OBSTRUCTIVE SLEEP APNEA AND DIABETES MELLITUS

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OBSTRUCTIVE SLEEP APNEA AND DIABETES MELLITUS

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DM and OSA – two common diseases

Diabetes mellitus

- 25.8 million of US population has DM (8.3%)
  - 18.8 million (diagnosed)
  - 7 million (undiagnosed)
- Pre-diabetes 79 million
- Costs of DM care 245 billion
  - 176 billion in direct costs
  - 69 billion in decreased productivity

Obstructive sleep apnea

Young T. Wisconsin Sleep Cohort Study NEJM 1993

Prevalence OSA in middle aged adults
- 9% in women (2%)
- 24% in men (4%)
Questions about the DM and OSA relationship

• Does OSA predispose to DM, if so what level of risk does untreated OSA pose?

If so, treatment of OSA could reduce the staggering burden of DM

• Does treatment of OSA in established DM lead to improved outcomes from DM?

Improvement in DM outcomes can lead reduced costs of care of DM

• Mechanistic bases of OSA – DM relationship
Obstructive Sleep Apnea and Diabetes: Cause or Association?
Pathophysiology of Sleep Apnea

Awake: Small airway + neuromuscular compensation

- Loss of neuromuscular compensation
- Decreased pharyngeal muscle activity

Sleep Onset

Hyperventilate: connect hypoxia & hypercapnia

Airway opens

Pharyngeal muscle activity restored

Arousal from sleep

Increased ventilatory effort

Hypoxia & Hypercapnia

Apnea

Airway collapses
Physiologic consequences

AROUSALS

DISORDERED OXYGENATION
Clinical Consequences

Sleep Apnea

Sleep Fragmentation
Hypoxia/ Hypercapnia

Excessive Daytime
Sleepiness

Cardiovascular
Complications

Morbidity
Mortality
Categorization of OSA

- Based on apneas-hypopneas/hour
  - APNEA-HYPOPNEA INDEX

Mild – 5-15/hr
Moderate – 15-30/hr
Severe > 30/hr

Two key events that define the impact of OSA
- Arousals
- Hypoxemia
Positive Airway Pressure
Treatment of OSA

• Weight loss
• Avoidance of alcohol, sedatives, opiates
• Positional therapy
• Dental appliances
• Upper airway surgery
Obstructive Sleep Apnea and Diabetes: Cause or Association?

- Obesity
- Diabetes
- OSA

HYPOXIA
STRESS
ALTERED CIRCADIAN RHYTHM
Sleep Heart Health Study: 2656 subjects underwent sleep study and glucose tolerance testing

Odds ratio for impaired glucose tolerance was 1.5-2.0 in the individuals spending the highest quartile of sleep time below 90% saturation or the lowest quartile of average saturation during sleep.

Habitual snoring linked to DM in women
(Valham et al Sleep Med 2010)

Questions on SDB in the North Sweden component of WHO trends and monitoring of CVD 1999-2004 study (7905 subjects; 4047 W; 3858 M)

25-79 yr old women had 58% increased DM risk with habitual snoring and if they had witnessed apnea, 3-fold risk of DM independent of age, smoking, BMI or waist circumference.

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Non-snoring</td>
<td>1</td>
<td>1.13-4.66</td>
</tr>
<tr>
<td>Unknown snoring pattern</td>
<td>1.62</td>
<td>0.98-2.69</td>
</tr>
<tr>
<td>Habitual snoring</td>
<td>2.25</td>
<td>1.49-3.38</td>
</tr>
<tr>
<td>No witnessed sleep apnea</td>
<td>1</td>
<td>1.11-3.9</td>
</tr>
<tr>
<td>Unknown apnea pattern</td>
<td>1.85</td>
<td>1.27-2.70</td>
</tr>
<tr>
<td>Witnessed sleep apnea</td>
<td>4.66</td>
<td>1.93-11.2</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1</td>
<td>1.06-1.14</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.62</td>
<td>0.38-1.02</td>
</tr>
<tr>
<td>Age 25–44 (years)</td>
<td>1</td>
<td>1.00-1.19</td>
</tr>
<tr>
<td>45–54</td>
<td>1.23</td>
<td>0.59-2.56</td>
</tr>
<tr>
<td>55–64</td>
<td>3.61</td>
<td>1.99-6.55</td>
</tr>
<tr>
<td>65–74</td>
<td>6.13</td>
<td>3.47-10.83</td>
</tr>
<tr>
<td>75–79</td>
<td>7.73</td>
<td>3.39-17.65</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.11</td>
<td>1.08-1.14</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>1.06</td>
<td>1.04-1.07</td>
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Prevalence of OSA in DM (73%) (Pamidi et al Best Pract Res Clin Endocrinol Met 2010)

