our study we aimed to compare the levels of thyroid hormones and IGF-1 levels of COPD patients with healthy controls. We also investigated the relation between the severity of COPD and hormone levels.

In this study serum free T4 levels were found to be increased and IGF-1 levels were found to be decreased in COPD patients compared to healthy controls. Also we found negative correlation between free T4 levels and FEV_1. Serum free T3 and IGF-1 levels were found to be significantly decreased in very severe COPD patients compared to mild-to-moderate COPD patients.

There is not a sufficient amount of data regarding GH and IGF-1 levels of COPD patients. IGF-1 levels tend to be lower in stabile COPD cases. Decreased levels are thought to be related with suppressed GH axis. Studies are available investigating IGF-1 levels in COPD cases (8-10). In COPD, little is known about circulating GH or IGF-1 concentrations. Some authors find a decrease in GH or IGF-1, others an increase. An increase of GH might reflect a nonspecific response of the body to stress (for instance, hypoxaemia). In accordance with the other studies, IGF-1 levels were found to be significantly decreased in our study.

Nevertheless, high levels of GH in hypoxic COPD patient groups have been demonstrated in a previous study (8). We found lower serum levels of IGF-1, which is an active metabolite of GH, in hypoxic cases.

The association between IGF-1 levels and muscle strength has been investigated. A positive cor-

Table 4. Hormone levels of groups formed according to GOLD criteria (mean ± SE).

	Mild-Moderate COPD (n= 10)	Severe COPD (n= 24)	Very severe COPD (n= 27)
TSH (IU/mL)	1.1 ± 0.2	1.1 ± 0.2	0.5 ± 0.2
Free T3 (pg/mL)	3.4 ± 1.2*	3.04 ± 0.1	2.7 ± 0.3*
Free T4 (ng/mL)	1.2 ± 0.04	1.3 ± 0.1	1.3 ± 0.08
IGF-1 (ng/mL)	123.6 ± 7.0**	116.2 ± 9.3	84.9 ± 9.5**

* p< 0.05

** p< 0.01

TSH: Thyroid stimulating hormone.

Table 5. Pulmonary function tests of group 1.

		Predicted (%)
	Mean ± SE	Mean ± SE
Forced vital capacity (FVC) (L)	2.2 ± 0.1	63.8 ± 2.2
Forced expiratory volume in 1 second (FEV_1) (L/sn)	1.4 ± 0.1	50.01 ± 2.55
FEV_1/FVC (%)	60.6 ± 1.7	

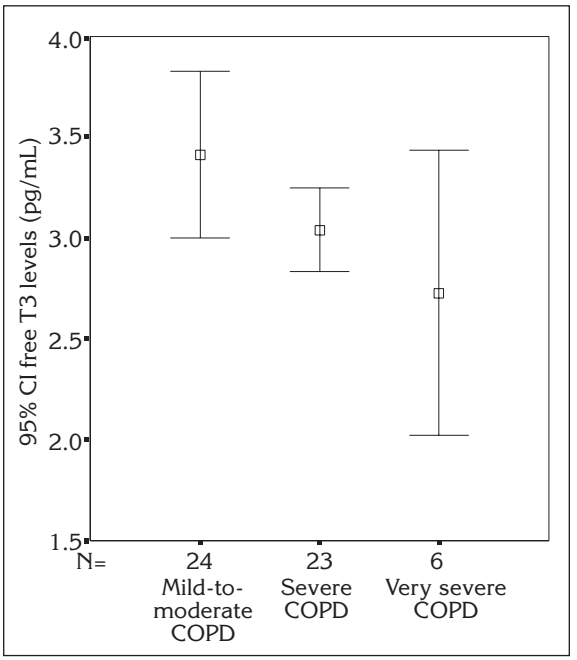

Figure 3. Free T3 levels of COPD cases according to the disease severity.

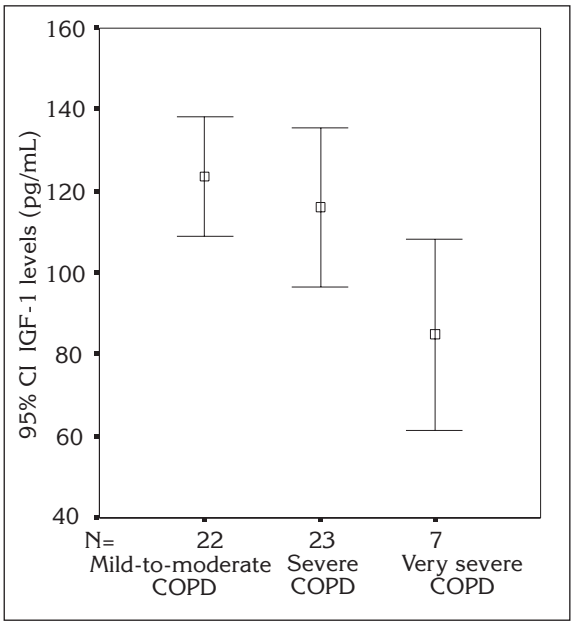

Figure 4. IGF-1 levels of COPD cases according to the disease severity.

