

# Hypothyroidism and Obstructive Sleep Apnea

Suhaila E. Al-Jawder<sup>1,2</sup> and Ahmed S. BaHammam<sup>1</sup>

<sup>1</sup>University Sleep Disorders Center, King Saud University, Riyadh,

<sup>2</sup>Department of Medicine, Salmaniya Medical Complex, Manama

<sup>1</sup>Saudi Arabia

<sup>2</sup>Kingdom of Bahrain

## 1. Introduction

Hypothyroidism is relatively a common disease worldwide. Overall prevalence in adults in the United States is 4.6%. (Golden et al., 2009) It can present as mild/subclinical form or overt hypothyroidism with a prevalence of 4.3% and 0.3% of adult populations, respectively. (Golden et al., 2009) Thyroid hormone deficiency has been linked to increased risk of cardiovascular morbidities and mortalities. (McQuade et al., 2011, Resta et al., 2004) Respiratory system like other body systems and organs is affected by hypothyroidism. The spectrum of diseases involvement can range from mild dyspnea to more severe and life-threatening respiratory failure. Several pathophysiological mechanisms are responsible for the compromise in the respiratory system including reduction in central respiratory drive, respiratory muscle weakness and sleep-related breathing disorders (SBD). (Duranti et al., 1993, Saaresranta and Polo, 2002, Curnock et al., 1999) Hypothyroidism is characterized by mucopolysaccharides accumulation in the dermis, hypopharynx, tongue and other tissues. (Skatrud et al., 1981, Orr et al., 1981) In its most severe form (myxedema), patients typically present with hypothermia, hypercapnia, hypotension and bradycardia. Both hypothyroidism and obstructive sleep apnea (OSA) share common signs and symptoms. Increased fatigue and sleepiness, decreased cognitive function, decreased libido, obesity and depressed mood are common findings in both disorders. (Grunstein et al., 1993, Misiolek M and 2007, Chan et al., 2010) Periorbital edema and pedal edema are other common findings in patients with either disorder. Nevertheless, snoring which is a hallmark of OSA is also reported in hypothyroid cases. (Misiolek M and 2007, Georgalas, 2011) The overlap between the two disorders may create a problem for the treating physician in differentiating both disorders and may result in a misdiagnosis or under-recognition of one of the disorders. Therefore, it is essential to consider both diseases in high risk patients and initiate the proper therapeutic plan accordingly. This chapter discusses how hypothyroidism interferes with respiratory physiology and then discusses the relationship between hypothyroidism and sleep disordered breathing.

## 2. Obstructive Sleep Apnea (OSA)

OSA is a disease characterized by repeated partial (hypopnea) or complete (apnea) collapse of the upper airway while asleep accompanied by surges in the sympathetic activity, cortical

arousals and episodes of hypoxia. (Chan et al., 2010) Patients usually present with complaints of excessive daytime sleepiness, un-refreshing sleep, fatigue or insomnia. Patients might have nocturnal awakenings with breathe holding, gasping, or choking. (Park et al., 2011, Madani and Madani, 2009) Very frequently, the bed partner report breathing interruptions, loud snoring or both during patient's sleep. The main risk factors for OSA are obesity, older age, family history, increasing neck circumference and male gender. (BaHammam et al., 2008, Tsara et al., 2010) Menopause is the main risk factor for women even after adjustment for age and body mass index (BMI). (Ancoli-Israel et al., 1989, Block et al., 1980) Other predisposing factors include craniofacial features, maxillomandibular malformation or adenotonsillar enlargements. (Johns et al., 1998, Moser and Rajagopal, 1987, Orr and Martin, 1981) The prevalence of OSA syndrome (AHI > 5/hour and excessive daytime sleepiness) is estimated to be 2% to 4% of adults. (Young et al., 2002, Punjabi, 2008) Epidemiologic data suggest that roughly 1 of every 5 adults has at least mild OSA and 1 of every 15 adults has at least moderate OSA. (Young et al., 2002) The National Sleep Foundation survey found that 26% of the population has a high probability of OSA. (Hiestand et al., 2006) It is always essential to identify and treat persons with OSA because of its strong association with several medical conditions, occupational and social consequences. Untreated OSA can result in increased risk of cardiovascular morbidities such as myocardial infarction, congestive heart failure, stroke, refractory hypertension, and cardiac arrhythmia. (Guilleminault et al., 1983, Logan and Bradley, 2010, Somers et al., 2008, Ehrmann et al., 2011) Furthermore, cognitive dysfunction, depression, impaired glucose tolerance, occupational and increased motor vehicle accidents are the other consequences. (Sateia, 2003, Kaplan, 1992, Horne and Reyner, 1999, Radun and Summala, 2004) Treatment with continuous positive airway pressure (CPAP) can help in restoring the airway and reversing the majority of the associated morbidities. (Jean-Louis et al., 2010, Ferini-Strambi et al., 2003)

### **3. Hypothyroidism and the respiratory system**

Respiratory system components (respiratory center, upper airway and lower respiratory system) can be affected by deficiencies in body hormones as well as excess hormonal secretion. (Saaresranta and Polo, 2002, Saaresranta and Polo, 2003, Behan et al., 2003, Takasaki and Hayashi, 1985) Thyroid hormone is one of the major body hormones. Its deficiency has been associated with multiple cardiovascular complications, respiratory failure and coma. (McQuade et al., 2011, Takamura et al., 2010, Behnia et al., 2000, Hall and Scanlon, 1979) The involvement of the respiratory system has resulted in a spectrum of clinical disorders including SBD, pulmonary hypertension, hypoventilation and severe respiratory failure. The following section explains the mechanisms through which hypothyroidism affect the respiratory system.

