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RESEARCH

RELATIONSHIP BETWEEN NON-THYROIDAL ILLNESS SYNDROME AND OBSTRUCTIVE SLEEP APNEA SYNDROME

ABSTRACT

Introduction: Obstructive sleep apnea syndrome(OSAS) and Non-Thyroidal Illness Syndrome(NTIS) are two separate disorders associated with inflammatory response to hypoperfusion/hypoxia.We investigated the presence of NTIS in subjects with OSAS and the relationship between thyroid hormone levels and the severity of OSAS.

Materials and Method: Study group composed of 146 subjects (52 male, 94 female), who underwent polysomnography and grouped as non-OSAS (AHI<5, n=22), mild-OSAS (5≤AHI<15, n=49) and moderate-severe OSAS (AHI≥15, n=75). Thyroid ultrasound was performed and plasma levels of thyroid hormones,C-reactive protein (hs-CRP), anti-thyroglobulin and anti-thyroid peroxidase antibodies were measured.

Results: Study population consisted of 146 subjects [52/94(F/M)] with a mean age of 45,9±9.8. Oxygen desaturation index (ODI), mean and minimum oxygen saturation ($minSaO_2$), time spent under SaO_2 of<90% and hs-CRP levels were statistically different between three groups (p<0.05). Ten patients (6F/4M; %13.3) were found to have NTIS, all of them were in the moderate-severe group. Serum average TSH, free-T3 and free-T4 levels were not significantly different (p>0.05) in OSAS patients compared to non-OSA subjects.Mean age and ODI were negatively correlated with free-T4 levels (r:-189, p<0.05), while $minSaO_2$ was positively correlated with free-T4 levels.Only age was negatively correlated with free-T3 levels.

Conclusion: NTIS is more frequent in OSAS patients and associated with the severity of OSAS. NTIS may be a predicting factor for mortality and severity of OSAS.In order to show the relationship between NTIS and OSAS, further randomized controlled studies are needed before and after treatment of OSAS.

Key Words: Aged; Euthyroid Sick Syndromes; Obstructive Sleep Apnea Syndrome.

ARAŞTIRMA

HASTA ÖTROİD SENDROM İLE OBSTRÜKTİF UYKU APNE SENDROMU ARASINDAKİ İLİŞKİ

ÖZ

Giriş: Obstrüktif Uyku Apne Sendromu (OUAS) ve Hasta Ötroid Sendrom (HÖS) Hipoksi/reperfüzyon sonucu gelişen inflamasyon cevabının eşlik ettiği iki farklı hastalıktır. OUAS'lu hastalarda HÖS varlığı ve troid hormon seviyeleriyle OUAS derecesi arasındaki ilişki incelenmiştir.

Gereç ve Yöntem: Çalışmaya 146 olgu alındı. Tüm olgulara polismonografi uygulanarak Apne Hipopne İndekslerine (AHI) göre OUAS olmayan (AHI<5, n=22), hafif derece-OUAS (5≤AHI<15,n=49) ve orta-ağır derece OUAS (AHI≥15, n=75) olarak 3 gruba ayrıldı.Tiroid ulrason, troid hormonları, HsCRP, anti-troglobin ve anti-troid peroksidaz antikorları ölçüldü.

Bulgular: Çalışmaya alınan 52 kadın ve 94 erkek olgunun ortalama yaşı 45.9±9.8 idi.Oksijen desaturasyon indeksi (ODI), gece ortalama ve en düşük oksijen saturasyonu($minSaO_2$), SaO_2<%90 altında geçen süre ve HsCRP değerleri her üç grup arasında istatistiksel anlamlı olarak farklı bulundu (p<0.05). HÖS tesbit edilen on hastanın (6K/4E, %13.3) hepsi orta-ağır OUAS grubundaydı. Serum ortalama TSH, serbest-T3 ve serbest-T4 seviyeleri OUAS'lu grupta OUAS olmayan gruba göre düşük olsa da fark anlamlı değildi (p>0.05). Olguların yaşı ve ODI değerleri serbest T4 değerlerine göre negativ yönde korelesyon gösterirken (r:-189, p<0.05), $minSaO_2$ positif yönde koreleydi. Serbest T3 ise sadece yaş ile negatif korelasyon gösteriyordu.

Sonuç: OUAS'lu olgularda HÖS sıklığı hastalığın ağırlık derecesine bağlı olarak (AHI>15) daha fazla görülmektedir. OUAS'lu olgularda HÖS varlığı, hastalığın ağırlık derecesi ve mortalite göstergeci olarak yorumlanabilir. İleride yapılacak çalışmalar hastalığın tedavisinin mortalite hızlarına etkisini inceleyecektir.

