Can impairments of thyroid function test affect prognosis in patients with respiratory failure?

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ÖZET

Tiroid fonksiyon testi bozuklukları solunum yetmezliği olan hastaların prognozunu etkiler mi?

Tiroid dışı organ disfonksiyonlarında tiroid fonksiyon testi (TFT) bozuklukları saptanabilir ve bunların başında kronik obstrüktif akciğer hastalığı (KOAH)'ndaki akut solunum yetmezliği (SY) gelir. Bu çalışmada; (i) SY olan olgularda TFT bozukluklarını değerlendirmek, (ii) TFT sonuçlarını SY olmayan kontrol grubu ile karşılaştırmak, (iii) tiroid disfonksiyonunun SY'nin klinik gidişine ve prognozuna etkilerini araştırmak amaçlandı. TFT parametreleri, SY olan 65 hastada (yaş ortalaması 65.0 ± 10.0, 49'u erkek) değerlendirildi ve akciğer hastalığı olup SY bulunmayan 18 hasta (yaş ortalaması 64.4 ± 9.8, 13'ü erkek) ile karşılaştırıldı (p> 0.05). Tümünde arteryel kan gazı analizleri, serbest T3 (sT3), serbest T4 (sT4) ve TSH düzeyleri ölçüldü. TFT bozuklukları SY olan 34 (%52.3) hastada ve SY bulunmayan 8 (%44.4) hastada saptandı. Her iki grupta da en sık bulgu, TFT parametrelerinden en az birinde azalma olmasıydı (sırasıyla, %43.1'e karşı %44.4). Solunum yetmezliği grubunda; TFT sonuçları ile cinsiyet, yaş, tanı ve ek hastalıklar arasında anlamlı ilişki saptanmadı. Ancak sT3 ve sT4 düşük olanlarda, invaziv mekanik ventilasyon gereksinimi TFT normal olanlara göre daha fazlaydı (sırasıyla, p= 0.001 ve p= 0.003). Hastanedeki mortalite oranları da, hem sT3 hem de sT4 düşük olanlarda diğerlerinden daha yüksekti (sırasıyla, p= 0.006 ve p= 0.01). SY olan hastalarda, TFT bozukluklarının SY olmayanlardan daha sık gözlenmediği sonucuna vardık. Yine de, düşük sT3 ve sT4 düzeyleri, invaziv mekanik ventilasyon gereksinimini ve mortaliteyi arttırmaktadır.

Anahtar Kelimeler: *Tiroid fonksiyon testi, KOAH, solunum yetmezliği, tiroid disfonksiyonu, mortalite.*

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SUMMARY

Can impairments of thyroid function test affect prognosis in patients with respiratory failure?

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Thyroid function test (TFT) impairments can be detected in extrathyroidal dysfunction, primarily in chronic obstructive pulmonary disease (COPD) with acute respiratory failure (RF). The aims of this study were to: (i) evaluate TFT impairments in patients with RF, (ii) compare TFT results to a control group without RF and (iii) assess the effects of thyroid dysfunction on clinical outcome and prognosis of RF. The TFT parameters were assessed in 65 patients (65.0 ± 10.0 years, 49 males) with RF and compared to 18 patients (64.4 ± 9.8 years, 13 males) with lung disease and no RF (p> 0.05). Arterial blood gas analysis, free T3 (FT3), free T4 (FT4) and TSH levels were all measured. The impairments of TFT were demonstrated in 34 (52.3%) patients with RF and 8 (44.4%) patients without RF (p> 0.05). The most common finding was a decrease in at least one of the TFT parameters in both groups (43.1% vs. 44.4%, respectively). In RF group, there was no significant association between TFT results and gender, age, diagnosis and co-morbid disease. However, need for invasive mechanical ventilation was higher both in patients with low FT3 and low FT4 when compared to those with normal TFT results (p= 0.001 and p= 0.003, respectively). In-hospital mortality rate was also higher both in the patients with low FT3 and low FT4 than the others (p= 0.006 and p= 0.01, respectively). We conclude that TFT impairments are not observed more frequently in patients with RF when compared to the patients without RF. However, low FT3 and FT4 levels increase the rates of invasive mechanical ventilation and mortality.