#### **Ventilatory drive**

Hypothyroidism is associated with diminished ventilatory drive for both hypoxia and hypercapnia. In animal models of induced hypothyroidism, a decrease in peripheral chemoreceptor response to hypoxia and hypercapnia has been observed. (Simsek et al., 2004) In humans, approximately, one third of the hypothyroid patients have a blunted

ventilatory response to hypoxia/hypercapnia. (Zwillich et al., 1975, Duranti et al., 1993, Massumi RA, 1964) Predictors of blunted ventilatory response in hypothyroidism have been identified as female gender and very high levels of thyrotropin ( $>90$  mIU/l). (Ladenson et al., 1988) It is the severe form of hypothyroidism that is associated with diminished ventilatory control. Cases of myxedema and severe hypothyroidism (thyroid ablation) were found to have a diminished hypoxic ventilatory drive that was reversible with hormonal replacement therapy. (Zwillich et al., 1975) However, diminished hypercapnic ventilator drive was only seen in myxedema cases and was not responsive to hormonal therapy. (Zwillich et al., 1975) In a case report of a patient with hypothyroidism, central sleep apnea with blunted ventilatory response to hypoxia but normal hypercapnic ventilatory response, treatment with thyroxine therapy have resolved the central apneas and restored the hypoxic drive. The normal hypercapnic ventilatory drive has doubled with thyroxine therapy. (Millman et al., 1983) Hypoxic ventilatory drive has a rapid response to thyroxine replacement than hypercapnic ventilator drive. It might be that the central chemoreceptors require longer duration of therapy or they sustain a long-term impairment. The use of intravenous thyroxine therapy was shown to improve both hypoxic and hypercapnic ventilatory drive within one week of therapy. (Duranti et al., 1993) Severe degrees of alveolar hypoventilation and coma have also been reported in cases of severe hypothyroidism (myxedema). (Behnia et al., 2000, Orr et al., 1981, Wall, 2000, Jordan, 1995)

Hypothyroidism is reported in 3% of difficult to wean mechanically ventilated patients. (Datta and Scalise, 2004) Despite this low rate, it is a potentially treatable cause and should be considered when evaluating patients who fail to wean. Successful weaning from ventilator following correction of hypothyroidism has been reported. (Pandya et al., 1989) Difficulty in weaning can be multifactorial in hypothyroid patients due to the multiple effects exerted by the hormone deficiency on different levels of the respiratory system.

### Upper respiratory tract

- **Mechanical Obstruction:** Enlargement of the thyroid gland (goiter) in the presence of hypothyroidism or euthyroid state can create a mass effect on the upper airway. (Deegan PC, 1997, De Felice et al., 2006, Eloy et al., 2007) particularly when resuming the supine position. Such mechanical obstruction becomes prominent and can be associated with severe apneas. (Teramoto et al., 1995) Progressive enlargement of the thyroid goiter can further lead to stridor and an emergency intervention might be required in such severe cases. (Deegan PC, 1997) Reports have showed improvement of OSA with thyroidectomy. (Agrama, 2011)
- **Soft Tissue Infiltration:** As a part of the generalized skin and soft tissue infiltration in hypothyroidism, the upper airway and particularly the pharynx gets narrowed. In hypothyroidism, mucopolysaccharides and proteins infiltrate the skin causing skin thickening, infiltrate the tongue causing enlargement and infiltrate the neck soft tissue resulting in variable degrees of upper airway obstruction. (Devdhar et al., 2007, Batniji RK, 2006, Watson and Pearce, 1949) Hypothyroidism also alters the myosin heavy chain profile specifically in the main dilator muscle the genioglossus muscle, which

results in compromising the muscle function. (Petrof et al., 1992) Despite these changes in upper airway structure and function, hypothyroidism per se is not an independent risk factor for OSA if other known risk factors as male gender and obesity are not present. (Pelttari et al., 1994) Upper airway obstruction in hypothyroid patients might not be very evident initially. During stressful situations, occult hypothyroidism can result in devastating outcomes such as in post-extubation upper airway obstruction following emergency intubation or post-operatively. Cases of severe emergency obstruction in undiagnosed hypothyroidism have been reported. (Sherry and Hutchinson, 1984, Stahl N, 1988)

### Lower respiratory tract

As with upper respiratory tract, the different structures of the lower respiratory tract can be affected to a variable degree with alterations in thyroid hormone levels.

- **Airways:** Very few studies have investigated airway diseases in hypothyroidism. In one study, patients with treated hypothyroidism were found to have more symptoms of breathlessness and wheeze. (Birring et al., 2003) And when evaluated by Methacholine challenge test, patients with treated hypothyroidism had more airways hyperreactivity than normal healthy individuals. Induced sputum showed higher levels of inflammatory cells, absolute neutrophil count, absolute lymphocyte count and increased levels of sputum interleukin-8 suggesting increased airway inflammation compared to control. (Birring et al., 2005)
- **The lung parenchyma:** The interstitium can also be affected in hypothyroidism; two cases of lung fibrosis have been reported in patients with severe hypothyroidism. Initiating therapy for hypothyroidism was associated with significant clinical and radiological improvement in lung fibrosis. (George et al., 2009)
- **Respiratory Muscles:** Both inspiratory and expiratory respiratory muscles are weakened in hypothyroidism in a direct linear relationship to the thyroid hormone level and it is reversible with thyroxine therapy. (Siafakas et al., 1992) Furthermore, thyroid deficient muscles have impaired free fatty acid utilization, which enhances their glycogen consumption, thereby reducing skeletal muscle endurance. (Baldwin et al., 1980) One of the major inspiratory muscles that are involved in hypothyroidism is the diaphragm. Diaphragm weakness can be very severe and associated with hypoventilation. (Martinez et al., 1989, Laroche et al., 1988)
- **Pulmonary Vasculature:** Both hyper/hypothyroidism has been associated with pulmonary arterial hypertension (PAH). (Li et al., 2007, Arroliga et al., 2000) A prevalence of 22-24% of hypothyroidism is reported in patients with PAH. (Curnock et al., 1999, Silva et al., 2009) It is thought that hypoxia/hypercapnia in hypothyroid patients is responsible for causing and worsening PAH. It is also known that both disorders are associated with autoimmune diseases, which raises the possibility of an immune pathophysiological mechanism. (Badesch et al., 1993, Chu et al., 2002)