Anahtar Sözcükler: Yaşlı; Hasta Ötroid Sendrom; Obstruktif Uyku Apne Sendromu.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive, complete or incomplete upper airway obstructions resulting in intermittent hypoxia during sleep (1). Re-oxygenation and re-perfusion attacks caused by intermittent hypoxia leading to activation of inflammatory cells and increased release of cytokines particularly interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and generation of reactive oxygen species (2). Breathing cessation, intermittent hypoxia, continuous arousals and sleep fragmentation could activate both the systemic sympathetic and hypothalamic-pituitary axis (HPA) limbs of the stress system. Sympathetic activation and HPA dysregulation have also been proposed as potential triggering mechanisms for systemic inflammatory response in OSAS (3,4) and to be responsible for metabolic outcomes. Although mechanistic links are still controversial, OSAS has many serious consequences mostly related to the increased risk of cardiovascular diseases due to oxidative stress and inflammation.

Non-thyroidal illness syndrome (NTIS) is characterized by low circulating levels of thyroid hormone but inappropriately low or normal thyroid stimulating hormone (TSH) and diminished TSH pulsatility, suggesting the presence of central hypothyroidism (5). The condition has also been called as euthyroid sick syndrome. NTIS can be induced by a number of conditions including sepsis, trauma, burns, surgery, and cardiovascular disease (6). There is growing evidence about the role of inflammatory cytokines (especially IL-1, IL-6, TNF-α) in NTIS pathogenesis (5,7) most of which play important roles as mediators of inflammatory response in hypoperfusion/hypoxia, oxidative stress and HPA dysregulation as well as in OSAS. Thyroid hormone levels in NTIS negatively correlate with the severity of the underlying disease and low thyroxin (T_4) levels are known to be associated with increased mortality (6-8). However the dilemma of whether or not to treat these patients remains unresolved (7). OSAS and NTIS can be two co-morbid conditions while one may lead to the other. In this study we investigated the presence of NTIS in OSAS patients and the relationship between the thyroid hormone levels and the severity of OSAS.

MATERIALS AND METHOD

Study Subjects

Two hundred and five subjects with sleep disorders based on the presence of witnessed apnea, snoring or daytime sleepiness were enrolled for the study. Subjects with existing thyroidal disease, acute or chronic other medical conditions or who were on medications were excluded. Study subjects underwent polysomnography, thyroid ultrasound and laboratory tests including complete blood count, complete metabolic panel, thyroid hormones, high sensitivity C-reactive protein (hs-CRP), anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) antibodies. Fifty-nine patients who had abnormal thyroid ultrasound (USG) and/or laboratory results showing abnormal hepatic/renal functions, abnormal complete blood count and antibody positivity were excluded. Finally, 146 subjects were included in the study. Our study was conducted between September, 2009 and April, 2010. The study complied with the declaration of Helsinki and was approved by the local research ethics committee. Informed consent was obtained from all subjects.

Methods and Definitions

Study subjects participated in a full montage diagnostic polysomnography. Polysomnography (Compumedics E Series®) records were analyzed by one physician, and reviewed using Profusion PSG 3 software. The diagnosis and severity of obstructive sleep apnea was based on the definitions and cut-offs for apnea-hypopnea index (AHI) recommended by the American Academy of Sleep Medicine in 2007. Study population was divided into three groups according to the apnea-hypopnea indices as non-OSA (AHI<5), mild OSAS (5≤AHI<15) and moderate-severe OSAS (AHI ≥ 15).

Blood samples were collected after an overnight fasting for complete blood count, basic metabolic panel, thyroid function test (TFT) including free tri-iodothyronine (fT_3), free thyroxin (fT_4), thyrotrophic hormone (TSH), and anti-thyroid antibodies, anti-TG and anti-TPO. The serum fT_3, fT_4, TSH, Anti-TPO and Anti-TG levels were measured by ECLIA (electro-chemiluminescence immunoassay) method with a commercially available kit (Immulite 2000, Bio DPC, Los Angeles, CA, USA) with normal ranges for TSH: 0.27-4.2 mIU/mL, fT_4: 0.93-1.7 ng/mL, fT_3: 2.0-4.4 pg/mL, Anti-TPO: 5-60 U/mL, and for Anti-TG: 10-115 IU/mL. High sensitivity CRP levels were measured by highly sensitive immunoturbidimetric assay method. The hs-CRP serum levels < 3 mg / L were accepted to be within the normal range. The participants who had less than 0.93 ng/ml of fT_4 and/or less than 2.0 pg/mL of fT_3 levels with normal TSH, negative anti-TG and anti-TPO antibodies, and normal thyroid USG were considered as having NTIS.