Key Words: *Thyroid function test, COPD, respiratory failure, thyroid dysfunction, mortality.*

Endocrine disorders can lead to a variety of respiratory abnormalities (1). Hypothyroidism may result in respiratory failure (RF) due to depression of the respiratory drive, upper airway obstruction, and decrease in alveolar ventilation and lung volumes (1-4). Hyperthyroidism may cause shortness of breath secondary to increased minute ventilation due to stimulation of the respiratory drive (5). Further, both hypothyroidism and hyperthyroidism can cause reversible respiratory muscle weakness (6,7).

Changes in serum thyroid hormone levels are also observed in extrathyroidal disorders with reduced triiodothyronine (T3) and/or thyroxine (T4) levels, whereas thyroid-stimulating hormone (TSH) levels are usually normal. This condition is known as "Euthyroid Sick Syndrome" and is observed in a variety of clinical conditions such as chronic obstructive pulmonary disease (COPD), diabetic ketoacidosis, malignancies, cardiovascular diseases, renal failure, liver diseases, sepsis, collagen vascular diseases, peripheral artery diseases and acute cerebrovascular diseases (8-10).

In normal population, 80% of T3 in the circulation is produced by 5-deiodination of T4 in tissues. The activity of 5-deiodinase is reduced in 25-50% of the hospitalized patients with chronic diseases and this reduction in the levels of T3 generally correlates with the severity of underlying disease (11).

The reductions in T3 and T4 levels are also associated with a defect in binding of T4 to thyroxin-binding globulin. Oleic acid released from injured tissues prevents this binding of T4, seen especially in severe life-threatening conditions with higher mortality rates (8,10,12).

The abnormalities of TSH are detected in 15% of the patients hospitalized for extrathyroidal disorders (13). It was suggested that one of the re-

asons of these abnormalities may be the abrupt discontinuation of glucocorticoid and dopamine therapy, which results in transient increase in secretion of endogenous thyrotropin-releasing hormone and resolves two-five days after improvement of the disease. However, recovery may take a long time in patients receiving glucocorticoid and dopamine therapy (14,15).

As thyroid dysfunctions correlate with the severity of underlying disease, we hypothesized that higher rates of thyroid function test (TFT) abnormalities (decrease and/or increase in at least one of the thyroid hormone levels) can be detected in patients hospitalized for respiratory failure compared to those with less severe disease and no RF. Besides, any changes in thyroid hormone levels observed in patients with RF can be associated with worse clinical outcome and increased risk of death, that is indicate poor prognosis. The aims of the present study were, therefore, to evaluate the changes in thyroid functions in patients with RF and, to assess the effect of this alteration on the clinical outcome and prognosis. We also compared TFT results to a control group without RF.

MATERIALS and METHODS

Sixty-five consecutive patients referred to the respiratory intensive care unit (ICU) of chest disease department with a diagnosis of RF which was secondary to COPD in most cases, were included in this prospective study (RF group). Eighteen patients with lung disease, but have no respiratory failure were enrolled consecutively as a control group (non-RF group). The study and control groups were age and sex matched, hospitalized during the same period of time and besides none of them had primary thyroid disease (e.g. hypo or hyperthyroidism) on admission. Co-morbid diseases (cardiovascular, gastrointestinal, urinary tract and other endocrine diseases) and use of medications (i.e., iodine, lithium, amiodarone, corticosteroid, and dopamine) that could affect the thyroid function test results were recorded in all patients.

Arterial blood samples were obtained by percutaneous arterial puncture of femoral artery at room air and at rest, were analyzed by a gas analyzer (Ciba Corning, 238 pH-Blood gas analyzer, UK). The criteria of RF was PaO_2 < 55 mmHg [hypoxemic (Type I) RF] and/or $PaCO_2$ > 45 mmHg [hypercapnic (Type II) RF] in arterial blood gas analysis at room air (16). In our ICU, the patients who had hypoxemic RF and did not respond to the supplemental oxygen inhalation were mechanically ventilated. Besides, the patients who had hypercapnic RF and decompensate respiratory acidosis were treated with mechanical ventilation.

The baseline measurements of TFT were performed in RF group and non-RF group on admission. Venous blood samples were collected at 9 am; sera were separated and stored at -70°C until the process. TSH, free T3 (FT3) and free T4 (FT4) analysis were done in all samples (Immunometric assay, IMMULITE 2000 Automated Analyzer, USA) and the normal ranges were considered as 0.3-5.5 µIU/mL, 3.2-12.6 pg/mL and 0.8-1.8 ng/dL, respectively. The presence and type of TFT impairments were assessed. Besides, in RF group, TFT results were compared to gender, age, diagnosis, co-morbid diseases; type, treatment and mortality rate of RF.