## 4. Prevalence studies of hypothyroidism in OSA

The first case reporting an apneic episode in a patient with myxedema was published in 1964. (Massumi RA, 1964) Following that, studies have investigated further the prevalence

of OSA in hypothyroidism population and vice versa (Table 1). Overall, the prevalence of clinical hypothyroidism in patients diagnosed with OSA or referred to sleep centers with a clinical suspicion of OSA is not higher than the prevalence in the general population. The prevalence in patients evaluated by polysomnography for OSA is 0.7-3.4%, depending on the upper limit set for normal TSH, gender and age distribution of the studied samples. (Lin CC, 1992, Meslier et al., 1992, Winkelman JW, 1996, Kapur VK and BM, 1998, Winkelman et al., 1996) Kapur et al, reported a prevalence of 1.4% of subclinical hypothyroidism in OSA patients and this association was greater in females and those less than 50 years of age. (Kapur VK and BM, 1998) In a group of Taiwanese patients with OSA, a prevalence of 3.1% was reported despite using higher TSH level (>25 mIU/l) to define hypothyroidism. (Lin et al., 1992) The prevalence is also not significantly different in patients highly suspected to have OSA (1.5%) than those already diagnosed to have OSA by overnight sleep study (2.4%). (Skjoldt et al., 1999) This is similar to Winkelman and co-workers who reported a prevalence of 1.6% in patients suspected to have OSA and 2.9% in those confirmed to have OSA. (Winkelman et al., 1996) Other studies have reported a much higher prevalence. In a study of 78 overweight and obese adult patients referred to a sleep clinic, a prevalence rate of 11.5% was reported. (Resta O, 2004) The studied population was characterized by higher BMI, older age and more females. All these three variables are known risk factors for hypothyroidism, which might have resulted in a higher rate. (Sawin CT, 1979, Bilous and Tunbridge, 1988, Fox et al., 2008) Females with OSA have been reported to have higher rates of undiagnosed and diagnosed hypothyroidism. (Winkelman et al., 1996, Alotair and Bahammam, 2008) In clinical practice, these variables are important to consider when assessing the risk of hypothyroidism in patients with suspected or diagnosed OSA. Female gender, increased BMI and older age are also well established risk factors for hypothyroidism. (Sawin CT, 1979) This might explain the higher prevalence of hypothyroidism reported in some studies. (Resta O, 2004) Nevertheless, increased age and BMI are the main risk factors for OSA. (Punjabi, 2008, Hiestand et al., 2006) Thus, the co-existence of both diseases is expected and a high index of suspicion is required in high risk patients.

Some of the previous studies defined hypothyroidism as the presence of a high serum thyroid-stimulating hormone (TSH) level without commenting on thyroxine hormone level. This means that some of the patients thought to have hypothyroidism may actually have had subclinical hypothyroidism, which carries different therapeutic and prognostic implications (Miller and Husain, 2003, Winkelman et al., 1996, Pham and Shaughnessy, 2008). In a recent study, Bahammam et al. reported the prevalence of newly diagnosed clinical hypothyroidism as 0.4%, and the prevalence of newly diagnosed subclinical hypothyroidism as 11.1%. (Bahammam et al., 2011) In the non-OSA patients, the prevalence of newly diagnosed clinical hypothyroidism was reported as 1.4%, and the prevalence of newly diagnosed subclinical hypothyroidism as 4%. (Bahammam et al., 2011) The authors concluded that the prevalence of newly diagnosed clinical hypothyroidism was low; however, subclinical hypothyroidism was common among patients with OSA. In lieu of the uncertainty of the benefit achieved by treating subclinical hypothyroidism, the authors recommended not to perform routine thyroid function testing for OSA patients. (Bahammam et al., 2011)

	Number of OSA patients	Measurements used for diagnosing hypothyroidism	Mean age (year)	Mean BMI	Mean AHI	Previously diagnosed hypothyroidism	Newly diagnosed clinical hypothyroidism	Newly diagnosed subclinical hypothyroidism
Kapur et al (Kapur et al., 1998)	284	TSH and FT4	50.2			17 (5.1)	0	4 (1.41%)
†Miller et al (Miller and Husain, 2003)	75	TSH	49.8	36.2	36.4	0	7 (9.3%)	0 (FT4 not measured)
Lin et al (Lin et al., 1992)	65	TSH and FT4	49.7	--	37.9	0	2 (3.1)	0
Skjodt et al (Skjodt et al., 1999)	124	TSH and FT4	--	--	--	0	3 (2.4)	0
Winkelman et al (Winkelman et al., 1996)	103	TSH	43.9	--	20.1±29	1 (0.9)	2 (1.9)	0 (FT4 not measured)
Resta et al (Resta et al., 2004)	78	TSH and FT4	49.4	37.6	38.3	Excluded	--	9 (11.5%)
BaHamam (Bahammam et al., 2011)	271	TSH and FT4	48.7	37.7	55.2	26 (9.6%)	1 (0.4)	27 (11.1%)
AlOtair et al (Alotair and Bahammam, 2008)	191 females 193 males	--	F 53.9 M 43	F 41.8 M 37.2	F 51.4 M 61.4	F 23.6% M 6.2%	--	--

† Female only

Table 1. Summary of the studies that assessed the prevalence of hypothyroidism in OSA patients.

## 5. Prevalence studies of OSA in hypothyroidism

Limited data are available about the prevalence of OSA in hypothyroid patients (Table 2). The incidence is estimated to range from 25-82%. Most of the obtained data are from case reports and case series and their findings are variable. In a study of 50 patients with primary hypothyroidism, 30% were found to have OSA (AHI  $\geq$ 5/hour). (Jha et al., 2006) These patients had overt severe hypothyroidism as manifested by TSH levels and symptoms. For milder cases and subclinical cases, the prevalence might be less. The variability in the results is influenced by the characteristics of the studied group. Predominance of male gender can result in a higher prevalence of OSA as it is one of the main risk factors for OSA. In smaller studies, a higher prevalence has been reported. (Rajagopal et al., 1984)