Statistical Analyses

Data analysis was performed by using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL, United States). Whether the continuous variables were distributed normally or not was determined by Shapiro Wilk test. Levene test was used for evaluation of homogeneity of variances. The mean differences among groups were compared by using One-Way ANOVA, otherwise, Kruskal Wallis test was applied for comparisons of the median values. Nominal data were analyzed by Pearson's Chi-square test. The degree of association between continuous variables was analyzed by Spearman's correlation test. The variables, which had a significant correlation with thyroid hormones, were evaluated in the linear regression analysis models to assess the independent associations. A p value less than 0.05 was considered statistically significant.

RESULTS

The study population consisted of 146 subjects with a mean age of 45.9 ±9.8 years. There were 52 females (F) and 94 males (M). The distribution of the subjects (F/M) among the groups was 8/14 for non-OSA group, 17/32 for mild OSAS and 27/48 for moderate – severe OSAS. The ratio of genders, mean age, the number of former smokers and the amount of alcohol consumption were not statistically different between the groups. However body mass indices (BMI-kg/m^2) were higher in moderate-severe OSAS patients compared to non-OSA group (p=0.03). On the other hand apnea-hypopnea indices, oxygen desaturation indices (ODI), minimum oxygen saturation (SaO_2) levels during night and time spent (minutes) under SaO_2 <90% (T 90) and hs-CRP levels were statistically different between the three groups, sleep efficiency and total sleep time and daytime arterial blood gas analysis (PO2, PCO2, SaO2) were similar (Table 1). In post-hoc analysis with Tukey's test; Moderate-severe OSA group was significantly different from non-OSA and mild OSA group (p<0.01), while there was no significant difference between non-OSA and mild OSA group.

Mean serum TSH levels were found to be lower in the OSAS subjects (1.59 and 1.87 mIU/mL respectively) than in the non-OSA subjects (1.99 mIU/mL), but the difference was not statistically significant between the groups. Mean fT_4 and fT_3 levels in moderate-severe OSAS group (1.19 ± 0.21 ng/mL, 3.12 ± 0.46 pg/mL) were lower than the non-OSAS (1.27 ng/mL, 3.17 pg/mL) and mild OSAS groups (1.25 ng/mL, 3.24 pg/mL) but the difference was not significant. Non-thyroidal illness syndrome was not determined in either the non-OSAS or the mild OSAS group, but all of the 10 (13.3%) patients (6 F / 4 M) with NTIS were in the moderate-severe OSAS group (AHI: 40.5 ± 8.2 (SEM) (18-102). Six

Table 1— Polysomnographic Findings and Blood Sample Analysis of The Groups

	Non-OSAS (n = 22)	Mild OSAS (n = 49)	Moderate-Severe OSAS (n = 75)	P
Sleep Efficiency (%)	89.1 (68.5-97.5)	88.6 (61.6-99.3)	89.6 (65.6-99.3)	0.42
Total Sleep Time (minute)*	372.7 ± 44	370.1 ± 44.7	377.1 ± 42.2	0.67
AHI	2.4 (0.3-4.6)	9 (5.3-14.9)	37.2 (15.1-110.6)	**<0.001**
ODI	1.7 (0-6.7)	6.6 (1.1-12.1)	37.2 (11.2-108.5)	**<0.001**
T90 (minute)	0.28 (0-6)	3.8 (0-99)	17.6 (0-85)	**<0.001**
Mean. SaO_2	94 (92-97)	94 (88-97)	91 (72-96)	**<0.001**
Min. SaO_2	89 (85-93)	86 (69-92)	79 (53-92)	**<0.001**
pO_2*	83.1± 9	80.5± 9.5	79.9 ± 9.7	0.48
pCO_2*	34.9 ± 3.8	36 ± 3.6	36.5 ± 3	0.22
SaO_2	96.2 (93.2-98.8)	95.3 (84.5-98.5)	95.5 (88.5-98.3)	0.60
fT3*	3.2 ± 0.5	3.2 ± 0.5	3.1± 0.5	0.38
fT4*	1.3± 0.1	1.3 ± 0.1	1.2 ± 0.2	0.13
TSH*	2 ± 0.7	1.6 ± 0.9	1.9 ± 0.9	0.10
hs-CRP	1.73 (0.15-6.86)	2.3 (0.3-7.2)	3.9 (0.3-10.4)	**<0.05**
Anti-T	13.1 (9-50.7)	13.3 (4-67.4)	13.2 (9-88.7)	0.59
Anti-M	5.3 (4-14.2)	6.6 (0.2-33.3)	7.2 (4-44.9)	0.71

*Distribution is normal.

