Association between thyroid disorders and obstructive sleep apnea

M.BRUYNEEL, MD, PHD
PULMONOLOGIST
SOMNOLOGIST
What is OSAS?

Normal Breathing
Airway is open, Air flows freely to lungs

Obstructive Sleep Apnea
Airway collapses, Blocked air flow to lungs
Risk factors in OSAS

- Craniofacial abnormalities
- Obesity
- Male sex
- Age
- Acromegaly, hypothyroidism
- Heart failure
- End-stage renal disease

Upper airway collapse

- Palate
- Oropharynx
- tongue base
- Hypopharynx
- epiglottis

Normal breathing
During sleep, air can travel freely to and from your lungs through your airways.

Obstructive Sleep Apnoea
Your airway collapses, stopping air from traveling freely to and from your lungs and disturbing your sleep.
Morbidity in OSAS

- Impaired QoL
- MVA
- HTA
- Coronary artery disease
- Arrhythmias
- Congestive heart failure
- Stroke
- Diabetes
- Metabolic syndrome

Upper airway collapse
- palate
- oropharynx
- tongue base
- hypopharynx
- epiglottis

INTERMITTENT HYPOXIA-AWAKENINGS-OXYDATIVE STRESS
Symptoms of OSAS

Night time symptoms
✓ waking up with dry mouth
✓ breathing interruptions
✓ choking
✓ gasping
✓ snoring
✓ sweating
✓ nocturia,

Daytime symptoms
✓ daytime sleepiness
✓ mood disturbances
✓ memory impairment
✓ morning headaches
✓ non restorative sleep,..
Polysomnography
Definition of OSAS

**Apnea-hypopnea index (AHI):** apnea + hypopnea per hour of sleep

- **AHI>5** in a patient suffering from **one or more** of the following conditions:
  - Sleepiness, non restorative sleep, fatigue, insomnia
  - Waking up with breath holding, gasping, choking
  - Habitual snoring, breathing interruptions

<table>
<thead>
<tr>
<th>Co morbidities</th>
<th>Hypertension</th>
<th>Mood disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>cognitive dysfunction</td>
<td>coronary artery disease</td>
<td></td>
</tr>
<tr>
<td>stroke</td>
<td>congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>atrial fibrillation</td>
<td>type 2 diabetes</td>
<td></td>
</tr>
</tbody>
</table>

- **AHI>15** regardless of the presence of symptoms/co morbidities.
Prevalence of obstructive sleep apnea syndrome (OSAS)

Sitting is the smoking of our generation

Young T 1988-1993
Peppard PE 2007-2010
Heinzer R 2009-2013

Females
Thyroid disorders

• Overt Hypothyroidism (OHT)
  • ↑ TSH, fT4 ↓
    • <auto-immunity
    • Surgery
    • Radioiodine treatment
  • Prevalence: 0·2%-5·3% (Europe)
  • Prevalence: 1-2% (US) 3.7% (US) 9.6% (US)
  • Prevalence in Obese patients: 14%
  • Females > males

• Subclinical hypothyroidism (SCH)
  • ↑ TSH, fT4 normal
  • Prevalence: 3-15% (worldwide)
  • Prevalence: 1-2% (US)
  • Prevalence in Obese patients: 14.6%

_Sorensen JL 2016 - Van Hulsteijn L 2019 - Tharavaputta S 2019_
Thyroid disorders and OSAS

Bidirectional interactions?

OSAS in hypothyroid population
• OHT is a risk factor for OSAS
• Subclinical hypothyroidism?
• Does OHT treatment reverses OSAS?

Thyroid metabolism disorders in OSAS population
• OHT, SCH and goiters

Presentation of our recent data

Discussion

Conclusion
OSAS in hypothyroid population

• prevalence of OSAS in hypothyroidism is 25-50%.

• Systematic review from Sorensen JR. Thyroid 2016

• Including study of Jha A Sleep Med 2006

• 30% of 50 patients with recently diagnosed primary OHT suffer from OSAS,
  – TSH > 5μIU/mL
  – PSG-based OSA diagnosis (AHI> 5/h)
## Prevalence of OSAS in hypothyroidism

cross sectional study: Tharavaputta S J Clin Endocr Metab 2019

<table>
<thead>
<tr>
<th></th>
<th>Controls N=4917</th>
<th>Hypothyroidism N=514</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex (%)</td>
<td>51</td>
<td>22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age&gt;65 (%)</td>
<td>14</td>
<td>34</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI 25-29 (%)</td>
<td>35</td>
<td>32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI&gt;30 (%)</td>
<td>32</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>OSA (%)</td>
<td>4.3</td>
<td>8.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR=1.88</td>
<td></td>
</tr>
<tr>
<td>Anti-TPO + (%)</td>
<td>8</td>
<td>45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Comorbidities index (cardiometabolic + asthma)</td>
<td>0.83</td>
<td>1.35</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
After adjustment for BMI, demographics, comorbidities...