	No. of Patients	OSA Criteria	No. of OSA (%)	Patients Characteristics
Jha A, et al (Jha et al., 2006)	50	AHI $\geq$ 5/hour	15 (30%) Mild OSA 8, Moderate 1, Severe 6	Females 58%, Mean Age 34 $\pm$ 11 years, Overweight 36%, Obese 16%
Rajagopal et al (Rajagopal et al., 1984)	11	--	9 (82%) Mean AHI (71.8/hour)	6 patients obese (AHI 99/hour) 3 non-obese (AHI 16.3/hour)
Misiolek et al (Misiolek M and 2007)	15	RDI> 10/hour	5 (33%)	11 Females, Mean Age 50.3 (30-70) years, Mean BMI 29.2 (21.3-41)kg/m <sup>2</sup>
Lin et al (Lin et al., 1992)	20	AHI $\geq$ 5/hour	5 (25%) 3 mild OSA, 2 severe OSA	4 Females, Mean Age 49.4 $\pm$ 7.3 years, IBW 134.6 $\pm$ 23.2%
Hira et al (Hira HS, 1999)	20		9 (45%)	----
Mikelson et al (Mickelson et al., 1999)	10	RDI> 10/hour	4 (40%)	----

RDI: Respiratory Disturbance Index, IBW: Ideal Body Weight

Table 2. Prevalence Studies of OSA in Hypothyroidism

## 6. The clinical effects of treating hypothyroidism in OSA patients

Theoretically, replacing thyroid hormone should reverse most if not all the complications associated with the state of deficiency. However, in real clinical practice, this is not absolutely correct. Changes such as respiratory muscle weakness can be reversible with thyroxine therapy. Difficult weaning in hypothyroid patients can be facilitated with thyroxine therapy too and mechanical obstruction due to thyroid goiter can be reverted with thyroidectomy. However, OSA response to thyroxine therapy is variable. In a case series of 10 hypothyroid patients with OSA, treatment with thyroxine was associated with nocturnal

angina and arrhythmia in two patients. Initiation of CPAP therapy prevented angina and arrhythmia. Eight of these patients were followed after achieving euthyroid state and six of them had persistent sleep apnea requiring CPAP therapy. (Grunstein and Sullivan, 1988) Thereby, treatment of hypothyroidism in the presence of OSA can be potentially hazardous and lead to cardiovascular complications even with small doses of thyroxine as thyroxine therapy may increase metabolic rate in the presence of significant hypoxia. Combination therapy (CPAP + Thyroxine) can be helpful in such situation. In another series of nine hypothyroid patients with OSA (AHI range 17-176/hour), thyroxine therapy improved outcome. Six of them were obese and had the higher range of AHI and showed significant improvement in AHI after 3-12 months of thyroxine therapy despite no improvement in weight. (Rajagopal et al., 1984) Another series of 5 patients with OSA who received thyroxine therapy showed significant reduction in AHI after 4 months of therapy; however, snoring persisted and required longer duration of therapy to improve. (Lin et al., 1992) Snoring refers to upper airway resistance and the longer duration required to improve it is basically related to the duration needed to resolve or improve upper airway changes induced by hypothyroidism. In a larger group of patients, Resta and co-workers divided patients into 3 groups: group A: 63 patients with normal thyroid function, group B: 30 patients affected with subclinical hypothyroidism and treated with levothyroxine for at least 2 years and group C: 15 patients with TSH >4mIU/l and not treated with levothyroxine. (Resta et al., 2005) The prevalence and severity of OSA did not differ between the three groups and levothyroxine therapy did not influence OSA outcome in patients with subclinical hypothyroidism. It was also noticed that levothyroxine therapy in patients with subclinical hypothyroidism and OSA was associated with less daytime sleepiness as measured by the Epworth sleepiness scale when compared to the untreated group. (Resta et al., 2005) Untreated subclinical hypothyroidism by itself is a known cause of excessive daytime sleepiness measured both subjectively and objectively, which improved with thyroxine therapy. (Shinno et al., 2009) On the other hand, the outcome of treating primary hypothyroidism with levothyroxine in patients with OSA has resulted in a significant improvement in AHI within 7-11 months of therapy. This improvement was accompanied by significant reduction in BMI, skinfold thickness, pedal edema and other biochemical markers. (Jha et al., 2006) However, in the same study, two patients have lost follow-up and both failed to show any improvement in OSA following levothyroxine therapy. One is thought to be due to his overweight that did not reduce with therapy. (Jha et al., 2006) Failure to improve OSA by achieving euthyroid state suggests that hypothyroidism is not the only factor and other factors play a role in causing OSA. It is also thought that thyroid hormone deficiency results in long term changes in the upper airway and thus improvement in OSA lags behind achieving the euthyroid state. (Grunstein et al., 1993) Furthermore, it is the treatment of the severe forms of hypothyroidism (myxedema) that improves the concomitant OSA. (Orr et al., 1981) Based on the available evidence, thyroxine cannot be considered as the only therapeutic option for OSA in patients with hypothyroidism especially in elderlies and those with cardiovascular diseases. (Veasey et al., 2006) The degree of hypoxia accompanying apneas may worsen with initiation of thyroxine therapy. In the hypothyroid state and as a result of the low metabolic rate, oxygen consumption by several body organs is less than usual, which can help to maintain a reasonable oxygen level compared to the duration and severity of apneas. With the increment in basal metabolic rate



seen with the commencement of thyroxine therapy, oxygen consumption is increased by body organs and short-duration apneas/hypopneas can result in dramatic oxygen desaturation. Therefore, CPAP therapy should not be delayed for months awaiting the results of thyroxine use. The lack of response to thyroxine suggests that either there is no casual association between hypothyroidism and OSA or those alterations in breathing mechanics and upper airways require longer duration of therapy to reverse them and that longer duration of follow up might show a beneficial effect of thyroxine therapy.