Table 2— Correlation Between Thyroid Hormones and Patient Related Factors

		fT3	fT4	TSH
Age	rho	-0,254**	-0,189*	-0.043
	p	0,002	0,022	0,604
BMI	rho	-0,052	-0,133	0,124
	p	0,53	0,109	0,136
pO_2	rho	0,077	0,139	-0,034
	p	0,399	0,129	0,714
pCO_2	rho	0,092	0,018	0,002
	p	0,31	0,843	0,984
sO_2	rho	0,109	0,103	-0,032
	p	0,227	0,256	0,726
AHI	rho	-0,046	-0,146	0,031
	p	0,578	0,079	0,713
T90	rho	-0,098	0	0,104
	p	0,241	0,991	0,214
ODI	rho	-0,074	-0,189*	0,052
	p	0,394	0,027	0,546
Min_O_2_sat	rho	0,148	0,275**	-0,071
	p	0,076	0,001	0,399
Mean_O_2_sat	rho	0,077	0,101	-0,057
	p	0,354	0,226	0,491
HsCRP	rho	-0,137	-0,06	0,038
	p	0,117	0,495	0,661

of the 10 patients with NTIS had an AHI>30. One patient had NTIS with low free T_3 and T_4 levels, but all the others had NTIS with low T_4 levels only.

We also wanted to see the degree of association between fT3, fT4, TSH and the parameters known to affect inflammation for all subjects. We found that age and ODI were significantly and negatively correlated with fT4 levels, while Minimum SaO_2 of the night was positively correlated. Only age was also negatively correlated with fT3 levels. There were no correlations with other parameters (Table 2).

Linear regression analysis model was used to assess the independent association between FT4 and ODI: After adjustment for age, ODI was significantly associated with FT4 (beta= -0.001, 95%CI: -0.003 to 0, p = 0.046).

Discussion

In this study we investigated the relationship between the severity of OSAS and the presence of non-thyroidal illness syndrome (NTIS), both of which likely have common etiopathogenesis corresponding to inflammation and stress. We showed that non-thyroidal illness syndrome (NTIS) was more frequent in moderate-severe OSAS patients with AHI >15 than non-OSA or mild OSA subjects (AHI≤15). Obstructive sleep apnea is an increasingly prevalent condition which is related to serious cardiovascular and endocrine complications such as atherosclerosis, hypertension and diabetes. There is growing experimental and clinical evidence about the role of hypoxia in the inflammatory response which has been proposed for this causal relation (9,10). Sleep fragmentation secondary to arousal caused by apneic episodes has been shown to activate the hypothalamic-pituitary-adrenal axis, mediate the reaction to acute physical-psychological stress and disrupt secretion of certain hormones (11-13). In numerous studies, arousals have been associated with elevated cortisol and catecholamine in patients with OSAS (3,11-14). In a study, corticotropin-releasing hormone (CRH) administration resulted in a higher corticotropin (ACTH) response in apneic patients suggesting that in non-distressed subjects, HPA axis activity is lower due to hyposecretion of hypothalamic CRH (15). Hypoxia can also have a direct effect on HPA and peripheral endocrine functions via central neurotransmitters (12,13). Proposed mechanisms to explain hormonal abnormalities (low free T3 and/or free T4, normal and mostly low TSH levels) in

NTIS are multi-factorial and related to the severity of disease. Bratel et al (14) found that severity of airway obstruction is associated with reduced basal and stimulated TSH levels in patients with chronic obstructive pulmonary disease. In our study, patients with OSAS had lower TSH levels than subjects with AHI less than 5, although this finding was not statistically significant. The serum TSH levels at the lower limit of normal range in NTIS may be explained by central inhibition of pituitary TSH production. In a recent study patients with NTIS had lower TRH-mRNA levels in hypothalamic paraventricular nuclei (16). Van De Berghe and colleagues established elevation in TSH, T_4, T_3 levels respectively after TRH administration to NTIS patients (17). These findings suggest that hypothalamic dysfunction can be the reason for NTIS as well in OSAS patients. Moreover, hypothalamic TRH production and other TRH related events can be induced by cytokines and glucocorticoids. Diurnal variation of glucocorticoid concentrations were supposed to affect pituitary response to TRH and be responsible for diurnal changes in TSH. Benker G claimed that high cortisol levels in Cushing's disease suppress pituitary response, as well as TSH and thyriod hormone levels (18). Many factors -discussed above- known to induce stress in OSAS (11-14), therefore stress induced hypercortisolemia may be the reason of NTIS in OSAS, especially in severe patients (AHI>30) with deeper hypoxemia.