The study was approved by the local ethics committee and informed consent was obtained from the patients or their surrogates.

Statistical Analysis

For parametric measures Student's t-test was used. Analysis of categorical variables was done using Chi-Square Test and Fisher's Exact Test. Pearson's correlation coefficient was used to analyze the relationship between the results of TFT and gender, age, diagnosis, co-morbid diseases; type, treatment modalities and mortality rate of RF. A value of $p < 0.05$ was considered significant for all statistical analysis.

RESULTS

The study population consisted of 65 patients in RF group (mean age 65.0 ± 10.0 years, 49 males). Primary cause of RF was COPD exacerbation in 51 (78.5%) patients. Thirty-two patients had co-morbid diseases, 87.5% of which were associated with cardiovascular system (CVS) disease. Fourteen (21.5%) patients had hypoxemic RF, 14 (21.5%) patients had hypercapnic and 37 (56.9%) patients had both hypoxemic

and hypercapnic RF. There was no patient with chronic respiratory failure and all the patients without COPD had acute respiratory failure. Out of 51 patients with COPD, 13 (25.5%) had acute and 38 (74.5%) had acute on chronic respiratory failure. Supplemental oxygen inhalation was given to 41 (63.1%) patients, whereas 24 (36.9%) patients required invasive mechanical ventilation. The in-hospital mortality rate in the RF group was 29.2%.

The non-RF group consisted of 18 patients (mean age 64.4 ± 9.8 years, 13 males) who were age and sex matched and the majority of them (66.7%) were hospitalized for COPD exacerbations. Six (33.3%) patients had co-morbid diseases, most of them with CVS disease. The patients in this group all survived. Demographic characteristics of RF and non-RF groups are shown in Table 1.

Table 1. Demographic characteristics of RF and non-RF groups.

	RF group (n= 65)	Non-RF group (n= 18)
Gender (male/female) (n)	49/16	13/5
Age (mean ± SD) (yrs)	65.0 ± 10.0	64.4 ± 9.8
Diagnosis*		
COPD	51 (78.5%)	12 (66.7%)
Pneumonia	10 (15.4%)	5 (27.8%)
Pulmonary embolism	2 (3.1%)	1 (5.5%)
Postoperative RF	1 (1.5%)	-
Obesity-hypoventilation	1 (1.5%)	-
Co-morbid disease*,#		
None	33 (50.8%)	12 (66.7%)
CVS disease	28 (43.1%)	5 (27.8%)
DM	8 (12.3%)	1 (5.5%)
Chronic renal failure	1 (1.5%)	-
Scleroderma	1 (1.5%)	-
Bladder tumour	1 (1.5%)	-

* Values are expressed as the number of patients (%).
# Seven patients in RF group had more than one co-morbid disease.
RF: Respiratory failure, COPD: Chronic obstructive pulmonary disease, CVS: Cardiovascular system, DM: Diabetes mellitus.

There was no significant difference between the mean values of TSH, FT3, FT4 in RF and non-RF groups (Table 2). The impairments of TFT (increase or decrease in FT3, FT4, and TSH alone or with combination) were detected in 34 (52.3%) patients in RF group and 8 (44.4%) patients in non-RF group and the difference between two groups was not statistically significant. The respiratory failure indicators (PaO_2, $PaCO_2$, PaO_2/FiO_2 or type of RF) in the RF group were not significantly different between the patients with increased and decreased thyroid hormone levels. In RF group, at least one of the thyroid function parameters decreased in 28 patients (43.1%), whereas eight patients (44.4%) had a decrease in non-RF group. Table 3 summarizes the TFT impairments in both groups.

The relationship between TFT results and gender, age, diagnosis, co-morbid disease and mortality rate was evaluated in the RF group and no significant association was observed. However, the need for invasive mechanical ventilation during hospitalization was higher in patients with TFT impairments when compared to those with normal TFT results (52.9% vs. 19.4%, respectively, p= 0.005) (Table 4). There were also decreased FT3 (58.3% vs. 17.1%, respectively, p= 0.001) or FT4 (29.2% vs. 2.4%, respectively, p= 0.003) results in mechanically ventilated patients than the ones who did not need mechanical ventilation. Moreover, the in-hospital mortality rate was higher in the patients with low FT3 than

Table 2. Thyroid function test levels of RF and non-RF groups.*

	RF group (n= 65)	Non-RF group (n= 18)
FT3 (pg/mL)#	2.4 ± 0.7 (0.8-4.0)	2.7 ± 0.6 (1.7-3.7)
FT4 (ng/dL)#	1.3 ± 0.4 (0.4-2.6)	1.2 ± 0.3 (0.7-1.8)
TSH (μIU/mL)#	1.3 ± 1.2 (0-6.3)	1.5 ± 1.0 (0.1-2.8)

* There was no significant difference between two groups (p> 0.05).
# Values are expressed as means ± SD (range).
RF: Respiratory failure, FT3: Free triiodothyronine, FT4: Free thyroxine, TSH: Thyroid stimulating hormone.