	No. of Patients	Mean Duration of Therapy	Clinical Outcome of OSA	Other Outcomes
Jha A, et al (Jha et al., 2006)	12	9 months	Significant improvement of AHI (14.3 (7.4–33.6) to 2.1 (0.8–4.6))	Significant improvement of BMI and skinfold thickness
Rajagopal et al (Rajagopal et al., 1984)	9	3-12 months	AHI decreased 71.8 ± 18.0 to 12.7 ± 6.1	No change in BMI
Misiolek et al (Misiolek M and 2007)	5	5-6 months	RDI persisted in two patients, increased in one, two patients showed insignificant reduction in RDI	BMI and loud snoring improved
Lin et al (Lin et al., 1992)	5	One year	Improved AI after 4months of therapy	Improved snoring after one year of therapy Improved hypoxic/hypercapnic ventilator response after 4 months
Hara et al, (Hira HS, 1999)	9	3 months	6 complete recovery, partial recovery in two and no recovery in one	

Table 3. Summary of outcome studies of thyroxine therapy in OSA patients

## 7. Evaluating thyroid function in OSA patients

It is important when ordering a laboratory investigation for any disease to consider the prevalence of the problem, the associated complications, cost-effectiveness and the effectiveness of treating the disease. Blood tests TSH, thyroxine (T4) are not clinically indicated in patients with OSA. Hypothyroidism can be associated with severe cases of OSA +/- hypoventilation but it is not an independent risk factor. Nocturnal upper airway obstruction has been evaluated in both hypothyroid and euthyroid subjects. The incidence of upper airway obstruction is higher in hypothyroid 7.7% compared to euthyroid 1.5% but after controlling for weight, age and gender, hypothyroidism does not significantly

predict upper airway obstruction. (Pelttari et al., 1994) Thus, upper airway obstruction is related to obesity and male gender and not to hypothyroidism per se. The prevalence of clinical hypothyroidism, as mentioned above, is not higher than the general population. Furthermore, there is no strong evidence to support the resolution of OSA with thyroxine therapy. However, thyroxine therapy should be initiated in hypothyroid patients to manage the other co-morbidities associated with hypothyroidism but not as a medical therapy for OSA. Thyroxine therapy can not abandon the need for CPAP therapy and should not delay its initiation. The recommended practice is to be selective when ordering TSH/T4 test to high risk population (females, morbidly obese and older age), persistent symptoms of fatigue and sleepiness despite proper CPAP therapy and in those with secondary causes for hypothyroidism (thyroid ablation, thyroidectomy, panpituuitarism).

## 8. Conclusion

For OSA patients, the prevalence of clinical hypothyroidism is not higher than the general population. It is essential to consider the risk factors for hypothyroidism when evaluating patients for sleep apnea as well as considering OSA risk factors when evaluating hypothyroid cases. Routine blood testing for TSH and T4 should be saved for OSA patients with severe obesity, persistent sleepiness despite adequate CPAP therapy and with overt hypothyroid symptoms and signs. For hypothyroid patients with symptoms suggestive of OSA, a diagnostic sleep study is warranted and CPAP therapy should be commenced prior to thyroxine therapy especially in the elderly and patients with cardiovascular diseases. Re-evaluating OSA patients after achieving euthyroid state can be done, especially if accompanied by weight reduction. Some of OSA cases might resolve but the majority seems to persist. Long-term studies might be able to explore better the impact of thyroxine therapy and help in understanding time-course of the problem.

## 9. References

- Agrama, M. T. 2011. Thyroidectomy for goiter relieves obstructive sleep apnea: Results of 8 cases. *Ear Nose Throat J*, 90, 315-7.
- Alotair, H. & Bahammam, A. 2008. Gender differences in Saudi patients with obstructive sleep apnea. *Sleep Breath*, 12, 323-9.
- Ancoli-Israel, S., Klauber, M. R., Kripke, D. F., Parker, L. & Cobarrubias, M. 1989. Sleep apnea in female patients in a nursing home. Increased risk of mortality. *Chest*, 96, 1054-8.
- Arroliga, A. C., Dweik, R. A. & Rafanan, A. L. 2000. Primary pulmonary hypertension and thyroid disease. *Chest*, 118, 1224-5.
- Badesch, D. B., Wynne, K. M., Bonvallet, S., Voelkel, N. F., Ridgway, C. & Groves, B. M. 1993. Hypothyroidism and primary pulmonary hypertension: an autoimmune pathogenetic link? *Ann Intern Med*, 119, 44-6.
- Bahammam, A. S., Alrajeh, M. S., Al-Jahdali, H. H. & Binsaeed, A. A. 2008. Prevalence of symptoms and risk of sleep apnea in middle-aged Saudi males in primary care. *Saudi Med J*, 29, 423-6.
- Bahammam, S. A., Sharif, M. M., Jammah, A. A. & Bahammam, A. S. 2011. Prevalence of thyroid disease in patients with obstructive sleep apnea. *Respir Med*, 105, 1755-1760.

- Baldwin, K. M., Hooker, A. M., Herrick, R. E. & Schrader, L. F. 1980. Respiratory capacity and glycogen depletion in thyroid-deficient muscle. *J Appl Physiol*, 49, 102-6.
- Batniji Rk, B. H. R., Cevera Jj, Gavin Jp, Seymour Pe, Parnes Sm 2006 Supraglottic myxedema presenting as acute upper airway obstruction. *Otolaryngol Head Neck Surg*, 134, 348-50.
- Behan, M., Zabka, A. G., Thomas, C. F. & Mitchell, G. S. 2003. Sex steroid hormones and the neural control of breathing. *Respir Physiol Neurobiol*, 136, 249-63.
- Behnia, M., Clay, A. S. & Farber, M. O. 2000. Management of myxedematous respiratory failure: review of ventilation and weaning principles. *Am J Med Sci*, 320, 368-73.
- Bilous, R. W. & Tunbridge, W. M. 1988. The epidemiology of hypothyroidism--an update. *Baillieres Clin Endocrinol Metab*, 2, 531-40.
- Birring, S. S., Morgan, A. J., Prudon, B., Mckeever, T. M., Lewis, S. A., Falconer Smith, J. F., Robinson, R. J., Britton, J. R. & Pavord, I. D. 2003. Respiratory symptoms in patients with treated hypothyroidism and inflammatory bowel disease. *Thorax*, 58, 533-6.
- Birring, S. S., Patel, R. B., Parker, D., Mckenna, S., Hargadon, B., Monteiro, W. R., Falconer Smith, J. F. & Pavord, I. D. 2005. Airway function and markers of airway inflammation in patients with treated hypothyroidism. *Thorax*, 60, 249-53.
- Block, A. J., Wynne, J. W. & Boysen, P. G. 1980. Sleep-disordered breathing and nocturnal oxygen desaturation in postmenopausal women. *Am J Med*, 69, 75-9.
- Chan, A. S., Phillips, C. L. & Cistulli, P. A. 2010. Obstructive sleep apnoea--an update. *Intern Med J*, 40, 102-6.
- Chu, J. W., Kao, P. N., Faul, J. L. & Doyle, R. L. 2002. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. *Chest*, 122, 1668-73.
- Curnock, A. L., Dweik, R. A., Higgins, B. H., Saadi, H. F. & Arroliga, A. C. 1999. High prevalence of hypothyroidism in patients with primary pulmonary hypertension. *Am J Med Sci*, 318, 289-92.
- Datta, D. & Scalise, P. 2004. Hypothyroidism and failure to wean in patients receiving prolonged mechanical ventilation at a regional weaning center. *Chest*, 126, 1307-12.
- De Felice, A., Fuschillo, S., Martucci, M., De Angelis, E. & Balzano, G. 2006. Euthyroid goitre and sleep apnea. *Monaldi Arch Chest Dis*, 65, 52-5.
- Deegan Pc, M. V., Morgan We 1997. Goitre: a cause of obstructive sleep apnoea in euthyroid patients *Eur Respir J* 10, 500-502.
- Devdhar, M., Ousman, Y. H. & Burman, K. D. 2007. Hypothyroidism. *Endocrinol Metab Clin North Am*, 36, 595-615, v.
- Duranti, R., Gheri, R. G., Gorini, M., Gigliotti, F., Spinelli, A., Fanelli, A. & Scano, G. 1993. Control of breathing in patients with severe hypothyroidism. *Am J Med*, 95, 29-37.
- Ehrmann, D. E., Deldin, P. J. & Pitt, B. 2011. Is sleep apnea a potential link between major depressive disorder and cardiovascular disease? *Int J Cardiol*, 147, 1-3.
- Eloy, J. A., Omerhodzic, S., Som, P. M. & Genden, E. M. 2007. Goitrous Hashimoto's thyroiditis presenting as obstructive sleep apnea. *Thyroid*, 17, 691-2.
- Ferini-Strambi, L., Baietto, C., Di Gioia, M. R., Castaldi, P., Castronovo, C., Zucconi, M. & Cappa, S. F. 2003. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). *Brain Res Bull*, 61, 87-92.

