Sleep in the Patient with Diabetes

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SEPTEMBER, 2017

Learning Objectives

1. Recognize the correlation between sleep apnea and diabetes
2. Review potential relationships between sleep and insulin resistance
3. Treatment of sleep disorders

I have no potential conflicts
Diabetes and sleep

- The majority of patients with diabetes likely have concomitant sleep disorders
- Frequent nocturnal urination
- Obstructive sleep apnea in 60-80% (autonomic dysregulation?)
- Restless legs syndrome
- Periodic limb movements
- Pain related to neuropathy
- Nocturnal hypoglycemia
- Increased heart failure

Bidirectional Relationship?

Sleep  Diabetes
Sleep Disorders

- Poor sleep quality - obstructive sleep apnea
- Short sleep duration - 24 hour lifestyle
- Irregular sleep patterns – Shift work

Obstructive Sleep Apnea

- Recurrent episodes of partial or complete collapse of the upper airway during sleep
- Leads to acute derangements in gas exchange and recurrent arousals
OSA Prevalence

- Data published in the American Journal of Epidemiology
- Estimated prevalence rates of obstructive sleep apnea have increased substantially over the last two decades
- Obesity epidemic
- More recent study using current diagnostic definitions reported a higher prevalence of moderate to severe OSA in 23% of women and 49% of men
OSA and Diabetes

- Growing evidence association between T2DM and OSA
- OSA independently associated with glucose intolerance and insulin resistance
- Likely related to hypoxia and sleep fragmentation
- Hypoxia causes increased epinephrine, norepinephrine and cortisol levels in healthy volunteers

What are the Suspected Causal Pathways that Underlie the Association?
Causal Pathways

- Several studies in animal models have shown that exposure to hypoxia (sustained or intermittent)
- Increasing fasting insulin concentrations
- Healthy participants show impairments in insulin sensitivity when exposed to sustained or intermittent Hypoxia
- Disruption of normal sleep continuity from recurrent arousals with acoustic stimuli reduce insulin sensitivity by 20-25%

Sleep Heart Health Study

- Key in the establishment of independent cross-sectional associations between obstructive sleep apnea severity, insulin resistance, and fasting and post-glucose challenge hyperglycemia
- large (6441)community cohort of middle-aged and elderly adults (age ≥40 years).
- An AHI of 15 or more events per h was associated with lower insulin sensitivity and a higher prevalence of impaired fasting glucose and glucose intolerance.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Participants</th>
<th>Study design</th>
<th>Outcome measures</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td>Reichmuth et al. (9)</td>
<td>1,397 subjects</td>
<td>Observational</td>
<td>T2DM prevalence and incidence; T2DM defined by physician report or FPG</td>
<td>Increased prevalence of T2DM if AHI &gt;15 (AOR 2.36); no increased incidence of T2DM with OSA after 4 years</td>
</tr>
<tr>
<td>Ronksley et al. (8)</td>
<td>2,149 subjects</td>
<td>Cross sectional</td>
<td>T2DM prevalence; T2DM defined by self-report and medication use</td>
<td>Independent association of severe OSA with T2DM (AOR 2.18); relationship confined to sleepy subjects</td>
</tr>
<tr>
<td>Botros et al. (7)</td>
<td>1,233 subjects</td>
<td>Observational</td>
<td>T2DM incidence</td>
<td>Increased incidence of T2DM with OSA (HR 1.43 per AHI quartile); OPAF use appeared to attenuate T2DM risk</td>
</tr>
<tr>
<td>Kent et al. (9)</td>
<td>6,616 subjects</td>
<td>Cross sectional</td>
<td>T2DM prevalence and control; T2DM defined by medication use, prior diagnosis or Hba1c ≥6.5%</td>
<td>Increased prevalence of T2DM with severe OSA (AOR 1.87); worse glycemic control in diabetes with severe OSA</td>
</tr>
<tr>
<td>Kazdanska et al. (6)</td>
<td>8,678 subjects</td>
<td>Historical cohort</td>
<td>T2DM incidence; T2DM defined by related healthcare utilisation</td>
<td>Increased incidence of T2DM with severe OSA (HR 1.31)</td>
</tr>
</tbody>
</table>
| OSA, insulin resistance and glucose intolerance
| Punjabi et al. (10)     | 2,696 subjects | Cross sectional | IGT measured by OGTT; IR estimated by HOMA-IR                                      | Increased IGT with AHI >15 (AOR 1.46); elevated HOMA-IR with AHI >15 and increasing nocturnal hypoxemia |
| Theorell-Hagström et al. (11) | 400 female subjects | Cross sectional | Insulin sensitivity index derived from OGTT                                        | Increasing AHI associated with reduced insulin sensitivity                                  |
| Priou et al. (12)       | 1,599 subjects | Cross sectional | Pre-diabetes (Hba1c 6-6.49%)                                                         | Pre-diabetes more common with severe (AOR 2.02) or very severe OSA (AOR 2.96)               |
| Kent et al. (13)        | 5,294 subjects | Cross sectional | Adjusted mean Hba1c levels by AHI quartile; pre-diabetes (Hba1c 6-6.49%)             | Increasing Hba1c levels with increasing AHI; pre-diabetes more common in highest AHI quartile (AOR 2.12) |

OSA, obstructive sleep apnoea; T2DM, type 2 diabetes mellitus; AHI, apnoea/hypopnea index; CPR, continuous positive airway pressure; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance testing; HOMA-IR, homeostasis model assessment of insulin resistance.