Table 3. TFT results of RF and non-RF groups.

	RF group (n= 65)	Non-RF group (n= 18)
Normal*	31 (47.7%)	10 (55.6%)
Decrease*		
FT3	11 (16.9%)	4 (22.2%)
FT4	2 (3.1%)	-
TSH	5 (7.7%)	3 (16.7%)
FT3 + FT4	6 (9.2%)	-
FT3 + TSH	4 (6.2%)	-
FT4 + TSH	-	1 (5.5%)
Increase*		
FT4	5 (7.7%)	-
FT4 + TSH	1 (1.5%)	-
Changes in TFTs (total)*	34 (52.3%)	8 (44.4%)

* Values are expressed as the number of patients (%).
RF: Respiratory failure, FT3: Free triiodothyronine, FT4: Free thyroxine, TSH: Thyroid stimulating hormone, TFT: Thyroid function test.

the patients with normal FT3 (57.9% vs. 21.7%, respectively, p= 0.006). Also the mortality rate increased in patients with low FT4 compared to the ones with normal FT4 results (21.6% vs. 4.3%, respectively, p= 0.01). Thyroid function impairments did not correlate with the presence of hypoxemic RF, mean PaO_2 levels or rates of PaO_2/FiO_2. However, the percentage of patients with a decrease in FT4 level was higher in hypercapnic RF patients than the others (29.4% vs. 6.3%, p= 0.03).

Euthyroid sick syndrome was found in 18 patients (27.7%) of RF group and in 4 patients (22.2%) of non-RF group (p> 0.05). There was no significant relationship between demographic features, clinical outcome and euthyroid sick syndrome.

There was no association between TFT parameters and medications affecting TFTs (i.e., corticosteroid and dopamine). The impairments of TFT were found in 63.0% (17/27) of the patients on corticosteroid therapy, all patients (6/6) on dopamine therapy and 71.9% (23/32) receiving neither of them. None of the patients in non-RF group was given these medications.

Table 4. Comparison of TFT results with the characteristics of the patients in RF group.

	Abnormal TFT (n= 34)	Normal TFT (n= 31)
Gender (male/female) (n)	23/11	26/5
Age* (yrs)	63.8 ± 8.0	66.5 ± 11.8
Diagnosis**		
COPD	25 (73.6%)	26 (83.9%)
Pneumonia	7 (20.6%)	3 (9.7%)
Pulmonary embolism	1 (2.9%)	1 (3.2%)
Postoperative RF	1 (2.9%)	-
Obesity-hypoventilation	-	1 (3.2%)
Co-morbid disease**,#	9 (26.5%)	13 (41.9%)
PaO_2* (mmHg)	46.4 ± 11.3	46.7 ± 10.0
$PaCO_2$* (mmHg)	53.6 ± 13.4	59.7 ± 19.4
PaO_2/FiO_2*	202.7 ± 32.2	212.2 ± 37.3
Hypoxemic RF**	9 (26.5%)	5 (16.1%)
Hypercapnic RF**	7 (20.6%)	7 (22.6%)
Hypoxemic and hypercapnic RF**	18 (52.9%)	19 (61.3%)
Invasive mechanical ventilation**,##	18 (52.9%)	6 (19.4%)
Mortality**	13 (38.2%)	6 (19.4%)

* Values are expressed as means ± SD.
** Values are expressed as the number of patients (%).
# Five patients in RF group and two patients in non-RF group had more than one co-morbid disease.
Chi-Square test was used for the statistical analysis. The need for invasive mechanical ventilation was higher in patients with abnormal TFT (p= 0.005).
RF: Respiratory failure, TFT: Thyroid function test, COPD: Chronic obstructive pulmonary disease.