- Fox, C. S., Pencina, M. J., D'agostino, R. B., Murabito, J. M., Seely, E. W., Pearce, E. N. & Vasan, R. S. 2008. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. *Arch Intern Med*, 168, 587-92.
- Georgalas, C. 2011. The role of the nose in snoring and obstructive sleep apnoea: an update. *Eur Arch Otorhinolaryngol*, 268, 1365-73.
- George, J. T., Thow, J. C., Rodger, K. A., Mannion, R. & Jayagopal, V. 2009. Reversibility of fibrotic appearance of lungs with thyroxine replacement therapy in patients with severe hypothyroidism. *Endocr Pract*, 15, 720-4.
- Golden, S. H., Robinson, K. A., Saldanha, I., Anton, B. & Ladenson, P. W. 2009. Clinical review: Prevalence and incidence of endocrine and metabolic disorders in the United States: a comprehensive review. *J Clin Endocrinol Metab*, 94, 1853-78.
- Grunstein, R., Wilcox, I., Yang, T. S., Gould, Y. & Hedner, J. 1993. Snoring and sleep apnoea in men: association with central obesity and hypertension. *Int J Obes Relat Metab Disord*, 17, 533-40.
- Grunstein, R. R. & Sullivan, C. E. 1988. Sleep apnea and hypothyroidism: mechanisms and management. *Am J Med*, 85, 775-9.
- Guillemainault, C., Connolly, S. J. & Winkle, R. A. 1983. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. *Am J Cardiol*, 52, 490-4.
- Hall, R. & Scanlon, M. F. 1979. Hypothyroidism: clinical features and complications. *Clin Endocrinol Metab*, 8, 29-38.
- Hiestand, D. M., Britz, P., Goldman, M. & Phillips, B. 2006. Prevalence of symptoms and risk of sleep apnea in the US population: Results from the national sleep foundation sleep in America 2005 poll. *Chest*, 130, 780-6.
- Hira Hs, S. L. 1999. Sleep apnea syndrome among patients with hypothyroidism. *J Assoc Physicians India*, 47, 615-618.
- Horne, J. & Reyner, L. 1999. Vehicle accidents related to sleep: a review. *Occup Environ Med*, 56, 289-94.
- Jean-Louis, G., Brown, C. D., Zizi, F., Ogedegbe, G., Boutin-Foster, C., Gorga, J. & Mcfarlane, S. I. 2010. Cardiovascular disease risk reduction with sleep apnea treatment. *Expert Rev Cardiovasc Ther*, 8, 995-1005.
- Jha, A., Sharma, S. K., Tandon, N., Lakshmy, R., Kadhiravan, T., Handa, K. K., Gupta, R., Pandey, R. M. & Chaturvedi, P. K. 2006. Thyroxine replacement therapy reverses sleep-disordered breathing in patients with primary hypothyroidism. *Sleep Med*, 7, 55-61.
- Johns, F. R., Strollo, P. J., Jr., Buckley, M. & Constantino, J. 1998. The influence of craniofacial structure on obstructive sleep apnea in young adults. *J Oral Maxillofac Surg*, 56, 596-602; discussion 602-3.
- Jordan, R. M. 1995. Myxedema coma. Pathophysiology, therapy, and factors affecting prognosis. *Med Clin North Am*, 79, 185-94.
- Kaplan, R. 1992. Obstructive sleep apnoea and depression--diagnostic and treatment implications. *Aust N Z J Psychiatry*, 26, 586-91.