**OR of having OSAS in**
- treated HT: **2.51**
- untreated HT (mostly SCH): **0.33**

<table>
<thead>
<tr>
<th>Characteristics of Hypothyroid Population, Based on Thyroid Medications, TSH, and FT4</th>
<th>N</th>
<th>Weighted Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hypothyroidism</td>
<td>514</td>
<td>9.47</td>
</tr>
<tr>
<td>Taking hypothyroid medication</td>
<td>393</td>
<td>7.24</td>
</tr>
<tr>
<td>Not taking hypothyroid medication</td>
<td>121</td>
<td>2.39</td>
</tr>
<tr>
<td>Total hyperthyroid (taking hyperthyroid medication or TSH &lt;0.34)</td>
<td>84</td>
<td>1.19</td>
</tr>
<tr>
<td>Total euthyroid (control group)</td>
<td>4917</td>
<td>89.16</td>
</tr>
<tr>
<td>Total</td>
<td>5515</td>
<td>100</td>
</tr>
<tr>
<td>Among hypothyroid population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled (normal TSH)</td>
<td>253</td>
<td>52.17</td>
</tr>
<tr>
<td>Uncontrolled (abnormal TSH)</td>
<td>96</td>
<td>18.68</td>
</tr>
<tr>
<td>Other (unknown TSH)</td>
<td>44</td>
<td>8.56</td>
</tr>
<tr>
<td>Not on medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overt (high TSH, low FT4)</td>
<td>22</td>
<td>4.4</td>
</tr>
<tr>
<td>Subclinical (high TSH, normal FT4)</td>
<td>99</td>
<td>20.83</td>
</tr>
</tbody>
</table>
OSAS in hypothyroid population:
Subclinical hypothyroidism

• One single study: 53% OSAS in SCH - but same rate in euthyroid patients: selection bias
<Sleep lab population?

Resta J Endocr Invest 2005
Physiopathology: why does OSAS occurs in OHT?

**TRAITS of OHT**
- macroglossia
- thickening of vocal cords
- increased mucopolysaccharide and protein deposition in the upper airway
- depression of respiratory centers
- altered regulatory control of pharyngeal dilator muscles from neuropathy

**TRAITS of OSAS**
- P passive critical closing pressure
- A arousal threshold
- L loop gain
- M muscle responsiveness

*Bonsignore M Eur Respir Rev 2017*
Does LT4 replacement therapy reverses OSAS?

12 OSAS
10 were reversed by LT4 treatment after normalisation of thyroid function

*Jha A. Sleep Med 2006*
Does LT4 replacement therapy reverses OSAS?

Significant reduction in:

- apnea periods,
- oxygen desaturation events,
- snoring and choking

- PSG-documented OSAS
- 1) 20 P + OHT, 2 moderate and severe OSAS, 3 mild
- Normalized after 1 y

Lin CC, Chest 1992

- 2) 20 P + OHT: 9 P + OSAS,

-> resolved in 6, partial improvement in 2, no change in 1

Hira HS. J Assoc Physicians India 1999

- 3) 11 P OHT + OSAS.

-> Decrease AHI 73 to 17/h

Rajagopal KR. Ann Intern Med 1984
Additive role of obesity

58% OSAS are overweight or obese

30% OHT have OSAS

77% OHT are overweight or obese

26% Obese have OSAS

14% Obese have OHT

And how many OSAS Suffers from OHT?

Thyroid metabolism disorders in OSAS

? Increased prevalence in OSAS? - Controversial

• Case-control study (271 OSAS and 76 controls)
  – Incidence OHT: 0.4% vs 1.4% (NS)
    • OHT: more obese, more women
  – Incidence of SCH was more frequent in OSA: 11.1 vs 4% (S)
  – No correlations between TSH activity and the severity of OSAS Bahamman SA et al. Respir Med 2011
Thyroid metabolism disorders in OSAS

Meta-analysis-17 studies (5 case reports)

- Increased prevalence of OHT in OSAS: 8%
  - Associated with OSAS severity
  - But not for SCH: 11%
  - ! Confounding factor: obesity

Physiopathology

How could OSAS induce OHT/SCH?