DISCUSSION

This present study demonstrates that thyroid function impairments were observed in more than half of the patients (52.3%) with respiratory failure which was secondary to COPD. In the control group with lung disease and no respiratory failure, 44.4% of patients had TFT impairments. The most common finding was a decrease in at least one of the TFT parameters in both groups. Moreover, the need for invasive mechanical ventilation during hospitalization and in-hospital mortality rate were higher in the pati-

ents with low FT3 and FT4 levels. Thus, low TFT results on admission to ICU can be regarded as poor prognostic factors in the patients with RF.

Pechatnikov evaluated T3, T4 and TSH levels in patients with exacerbation of COPD and found a decrease in T3 (55.4%), T4 (13.9%), both T3 and T4 (20.8%) and, TSH (17.8%) levels (17). He hypothesized that this decrease represented a state of hypothyroidism which was secondary to COPD and did not require specific treatment. In our study, among 51 patients who had RF due to COPD exacerbation, 33.3% had a decrease in TSH, FT3 or FT4. In the previous studies, the association between hypothyroidism and respiratory failure was reviewed and need for excluding RF induced by hypothyrodism in patients with unexplained reason was expressed (18-20). Wawrzynska et al. found significant correlation between T3 and FT3 levels and PaO_2 in 22 patients with acute RF and, association between severe decrease in T3 level and poor prognosis (21). In another study, the levels of FT3 were correlated with the ratios of PaO_2/FiO_2 in patients with severe RF (22). We could not find any relationship between thyroid function impairments and the presence of hypoxemic RF, PaO_2 levels or rates of PaO_2/FiO_2. This may be explained by the presence of much younger patients and less severe RF in our study. However, the percentage of patients with a decrease in FT4 level was higher in hypercapnic RF patients than the others. Okutan et al. also evaluated the relationship between arterial blood gases, pulmonary function tests and TFTs in patients with stable COPD (23). There was a significant association between the values of $PaCO_2$ and FT3 in their COPD patients, whereas they could not find any correlation between TFT results and pulmonary function tests.

In our study, the patients with TFT impairments were more frequently treated with invasive mechanical ventilation when compared to those with normal TFT results. Furthermore, the in-hospital mortality rate was higher in the patients with low FT3 and FT4 levels. These findings are in agreement with those of Scoscia et al., who assessed thyroid functions in mechanically ventilated patients and found that FT3 level was the only factor significantly associated with an increased risk of death (22). Datta and Scalise also found that the incidence of hypothyroidism was 3% in patients with respiratory failure, receiving prolonged mechanical ventilation and failure to wean (24). Although they only assessed hypothyroidism in the patients, their results showed that low TFT levels can cause failure to wean. The data of these studies provide that low thyroid hormone level is a poor prognostic factor in patients with RF and should be measured on admission. It is known that thyroid hormone levels tend to decrease in severe acute and chronic diseases and this status has been considered as a transient adaptive process. Low thyroid hormones can cause RF by a depression of the respiratory drive and worsen the prognosis of the patients already having RF. Therefore, abnormal TFT results can be used as a marker of severity of the disease. The abnormalities in thyroid function test are transient and usually improve with the treatment of the underlying disease which causes respiratory failure. So, no specific treatment is required for the thyroid function abnormalities. In our study, six patients in RF group who had an increase in at least one of the TFT parameters all survived. However, we could not assess whether the increased thyroid hormone levels are good prognostic indicators because the number of patients was too small to make a definite comment.

It is known that glucocorticoid and dopamine therapy can affect the thyroid function tests. Therefore, we evaluated the effects of these agents on TFT impairments in our study population and found no statistical significance in TFT parameters between the patients given these drugs and the others. So, thyroid dysfunction can not be explained by the effect of the medicine in our study.

There are some limitations in our study. One of them is that we did not use any severity of classification system such as APACHE II scoring in this study. It should have been useful to measure the severity of the disease and to assess the relation of the ICU scoring system and thyroid function abnormalities. We did not evaluate the correlation between TFT results and duration of invasive mechanical ventilation or pulmonary

function tests. Besides, we could not perform follow-up visits especially in the study group, because some of the patients died and others could not come for the control visit as they were severely ill.

In conclusion, our study demonstrates that thyroid function test impairments can be observed in patients with respiratory failure and the majority of them are caused by a decrease in at least one of the thyroid function parameters. However, TFT impairments in RF are not more common than the patients without RF. These abnormalities tend to increase the treatment of RF with invasive mechanical ventilation and in-hospital mortality rate. Therefore, low TFT parameters can be predictors of poor prognosis in patients with respiratory failure and should be measured on admission. However, future studies comparing decreased thyroid hormone levels and other poor prognostic indicators (like albumin, ICU scoring systems) are required to highlight the importance of thyroid function parameters.