relation has been found between IGF-1 and quadriceps muscle strength which was suggested to implicate the role of IGF-1 levels in the development of peripheral muscle weakness in COPD cases. Some authors advocate that low levels of IGF-1 might be increasing the severity of the disease particularly in COPD patients by adversely affecting the respiratory muscles (9). Decreased levels of IGF-1, together with decreased peripheral muscle strength perhaps provide the major source of dyspnea. In their study, Debigare et al. investigated hormone levels, cross-sectional area of moderate-tension muscle and the ratios of catabolic/anabolic factors and they reported higher ratios of IL-6/IGF-1 in cases with lower cross-sectional area. Whereas these cases had significantly lower levels of dihydroepiandrestenedione sulfate (DHEA-S) compared to control group. Debigare et al. in-

terpreted these results as increased catabolism and decreased anabolism in COPD patients. In our study IGF-1 levels of COPD patients were significantly lower. We did not examine the muscle strength of our cases. Therefore, we are unable to have a conclusion about the affects of low serum levels of IGF-1 on the muscle strengths of our cases.

Studies have been directed towards administration of GH in the treatment of COPD considering the association between low levels of GH and its metabolite IGF-1 and systemic problems (5,6,11,12). One of our purposes of this study is to provide scientific data to hormone therapy which would play a role in the treatment of COPD in the future. Controlled study on GH supplementation has been published, which however did not reveal any functional benefits. Before GH supplementation can be advised as part of the treatment in COPD, further controlled studies must be performed to investigate its functional efficacy.

Studies demonstrate increased muscle IGF-1 levels by increased IGF-1 mRNA expression (13,14). These studies have been directed particularly in elder patients to increase muscle strength through the administration of anabolic hormones. The effects of hormone replacement are apparent displaying physiologic mechanisms of the GH. Administration of anabolic hormones together with GH in COPD patients has caused significant differences (15).

Thyroid hormones constitute important elements of metabolic processes. The prevalence of thyroid dysfunction in COPD and its role in pulmonary cachexia has not been extensively studied. So far, there is no evidence that thyroid function is consistently altered in COPD, except perhaps in a subgroup of patients with severe hypoxaemia. Further research is required to more extensively study the underlying mechanisms and consequences of disturbed thyroid function in this subgroup of COPD patients.

Hugli et al. reported normal levels of thyroid hormones in 11 clinically stabile COPD patients with normal weight (16). Dimopouleu et al. found normal levels of thyroid hormones in their patients with COPD. They measured serum total T3, total T4, resin T3 uptake and reverse T3 and TSH levels. Ratio of total T3 and T4 has been used as a marker for the peripheral conversions of thyroxine to T3. In patients with FEV_1 values below 50%, a positive correlation was found between the ratio of total T3/T4 and PaO_2 levels (17). In this study, hypoxemia appears to be the determinant of peripheral thyroid hormone metabolism which deserves further investigations to reveal whether this is an inappropriate adaptation mechanism in COPD cases. We found a significant difference between free T4 levels of COPD patients and controls. COPD cases were also divided into three groups according to FEV_1 values on the basis of GOLD criteria. Free T3 levels of mild-to-moderate COPD cases (FEV_1 > 50%) were significantly higher compared to free T3 levels of patients with very severe COPD (FEV_1 < 30%).

Bratel et al. investigated neuroendocrin functions in 12 male patients with stabile hypoxemic COPD receiving long-term oxygen supplementation following a treatment for four months (18). In this study low FEV_1 levels were found to be associated with low TSH levels. Free T3 levels have been found to be reduced by 20% in patients with chronic hypoxemia receiving long-term oxygen supplementation. The degree of airway obstruction has been associated with TSH levels. In our study, free T4 levels were significantly higher in patients with severe COPD and cut-off value for free T4 in patients having FEV_1 values below 70% was found to be 1.14 in roc curve analysis (95% CI, 0.567-0.829).