- Highest in Sleep-AHEAD study – obese DM (86%).
- Lowest in SHHS – 58% (65+, self-reported DM, hypopnea definition of 4%)
Prevalence of DM in OSA
(Pamidi et al Best Pract Res Clin Endocrinol Met 2010)

- Higher prevalence of Type 2 DM in OSA
  Unadjusted OR 4.06-11.2
  Adjusted OR 1.3-13.4
- Higher incidence of T2DM with increasing severity of OSA (Botros et al Am J Med 2009 & Wisconsin sleep cohort – AHI>15, DM prevalence 15%; AHI<5, fewer than 3% had DM)
- Longitudinal follow –up studies looking at causality
  - Wisconsin sleep cohort (1387 patients, after adjustment for age, sex and body habitus, OR for DM in 4 years was 1.62 with AHI≥15/h compared to AHI with AHI of 5/hr but not statistically significant) (Reichmuth AJRCCM 2005)
  - Busselton Health study even though showing independent association, sample sizes and incident DM was small (Marshall et al J Clin Sleep Med 2009)
544 nondiabetic subjects assessed for sleep disorders were then followed for a median of 2.7 years.

OSA was associated with subsequent risk of diabetes when corrected for age, race, baseline glucose, BMI, and change in BMI.

Effect of CPAP treatment
Methodologies used to understand impact

• Risk of developing DM

• Effects on glucose metabolism
  - Insulin levels
  - Insulin resistance
  - Glucose levels and HbA1C
  - Insulin sensitivity

• Risk of diabetic complications following CPAP treatment for OSA in DM
544 nondiabetic subjects assessed for sleep disorders were then followed for a median of 2.7 years.

Use of CPAP was associated with a decreased risk of developing diabetes.

HbA1C with and without CPAP

- **Effect of CPAP therapy on HbA1C**
  - Babu et al (Arch Intern Med 2005) showed benefit in 25 obese DM with >4 hours of CPAP in 3 months
  - 4 other studies showed no improvement in HbA1C

Aronsohn et al AJRCCM 2010
Effect of CPAP on glucose tolerance or insulin sensitivity

- Majority of studies done in obese men
- Out of 21 studies, 9 reported positive findings and 12 were negative
- Methods used ranged from
  - HOMA index
  - OGTT
  - Gold standard hyper-insulinemic euglycemic clamp technique rarely used.
Randomized studies on effect of CPAP in DM

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Sample</th>
<th>Observation Period</th>
<th>Age (SD) BMI (SD)</th>
<th>Measurement of Glucose Metabolism</th>
<th>Main Findings</th>
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<td>34 non-diabetic OSA patients</td>
<td>6 weeks</td>
<td>49.0 (8.3) 36.1 (7.6)</td>
<td>HOMA</td>
<td>No improvement of HOMA</td>
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<td>West et al., 2007</td>
<td>42 diabetic OSA patients</td>
<td>3 months</td>
<td>56.2 (9.9) 36.7 (4.8)</td>
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<td>No improvement of HOMA, HbA1c, or euglycemic clamp</td>
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<td>Lam et al., 2010</td>
<td>61 non-diabetic OSA patients</td>
<td>1 week RCT 12 weeks uncontrolled</td>
<td>46.3 (10.2) 27.5 (3.7)</td>
<td>HOMA Insulin sensitivity SITT</td>
<td>No improvement of HOMA Significant higher insulin sensitivity after one week</td>
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Note: Values are mean (SD); BMI, body-mass-index (kg/m²); HOMA, homeostasis model assessment derived from the fasting glucose and insulin to characterize insulin resistance; HbA1c, glycated hemoglobin; OSA, obstructive sleep apnea; RCT, randomized controlled trial; SITT, short insulin tolerance test.
But were they sufficiently powered?

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Other notable features of DM-OSA relationship

- CPAP therapy seems to reduce glucose variability at night (Pallayova et al Diabetes Res Clin Pract 2008)
- Higher proportion of central apneas in patients with DM than those without (Sanders et al Sleep Med 2003)
- DM related retinopathy strongly associated with OSA (West Diabetes Med 2010) with some suggestion of improvement of visual improvement (macular edema) with CPAP (Mason et al Respiration 2012)
- 4 fold risk of Restless Legs syndrome in DM patients (Merlino et al 2007)
Diabetes and sleep duration:

• A sleep duration of 6 hours or less, or 9 hours or more is associated with increased prevalence of type II diabetes and impaired glucose tolerance

  Gottlieb et al., 2005

• Healthy individuals restricted to four hours of sleep in a clinical study had impaired insulin secretion after a glucose challenge.