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REFERENCES

1. *Brussel T, Matthay MA, Chernow B. Pulmonary manifestations of endocrine and metabolic disorders. Clin Chest Med 1989; 10: 645-53.*
2. *Pelttari L, Rauhala E, Polo O, et al. Upper airway obstruction in hypothyroidism. J Intern Med 1994; 236: 177-81.*
3. *Choutet P, Lamisse F, Ginies G, et al. Laryngeal edema and alveolar hypoventilation as primary manifestations of hypothyroidism. Sem Hop 1980; 56: 782-4.*
4. *Schlenker EH, Burbach JA. The dystrophic hamster: An animal model of alveolar hypoventilation. J Appl Physiol 1991; 71: 1655-62.*
5. *Hellermann J, Kahaly G. Cardiopulmonary involvement in thyroid gland diseases. Pneumologie 1996; 50: 375-80.*
6. *Martinez FJ, Bermudez-Gomez M, Celli BR. Hypothyroidism. A reversible cause of diaphragmatic dysfunction. Chest 1989; 96: 159-63.*
7. *Siafakas NM, Alexopaulou C, Bouros D. Respiratory muscle function in endocrine diseases. Monaldi Arch Chest Dis 1999; 54: 154-9.*
8. *Di Napoli M, Reda G, Zannoni G, et al. The euthyroid sick syndrome. Its incidence and clinical significance in an internal medicine department. Minerva 1994; 85: 161-5.*
9. *Camacho PM, Dwarkanathan AA. Sick euthyroid syndrome. What to do when thyroid function tests are in critically ill patients. Postgrad Med 1999; 105: 215-9.*
10. *McIver B, Gorman CA. Euthyroid sick syndrome: An overview. Thyroid 1997; 7: 125-32.*
11. *Bermudez F, Surks MI, Oppenheimer JI. High incidence of decreased serum T3 concentration in patients with nonthyroidal disease. J Clin End Metabol 1975; 41: 27-40.*
12. *Slag MF, Morley JE, Elson MK, et al. Hypothyroxineemia in critically ill patients as a predictor of high mortality. JAMA 1981; 245: 43-5.*
13. *Spencer C, Eigen A, Shen D, et al. Specificity of sensitive assays of TSH used to screen for thyroid disease in hospitalized patients. Clin Chem 1987; 33: 1391-6.*
14. *Samuels MH, Luther M, Henry P, Ridgway EC. Effect of hydrocortisone on pulsatile pituitary glycoprotein secretion. J Clin End Metabol 1994; 78: 211-5.*
15. *Kaptein EM, Spencer CA, Kamiel MB, Nicoloft JT. Prolonged dopamine administration and thyroid hormone economia in normal and critically ill subjects. J Cli En Metabol 1980; 51: 387-93.*
16. *Grippi MA. Respiratory failure: An overview. In: Fishman AP, Elias JA, Fishman JA, Grippi MA, Kaiser LR, Senior RM (eds). Fishman's Pulmonary Diseases and Disorders. New York: McGraw-Hill Company, 1998: 2525-35.*
17. *Pechatnikov LM. Significance of hypophyseo-thyroid disorders in chronic obstructive bronchitis. Klin Med (Mosk) 1989; 67: 40-3.*
18. *Yamamoto T. Delayed respiratory failure during the treatment of myxedema coma. Endocrinol Jpn 1984; 31: 769-75.*
19. *Kubai S, Kida K, Mizuuchi T, et al. A case of primary hypothyroidism with repeated episodes of respiratory failure. Nippon Ronen Igakkai Zasshi 1991; 28: 58-62.*
20. *Rajagopal KR, Abbrecht PH, Derderian SS, et al. Obstructive sleep apnea in hypothyroidism. Ann Intern Med 1984; 101: 491-4.*
21. *Wawrzynska L, Sakowicz A, Filipecki S. Euthyroid sick syndrome in patients with respiratory failure. Pneumonol Allergol Pol 1996; 64(Suppl 2): 193-9.*
22. *Scoscia E, Baglioni S, Eslami A, et al. Low triiodothyronine (T3) state: A predictor of outcome in respiratory failure? Results of a clinical pilot study. Eur J Endocrinol 2004; 151: 557-60.*
23. *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.*
24. *Datta D, Scalise P. Hypothyroidism and failure to wean in patients receiving prolonged mechanical ventilation at a regional weaning center. Chest 2004; 126: 1307-12.*