Okutan et al. compared 32 COPD patients with 15 controls in which they found pulmonary function tests and partial oxygen pressures significantly lower and T3 levels to be higher (19). In our study free T4 levels of COPD patients were found higher than normal subjects. Also we found negative correlation between forced expiratory volume in 1 second (FEV_1) and free T4. We found relationship between free T4 and severity of disease. Maybe this result is depending on study group size. Also it may be using different measurement methods.

In conclusion, systemic response to chronic disease in COPD patients might cause hormonal imbalance which in turn affects the severity of the disease. The severity of hypoxia in COPD patients causes alterations in thyroid function tests and IGF-1 levels. In our study, free T4 levels were higher; IGF-1 levels were lower in the comparison of COPD cases with controls. Hormone replacements increase the exercise capacity by increasing body mass together with the increase in fat-free muscle mass, which improves life quality by reducing morbidity. We found relationship between hormone levels and severity of disease. The results of this study suggests that GH supplementation may begin to be considered part of the available ergogenic arsenal for lean body mass increase and structural and functional improvement of skeletal muscle in COPD. Also we suggest that determine thyroid function tests at severe and very severe COPD patients and if find any deficiency it may be replacement.

We believe that our study contributes to the literature regarding the applicability of hormone therapy.

REFERENCES

1. *Cherniack NS. Control of breathing in COPD. In: Cherniack NS (ed). Chronic Obstructive Pulmonary Disease. Philadelphia: WB Saunders Company, 1991: 117-26.*
2. *Creutzberg EC, Casaburi R. Endocrinological disturbances in chronic obstructive pulmonary disease. Eur Respir J 2003; 22(Suppl 46): 76-80.*
3. *Meek PM, Schwartzstein RM, Adams L, et al. Dyspnea, mechanisms, assessment, and management: A consensus statement. American Thoracic Society. Am J Respir Crit Care Med 1995; 159: 321-40.*
4. *Schols AMWJ, Buurman WA, Staal van den Brekel AJ, et al. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax 1996; 51: 819-24.*
5. *Pape GS, Friedman M, Underwood LE, Clemmons DR. The effects of growth hormone on weight gain and pulmonary function in patients with chronic obstructive pulmonary disease. Chest 1991; 99: 1495-500.*
6. *Burdet L, Muralt B, Schultz Y, et al. Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. Am J Respir Crit Care Med 1997; 156: 1800-6.*
7. *Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319-38.*
8. *Scalvini S, Volterrani M, Vitacca M, et al. Plasma hormone levels and haemodynamics in patients with chronic obstructive lung disease. Monaldi Arch Chest Dis 1996; 51: 380-6.*
9. *Debigare R, Marquis K, Cote CH, et al. Catabolic/anabolic balance and muscle wasting in patients with COPD. Chest 2003; 124: 83-9.*
10. *Spruit MA, Gosselink R, Troosters T, et al. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-1. Thorax 2003; 58: 752-6.*
11. *Suchner U, Rothkopf MM, Stanislaus G, et al. Growth hormone and pulmonary disease. Metabolic effects in patients receiving parenteral nutrition. Arch Intern Med 1990; 150: 1225-30.*
12. *Iioka Y, Tatsumi K, Sugito K, et al. Effects of insulin-like growth factor on nitrogen balance during hypoxic exposure. Eur Respir J 2002; 20: 293-9.*
13. *Lewis MI, Horvitz GD, Clemmons DR, Fournier M. Role of IGF-1 and IGF-binding proteins within diaphragm muscle in modulating the effects of nandrolone. Am J Physiol Endocrinol Metab 2002; 282: 483-90.*
14. *Urban RJ, Bodenburg YH, Gilkison C, et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Am J Physiol 1995; 269: 820-6.*
15. *Brill KT, Weltman AL, Gentili A, et al. Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. J Clin Endocrinol Metab 2002; 87: 5649-57.*
16. *Hugli O, Frascarolo P, Schutz Y, et al. Diet-induced thermogenesis in chronic obstructive pulmonary disease. Am Rev Respir Dis 1993; 148: 1479-83.*
17. *Dimopoulou I, Ilias I, Mastorakos G, et al. Effects of severity of chronic obstructive pulmonary disease on thyroid function. Metabolism 2001; 50: 1397-401.*
18. *Bratel T, Wennlund A, Carlstrom K. Impact of hypoxaemia on neuroendocrine function and catecholamine secretion in chronic obstructive pulmonary disease (COPD). Effects of long-term oxygen treatment. Respir Med 2000; 94: 1221-8.*
19. *Okutan O, Kartaloglu Z, Onde ME, et al. Pulmonary function tests and thyroid hormone concentrations in patients with chronic obstructive pulmonary disease. Med Princ Pract 2004; 13: 126-8.*