The relationship between proinflammatory cytokines (particularly IL-1, IL-6 and TNF-α) and sleep disorders has been evaluated, as well as in NTIS, and some common results were observed. Trakada et al (11) demonstrated that IL-6 and TNF-a levels were significantly elevated in patients with sleep apnea and positively correlated with the severity of the disease. Vgontzas et al showed elevated levels of TNF-α and IL-6 in sleep apnea patients independent of obesity (19). On the other hand, elevated levels of TNF-α were related with many causative conditions for NTIS. Stoutard and colleagues (20) showed TSH suppression after short term IL-6 infusion while Mastorakos G (21) showed that increased secretion or exogenous administration of IL-6 to humans were associated with excessive daytime sleepiness. Interleukin-1 is another crucial cytokine which is involved in physiological sleep regulation with a circadian pattern and also its level is known to be increased in sleep disorders (13). Hermus et al infused IL-1 to rats and showed a decrease in TSH, T3, T4 levels (22). There are a number of speculations for NTIS formation, the most popular one is the increased IL-1 levels which disrupt hormone production in the thyroid. In summary, inflammatory cytokines may play an important role in the pathogenesis of NTIS in patients with OSAS. This role should be elucidated by further studies, especially before and after treatment. We did not measure the cytokine levels; this is one of the limitations of our study. However we measured hs-CRP levels as a marker of inflammation and we found a significant difference between groups (p=0.03).

Thyroid hormone levels (free T3, T4) in NTIS are known to correlate with the severity of underlying disease. For example, in critically ill patients thyroxin levels of less than 4 Ìg/dl increases the risk of death to 50%, and accordingly when levels of T4 fall to less than 2 Ìg/dl, mortality increases even more, up to 80%. The decrease in serum T3 levels occurs in the acute phase and it persists in the chronic phase, whereas the drop in free T4 and TSH levels is associated with the prolonged phase of the illness (23,24). In our study, serum T4 levels were significantly lower in severe OSAS patients while T3 levels were not. However, it is still controversial whether these changes reflect a protective mechanism or a maladaptive process during prolonged illness. Our results may be associated with moderate to severe iodine deficiency which is still present in 27.8% of the Turkish population (25). Chronic iodine deficiency may lead to increased production of T3 by the thyroid gland as an adaptation mechanism. Accordingly, thyroid hormone levels should be investigated in iodine deficient areas. In our study none of the patients had hepatic or renal insufficiency that could alter type 1 deiodinase activity. The effects of cytokines on enzyme activities may also be the cause of thyroid hormone alterations. On the other hand in many studies, the thyroid autoimmunity has not been considered to have potential effects on serum thyroid hormone levels. In our study we measured anti-TPO and anti-TG levels and the patients with positive antibodies were excluded. Patients who had parenchymal heterogeneity in thyroid ultrasonography were also excluded despite normal laboratory tests, in order to eliminate any stages of acute or chronic thyroiditis.

Finally, treatment of NTIS has been shown to reduce mortality rates in a considerable number of studies although it is controversial. NTIS can be an indicator for mortality and severity of the disease in OSAS which may be used to assess response to therapy or possibly as a robust marker of disease severity. Further studies should be conducted to investigate the effects of treatment on mortality rates. In conclusion, we found that NTIS is more frequent in OSAS patients and is related to the severity of OSAS. Although there is no adequate data about the mechanism of NTIS in OSAS patients, we sug-

gest that NTIS may predict the severity/prognosis of OSAS. In order to show the relationship between NTIS and OSAS, further randomized controlled studies are needed, before and after treatment of OSAS.