• Intermittent hypoxia/hypercapnia
• Sympathetic nervous hyperactivity
• Increased oxydative stress/inflammation
• Disrupted sleep

• ?« chronic illness » pattern, reversible with CPAP?
• Seems more marked in severe OSAS
• Contradictory data

Grunstein R 1994, Bratel 1999
Goiters

- Few case reports described severe OSAS in euthyroid patients with goiters, reversed by surgery
- Physiopathology
  - UA oedema < decreased venous return from head and neck
  - Decreased activity of pharyngeal dilator muscles, hyoid muscle
  - Loading effect while supine

Attal P 2010, Deegan PC 1997, Gutierrez T 2012
Prevalence of newly established thyroid disorders in patients with moderate-to-severe obstructive sleep apnea syndrome

Marie Bruyneel¹² • Flora Veltri²³ • Kris Poppe²³
Aim of the study

PROSPECTIVE STUDY
To assess prevalence of undiagnosed endocrine disorders (glucose/thyroid metabolism) in OSAS

OSAS, AHI >15
In-lab attended PSG for CPAP titration

Fasting Blood sampling
HbA1C, glucose, C-peptide, TSH, FT4 dosages
## Results

### Patients characteristics, n= 280

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>33±7</td>
</tr>
<tr>
<td>Obesity = BMI ≥30 kg/m²</td>
<td>192 (69%)</td>
</tr>
<tr>
<td>Age</td>
<td>56±13 y</td>
</tr>
<tr>
<td>Age ≥60 years</td>
<td>120 (43%)</td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>49±25</td>
</tr>
<tr>
<td>Gender male/female</td>
<td>194/86 (70/30%)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>112 (40%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>147 (53%)</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>All patients N=280</th>
<th>Moderate OSAS AHI 15-29 n=54</th>
<th>Severe OSAS AHI ≥ 30 n=54</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly diagnosed SCH (TSH &gt;4.2 mIU/L) **</td>
<td>18 (7.0%)</td>
<td>4 (6.0%)</td>
<td>14 (7.4%)</td>
<td>0.685</td>
</tr>
<tr>
<td>Newly diagnosed OH (TSH &gt;4.2 mIU/L, FT4 &lt;12 pmol/L) **</td>
<td>3 (1.2%)</td>
<td>0 (0%)</td>
<td>3 (1.6%)</td>
<td>0.298</td>
</tr>
<tr>
<td>Newly diagnosed SCH + OH **</td>
<td>21 (8.2%)</td>
<td>4 (6.0%)</td>
<td>17 (9.0%)</td>
<td>0.450</td>
</tr>
<tr>
<td>All SCH (TSH &gt;4.2 mIU/L)</td>
<td>21 (7.5%)</td>
<td>6 (7.9%)</td>
<td>15 (7.3%)</td>
<td>0.878</td>
</tr>
<tr>
<td>All OH (TSH &gt;4.2 mIU/L, FT4 &lt;12 pmol/L)</td>
<td>4 (1.4%)</td>
<td>0 (0%)</td>
<td>4 (2.0%)</td>
<td>0.219</td>
</tr>
<tr>
<td>All SCH + OH</td>
<td>25 (8.9%)</td>
<td>6 (7.9%)</td>
<td>19 (9.3%)</td>
<td>0.711</td>
</tr>
<tr>
<td>Patients under LT4</td>
<td>25 (8.9%)</td>
<td>9 (11.8%)</td>
<td>16 (7.8%)</td>
<td>0.297</td>
</tr>
<tr>
<td>Any kind of thyroid problem</td>
<td>46 (16.4%)</td>
<td>13 (17.1%)</td>
<td>33 (16.2%)</td>
<td>0.852</td>
</tr>
</tbody>
</table>

** after the exclusion of patients treated with L-Thyroxine (n=25)
Discussion

- 8.2% of OSAS patients were diagnosed with SCH/OH
  - Mainly SCH

- High total prevalence of thyroid disorders: 16.4%
  - Prevalence > to general population (9%) and > obese (14%)
  - Especially in a 70% male cohort

Valdes S 2010; Tharavaputta S 2019
Systematic screening of hypothyroidism in OSAS

• Debate is ongoing
• **No recommendations** from AASM, ERS, ESRS to perform a systematic screening of hypothyroidism in OSAS
• Screening is simple
• Majority of SCH
  – And SCH should not be treated in all-> cost-effective?
• Proposed to avoid misdiagnosis *Skjodt NM 1999*
CONCLUSION

In this prospective study performed in moderate to severe OSAS

- High prevalence of thyroid disorders, with 8% undiagnosed
  - Mainly SCH

- Systematic screening should be assessed (cost-effective?)
- ! Associated metabolic disorders:
  - Dyslipidemia
  - Diabetes mellitus
  - GIT
  - Insulin resistance
Thank you for your attention
marie_bruyneel@stpierre-bru.be