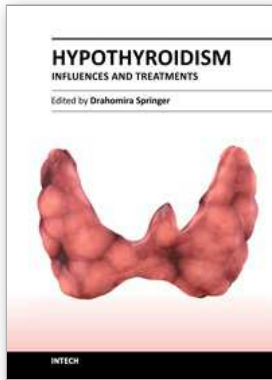
- Kapur, V. K., Koepsell, T. D., Demaine, J., Hert, R., Sandblom, R. E. & Psaty, B. M. 1998. Association of hypothyroidism and obstructive sleep apnea. *Am J Respir Crit Care Med*, 158, 1379-83.
- Kapur V, K. T., Demaine J, Hert R, Sandblom Re, Psaty & Bm 1998. Association of hypothyroidism and obstructive sleep apnea. *Am J Respir Crit Care Med*, 158, 1379-1383.
- Ladenson, P. W., Goldenheim, P. D. & Ridgway, E. C. 1988. Prediction and reversal of blunted ventilatory responsiveness in patients with hypothyroidism. *Am J Med*, 84, 877-83.
- Laroche, C. M., Cairns, T., Moxham, J. & Green, M. 1988. Hypothyroidism presenting with respiratory muscle weakness. *Am Rev Respir Dis*, 138, 472-4.
- Li, J. H., Safford, R. E., Aduen, J. F., Heckman, M. G., Crook, J. E. & Burger, C. D. 2007. Pulmonary hypertension and thyroid disease. *Chest*, 132, 793-7.
- Lin Cc, T. K., Chen Pj 1992. The relationship between sleep apnea syndrome and hypothyroidism. *Chest*, 102, 1663-1667.
- Lin, C. C., Tsan, K. W. & Chen, P. J. 1992. The relationship between sleep apnea syndrome and hypothyroidism. *Chest*, 102, 1663-7.
- Logan, A. G. & Bradley, T. D. 2010. Sleep apnea and cardiovascular disease. *Curr Hypertens Rep*, 12, 182-8.
- Madani, M. & Madani, F. 2009. Epidemiology, pathophysiology, and clinical features of obstructive sleep apnea. *Oral Maxillofac Surg Clin North Am*, 21, 369-75.
- Martinez, F. J., Bermudez-Gomez, M. & Celli, B. R. 1989. Hypothyroidism. A reversible cause of diaphragmatic dysfunction. *Chest*, 96, 1059-63.
- Massumi Ra, W. J. 1964. Severe depression of the respiratory center in myxedema. *Am J Med*, 36, 876-882.
- Mcquade, C., Skugor, M., Brennan, D. M., Hoar, B., Stevenson, C. & Hoogwerf, B. J. 2011. Hypothyroidism and Moderate Subclinical Hypothyroidism Are Associated with Increased All-Cause Mortality Independent of Coronary Heart Disease Risk Factors: A PreCIS Database Study. *Thyroid*, 21, 837-43.
- Meslier, N., Giraud, P., Person, C., Badatcheff, A. & Racineux, J. L. 1992. Prevalence of hypothyroidism in sleep apnoea syndrome. *Eur J Med*, 1, 437-8.
- Mickelson, S. A., Lian, T. & Rosenthal, L. 1999. Thyroid testing and thyroid hormone replacement in patients with sleep disordered breathing. *Ear Nose Throat J*, 78, 768-71, 774-5.
- Miller, C. M. & Husain, A. M. 2003. Should women with obstructive sleep apnea syndrome be screened for hypothyroidism? *Sleep Breath*, 7, 185-8.
- Millman, R. P., Bevilacqua, J., Peterson, D. D. & Pack, A. I. 1983. Central sleep apnea in hypothyroidism. *Am Rev Respir Dis*, 127, 504-7.
- Misiolek M, M. B., Namyslowski G, Scierski W, Zwirska- Korczała K, Kazmierczak-Zagorska Z, Kajdaniuk D, Misiolek H & 2007. Sleep apnea syndrome and snoring in patients with hypothyroidism with relation to overweight *J Physiol Pharmacol*, 58(Suppl 1) 77-85.
- Moser, R. J., 3rd & Rajagopal, K. R. 1987. Obstructive sleep apnea in adults with tonsillar hypertrophy. *Arch Intern Med*, 147, 1265-7.

- Orr, W. C., Males, J. L. & Imes, N. K. 1981. Myxedema and obstructive sleep apnea. *Am J Med*, 70, 1061-6.
- Orr, W. C. & Martin, R. J. 1981. Obstructive sleep apnea associated with tonsillar hypertrophy in adults. *Arch Intern Med*, 141, 990-2.
- Pandya, K., Lal, C., Scheinhorn, D., Day, I. K. & Sharma, O. P. 1989. Hypothyroidism and ventilator dependency. *Arch Intern Med*, 149, 2115-6.
- Park, J. G., Ramar, K. & Olson, E. J. 2011. Updates on definition, consequences, and management of obstructive sleep apnea. *Mayo Clin Proc*, 86, 549-54; quiz 554-5.
- Pelttari, L., Rauhalala, E., Polo, O., Hyyppa, M. T., Kronholm, E., Viikari, J. & Kantola, I. 1994. Upper airway obstruction in hypothyroidism. *J Intern Med*, 236, 177-81.
- Petrof, B. J., Kelly, A. M., Rubinstein, N. A. & Pack, A. I. 1992. Effect of hypothyroidism on myosin heavy chain expression in rat pharyngeal dilator muscles. *J Appl Physiol*, 73, 179-87.
- Pham, C. B. & Shaughnessy, A. F. 2008. Should we treat subclinical hypothyroidism? *BMJ*, 337, 290-291.
- Punjabi, N. M. 2008. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*, 5, 136-43.
- Radun, I. & Summala, H. 2004. Sleep-related fatal vehicle accidents: characteristics of decisions made by multidisciplinary investigation teams. *Sleep*, 27, 224-7.
- Rajagopal, K. R., Abbrecht, P. H., Derderian, S. S., Pickett, C., Hofeldt, F., Tellis, C. J. & Zwillich, C. W. 1984. Obstructive sleep apnea in hypothyroidism. *Ann Intern Med*, 101, 491-4.
- Resta, O., Carratu, P., Carpagnano, G. E., Maniscalco, M., Di Gioia, G., Lacedonia, D., Giorgino, R. & De Pergola, G. 2005. Influence of subclinical hypothyroidism and T4 treatment on the prevalence and severity of obstructive sleep apnoea syndrome (OSAS). *J Endocrinol Invest*, 28, 893-8.
- Resta, O., Pannacciulli, N., Di Gioia, G., Stefano, A., Barbaro, M. P. & De Pergola, G. 2004. High prevalence of previously unknown subclinical hypothyroidism in obese patients referred to a sleep clinic for sleep disordered breathing. *Nutr Metab Cardiovasc Dis*, 14, 248-53.
- Resta O, P. N., Di Gioia G, Stefano A, Barbaro Mp, De Pergola G 2004. High prevalence of previously unknown subclinical hypothyroidism in obese patients referred to a sleep clinic for sleep disordered breathing. *Nutr Metab Cardiovasc Dis*, 14, 248-53.
- Saaresranta, T. & Polo, O. 2002. Hormones and breathing. *Chest*, 122, 2165-82.
- Saaresranta, T. & Polo, O. 2003. Sleep-disordered breathing and hormones. *Eur Respir J*, 22, 161-72.
- Sateia, M. J. 2003. Neuropsychological impairment and quality of life in obstructive sleep apnea. *Clin Chest Med*, 24, 249-59.
- Sawin Ct, C. D., Azizi F, Mannix Je, Bachaeach P 1979. The Aging Thyroid: Increased Prevalence of Elevated Serum Thyrotropin Levels in the Elderly *J Am Med Assoc*, 242, 247-50.
- Sherry, K. M. & Hutchinson, I. L. 1984. Postoperative myxoedema. A report of coma and upper airway obstruction. *Anaesthesia*, 39, 1112-4.