REFERENCES

1. American Academy of Sleep Medicine: International Classification of Sleep Disorders: Diagnostic and Coding Manual. 2nd ed. Westchester IL. American Academy of Sleep Medicine, 2005. (ISBN:0-9657220-3-1).
2. Yamauchi M, Nakano H, Maekawa J, et al. Oxidative stress in obstructive sleep apnea. Chest 2005;127:1674–9. (PMID:15888845).
3. Cutler MJ, Swift NM, Keller DM, et al. Hypoxia-mediated prolonged elevation of sympathetic nerve activity after periods of intermittent hypoxic apnea. J Appl Physiol 2004;96: 754–61. (PMID:14555683).
4. Van Cauter E, Holmback U, Knutson K, et al. Impact of sleep and sleep loss on neuroendocrine and metabolic function. Horm Res 2007;67:2–9. (PMID:17308390).
5. Adler SM, Wartofsky L. The non-thyroidal illness syndrome. Endocrinol Metab Clin North Am 2007;36:657–72. (PMID:17673123).
6. Ronald M. Lechan. The dilemma of the Non-thyroidal illness syndrome. Acta Biomed 2008;79(3):165–71. (PMID:19260375).
7. De Groot LJ. Non-thyroidal illness syndrome is a manifestation of hypothalamic-pituitary dysfunction, and in view of current evidence, should be treated with appropriate replacement therapies. Crit Care Clin 2006;22:57–86. (PMID:16399020).
8. Rothwell PM, Lawler PG. Prediction of outcome in intensive care patients using endocrine parameters. Crit Care Med 1995;23:78–83. (PMID:8001391).
9. McNicholas WT, Bonsigore MR. Sleep apnea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 2007 Jan;29(1):156-78. (PMID:17197482).
10. Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome alterations in glucose metabolism and inflammation. Proc Am Thorac Soc 2008;5:207-17. (PMID:18250214).
11. Trakada G, Chrousos G, Pejovic S, VgontzasA. Sleep Apnea and its association with the Stress System, Inflammation, Insulin Resistance and Visceral Obesity Sleep Med Clin. 2007;2(2):251–61. (PMID:18516220).
12. Buckley TM, Schatzberg AF. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. J Clin Endocrinol Metab 2005;90:3106–3114. (PMID:15728214).
13. Entzian P, Linnemann K, Schlaak M, Zabel P. Obstructive sleep apnea syndrome and circadian rhythms of hormones and cytokines. Am J Respir Crit Care Med 1996;153:1080–6. (PMID:8630548).
14. Bratel T, Wennlund A, Carlström 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(12):1221-8. (PMID:11192959).
15. Opp M. Corticotropin-releasing hormone involvement in stressor-induced alterations in sleep and in the regulation of waking. Adv Neuroimmunol 1995;5:127–143. (PMID:7496608)
16. Filers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hyphothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal ilness. J Clin Endocrinol Metab 1997;82: 4032-36. (PMID:9398708).
17. Van den Berghe G, de Zegher F, Baxter RC, et al. Neuroendocrinology of prolonged critical illness: Effects of exogenous TRH and its combination with growth hormone secretagogues. J Clin Endocrinol Metab 1998;83:309-19. (PMID:9467533).
18. Benker G, Raida M, Olbricht T, Wagner R, Reinhardt W, Reinwein D. TSH secretion in Cushing's syndrome: relation to glucocorticoids excess,diabetes, goiter and sick euthyroid syndrome. Clin Endocrinol 1990;33:777-86. (PMID:2128925).
19. Vgontzas AN, Papanicolaou DA, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab 2000;85:1151–8. (PMID:10720054).
20. Stouthard JM, vander Poll T, Endert E, et al. Effects of acute and chronic IL-6 administration on thyroid hormone metabolism in humans. J Clin Endocrinol Metab 1994;79:1342-46. (PMID:7962327).
21. Mastorakos G, Chrousos GP, Weber JS. Recombinant interleukin-6 activates the hypothalamic–pituitary–adrenal axis in humans. J Clin Endocrinol Metab 1993;77:1690–4. (PMID:8263159).
22. Hermus RM, Sweep CG, van der Meer MJ, et al. Continuous infusion of IL-1 induces a non-thyroidal syndrome in the rat. Endocrinology 1992;131:2139-46. (PMID:1425414).
23. Plikat K, Langgartner J, Buettner R, et al. Frequency and outcome of patients with non-thyroidal illness syndrome in a medical intensive care unit. Metabolism 2007;56:239–44. (PMID:17224339).
24. Docter R, Krenning EP, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf) 1993;39:499-518. (PMID:8252737).
25. Erdoğan MF, Ağbaht K, Altunsu T, et al. Current iodine status in Turkey. J Endocrinol Invest. 2009;32(7):617-22. (PMID:19564718).