  Spiegel et al. 2008

• Other studies showed similar effects of less severe—5.5 hr of sleep curtailment.
Sleep quality: without a change in total sleep time, interrupted sleep impairs insulin sensitivity and glucose disposal.

Sleep was disrupted in 11 healthy volunteers with auditory and mechanical stimuli, resulting in more stage 1 and 2 sleep but markedly decreased slow wave sleep.

AM cortisol and sympathetic activation were higher after sleep interruption.

Do OSA patients have disrupted circadian rhythms?

These altered rhythms correlate with changes in cortisol, sympathetic tone, blood pressure, cytokine levels, and many more.
Relationship between clock genes and metabolic regulatory pathways

Direct Outputs
- Oscillating Transcription Factors
  - DBP
  - TEF
  - HLF
  - REV-ERB
  - E4BP4
- Oscillating RNAs within Metabolic Networks

Metabolic Flux
- Δ glucose
- Δ ATP/AMP
- Δ O2
- Δ glucocorticoids
- Δ catecholamines

Indirect Outputs
- Histone modification / Transcriptional Regulation (FOXO, STAT3, PGC1α)
- Post-Transcriptional Regulation

Bass & Takahashi, 2011
Voluntary Sleep Loss

- “Sleep in America 2005” poll
- National Sleep Foundation
- Adults average 6.9 hours of sleep

**Number of Hours Slept per Night on Weekdays (past two weeks)**

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<tr>
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<tbody>
<tr>
<td>Less than 6 hours</td>
<td>12%</td>
<td>13%</td>
<td>15%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>6 to 6.9 hours</td>
<td>23%</td>
<td>18%</td>
<td>24%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>7 to 7.9 hours</td>
<td>31%</td>
<td>29%</td>
<td>31%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 or more hours</td>
<td>36%</td>
<td>38%</td>
<td>30%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Mean (% of hours)</td>
<td>na</td>
<td>7.0</td>
<td>6.9</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Median (% of hours)</td>
<td>na</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
<td></td>
</tr>
</tbody>
</table>

**Minimum Hours of Sleep Needed Versus Actual Hours of Sleep (Weeknight)**

- Less than Needed
- The same
- More than Needed

- Total
- Male
- Female

**Minimum Hours of Sleep Needed Versus Actual Hours of Sleep (Weeknight)**

Note: Up arrow means the percentage is significantly higher than the percentage for the comparison group.

Base = Total sample (n=4,056)

Letters mean they are statistically significant at the 0.05 confidence interval.

na = Not available

Q5
Mechanisms for hypoxia-induced regulation

- Increased glycolysis
- Increased glucose uptake
- Decreased fat oxidation
- Angiogenesis
- Increased EPO
- Hypothalamic nutrient sensing

VHL → HIF1,2α → ARNT

HIF1α, HIF2β

DNA
HIF-1 and 2 and Metabolism
(Majumdar et al. Mol. Cell 40:294 (2010))
Other important pathways activated in OSA

- **Sympathetic nervous system activation**
  - Also during the wake state
  - Main trigger is hypoxia

- **Hypothalamic-pituitary-adrenal axis dysfunction**
  - Elevated cortisol levels impair insulin sensitivity

- **Systemic inflammation**
  - Sympathetic activation and intermittent hypoxemia (hsCRP, TNF-α, interleukin levels)

- **Adipokines** (elevated levels of leptin)
Linkage Between OSA and DM

Sleep Apnea
  - Sleep Fragmentation
  - Intermittent Hypoxemia
    - Sympathetic Activation
      - ↑ Catecholamines
    - HPA axis Alterations
      - ↑ Cortisol
    - Oxidative stress
      - ↑ ROS
    - Activation of Inflammatory Pathways
      - ↑ IL-6, ↑ TNF-α
    - Changes in Adipokine Profiles
      - ↑ Leptin, ↓ Adiponectin

Insulin Resistance/ Pancreatic β-cell Dysfunction

Glucose Intolerance / Type 2 Diabetes
Conclusions

• Current evidence strongly supports an independent association between OSA and insulin resistance and glucose tolerance, causality remains to be determined (Pamidi 2010)

• It is noteworthy to urge clinicians to systematically evaluate risk of OSA in type 2 diabetic patients and conversely, to assess glucose tolerance in patients with known OSA (Tasali et al Chest 2008)

“the International Diabetes Federation Taskforce on Epidemiology and Prevention strongly recommends that health professionals working in both type 2 diabetes and SDB adopt clinical practices to ensure that a patient presenting with one condition is considered for the other” International Diabetes Federation Taskforce on Epidemiology and Prevention 2008