- Shinno, H., Inami, Y., Inagaki, T., Kawamukai, T., Utani, E., Nakamura, Y. & Horiguchi, J. 2009. Successful treatment with levothyroxine for idiopathic hypersomnia patients with subclinical hypothyroidism. *Gen Hosp Psychiatry*, 31, 190-3.
- Siafakas, N. M., Salesiotou, V., Filaditaki, V., Tzanakis, N., Thalassinos, N. & Bouros, D. 1992. Respiratory muscle strength in hypothyroidism. *Chest*, 102, 189-94.
- Silva, D. R., Gazzana, M. B., John, A. B., Siqueira, D. R., Maia, A. L. & Barreto, S. S. 2009. Pulmonary arterial hypertension and thyroid disease. *J Bras Pneumol*, 35, 179-85.
- Simsek, G., Yelmen, N. K., Guner, I., Sahin, G., Oruc, T. & Karter, Y. 2004. The role of peripheral chemoreceptor activity on the respiratory responses to hypoxia and hypercapnia in anaesthetised rabbits with induced hypothyroidism. *Chin J Physiol*, 47, 153-9.
- Skatrud, J., Iber, C., Ewart, R., Thomas, G., Rasmussen, H. & Schultz, B. 1981. Disordered breathing during sleep in hypothyroidism. *Am Rev Respir Dis*, 124, 325-9.
- Skjodt, N. M., Atkar, R. & Easton, P. A. 1999. Screening for hypothyroidism in sleep apnea. *Am J Respir Crit Care Med*, 160, 732-5.
- Somers, V. K., White, D. P., Amin, R., Abraham, W. T., Costa, F., Culebras, A., Daniels, S., Floras, J. S., Hunt, C. E., Olson, L. J., Pickering, T. G., Russell, R., Woo, M. & Young, T. 2008. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). *Circulation*, 118, 1080-111.
- Stahl N, L. A. 1988. Acute upper airway obstruction due to myxoedema and upper airway abnormalities. *J Laryngol Otol*, 102, 733-4.
- Takamura, N., Hayashida, N. & Maeda, T. 2010. Risk of coronary heart disease and mortality for adults with subclinical hypothyroidism. *JAMA*, 304, 2481-2; author reply 2482.
- Takasaki, Y. & Hayashi, Y. 1985. [Effects of sex hormones on breathing during waking and sleep]. *Nihon Kyobu Shikkan Gakkai Zasshi*, 23, 286-95.
- Teramoto, S., Nagase, T. & Fukuchi, Y. 1995. Nocturnal upper airway obstruction in hypothyroidism. *J Intern Med*, 238, 473-4.
- Tsara, V., Amfilochiou, A., Papagrigrakis, J. M., Georgopoulos, D., Liolios, E., Kadiths, A., Koudounnakis, E., Aulonitou, E., Emporiadou, M., Tsakanikos, M., Chatzis, A., Choulakis, M. & Chrousos, G. 2010. Guidelines for diagnosing and treating sleep related breathing disorders in adults and children (Part 3: obstructive sleep apnea in children, diagnosis and treatment). *Hippokratia*, 14, 57-62.
- Veasey, S. C., Guilleminault, C., Strohl, K. P., Sanders, M. H., Ballard, R. D. & Magalang, U. J. 2006. Medical therapy for obstructive sleep apnea: a review by the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. *Sleep*, 29, 1036-44.
- Wall, C. R. 2000. Myxedema coma: diagnosis and treatment. *Am Fam Physician*, 62, 2485-90.

- Watson, E. M. & Pearce, R. H. 1949. The mucopolysaccharide content of the skin in localized (pretibial) myxedema. *Am J Clin Pathol*, 19, 442-7.
- Winkelman Jw, G. H., Piscatelli N, Lukas Se, Dorsey Cm, Cunningham S 1996. Are thyroid function tests necessary in patients with suspected sleep apnea? *Sleep* 19, 790-793.
- Winkelman, J. W., Goldman, H., Piscatelli, N., Lukas, S. E., Dorsey, C. M. & Cunningham, S. 1996. Are thyroid function tests necessary in patients with suspected sleep apnea? *Sleep*, 19, 790-3.
- Young, T., Peppard, P. E. & Gottlieb, D. J. 2002. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*, 165, 1217-39.
- Zwillich, C. W., Pierson, D. J., Hofeldt, F. D., Lufkin, E. G. & Weil, J. V. 1975. Ventilatory control in myxedema and hypothyroidism. *N Engl J Med*, 292, 662-5.





## **Hypothyroidism - Influences and Treatments**

Edited by Dr. Drahomira Springer

ISBN 978-953-51-0021-8

Hard cover, 348 pages

**Publisher** InTech

**Published online** 08, February, 2012

**Published in print edition** February, 2012

Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Suhaila E. Al-Jawder and Ahmed S. BaHammam (2012). Hypothyroidism and Obstructive Sleep Apnea, Hypothyroidism - Influences and Treatments, Dr. Drahomira Springer (Ed.), ISBN: 978-953-51-0021-8, InTech, Available from: <http://www.intechopen.com/books/hypothyroidism-influences-and-treatments/hypothyroidism-and-obstructive-sleep-apnea>

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.