**Thomas Edison**

"In 1882 Edison helped form the Edison Electric Illuminating Company of New York, which brought electric light to parts of Manhattan. But progress was slow. Most Americans still lit their homes with gas light and candles for another fifty years. Only in 1925 did half of all homes in the U.S. have electric power."
Sleep Duration Time Trends in US Adults

- More than 30% of between ages of 30-64 report sleeping less than 6 hours
- Decrease average in sleep have occurred over the same time period as the increase in obesity and diabetes
- Chronic partial sleep loss may impair glucose metabolism and increase diabetes independent of change in BMI
Short Sleep Time and Insulin Resistance

- Karine Spiegel and colleagues did the first thorough investigation of the effects of sleep loss on glucose metabolism in 11 healthy young men (aged 18–27 years)
- sleep was restricted to 4 h for six consecutive nights, with a subsequent recovery period of six nights with 12 h of sleep opportunity.
- decreases in glucose tolerance and insulin sensitivity after sleep loss
- Increased markers of insulin resistance have also been noted in adolescents after their sleep was restricted to 4 h for three consecutive nights
Sleep Duration

- Adult Health and Behavior Project registry, including 1214 Americans aged 30–54 years
- Prevalence metabolic syndrome rates increased to 48% in short sleepers
- US National Health Interview Survey (56,000 adults) showed that short (<7 h per night) and long (>8 h per night) sleep duration
- Increased probability of obesity, type 2 diabetes, hypertension, and cardiovascular disease

The relationship between sleep duration and risk of type 2 diabetes.

Zhilei Shan et al. Dia Care 2015;38:529-537
Short Sleepers and Weight

- 600,000 adults worldwide
- Results show an increased likelihood of obesity (BMI >30 kg/m²) in short sleepers (≤5 h per night) compared with regular sleepers

Short Sleep Duration and DM

- National Health and Nutrition Examination Survey (NHANES I) of 9000 Americans with a follow-up time of roughly 10 years
- Independent association between short sleep duration and the development of type 2 diabetes
- A sleep duration of less than 5 h per night was associated with an increase of 57% (OR 1.57, 95% CI 1.11–2.22) in risk for development of type 2 diabetes
- Adjustment for physical activity, depression, alcohol consumption, ethnic origin, education, marital status, and age
Sleep Debt and Hunger

Change in daytime levels of leptin, ghrelin, appetite and hunger from 10-hour to 4-hour bedtimes in 12 healthy lean subjects after 2 days of curtailed sleep. Hunger and appetite were measured on a visual analogue scale.

Purposed Mechanism in Sleep Debt

Schematic of the potential pathways leading from sleep loss to diabetes risk.
Henry Ford and Shift Work

Henry Ford in the early 1900's introduced shift work into the auto industry to meet the rising automobile market.

Shift Work

- Henry Ford implemented shift work to maximize profit at a 24-hour yield
- The popularity of scheduling irregular work hours has only grown
- The hazard of shift work is largely attributed to the disruption of the body's internal clock, or Circadian Rhythm
- The Circadian Rhythm Largely controlled by the Suprachiasmatic Nucleus (SCN) of the Hypothalamus
- The 24-hour clock is responsible for the release of 'sleepy' hormones around bedtime (i.e. melatonin), morning metabolizing hormones to provide energy after the night fast (i.e. cortisol) and the glucose-metabolizing hormone insulin at appropriate meal times
Shift Work Sleep Disorder

- Circadian rhythm sleep disorder
- Characterized by insomnia
- and excessive sleepiness
- affecting people whose work hours overlap with the typical sleep period

Shift Work

- Shift work is associated with increased risk of DM
- Meta-analysis including 12 studies, 226,652 participates
- Higher in men
- Higher in rotating shifts
- Meta-analysis including 12 studies, 226,652 participates

* Shift work and diabetes mellitus: a meta-analysis of observational studies
* Yong Huang, et al.
* Conclusion: Shift work is associated with an increased risk of DM. The increase was significantly higher among men and the rotating shift group, which warrants further studies.
Shift work and Diabetes

- Experimentally induced sleep restriction and/or circadian misalignment
- Generated by inducing recurrent 28-h sleep-wake cycles
- Decrease insulin sensitivity and glucose tolerance
- Data from epidemiological studies suggest that long-term alteration in sleep pattern increases the risk of obesity and metabolic diseases.

Purposed Causal Association with Shift Work and Diabetes

- Circadian misalignment shown to contribute to: leptin decrease, glucose increase, insulin increase, mean arterial blood pressure increase
- Reduced sleep efficiency
- Changes in unhealthy behaviors
- Shifting timing of food intake may influence postprandial glucose and insulin levels
Tools for the Evaluation of Sleep

- Epworth Sleepiness Scale
- Stop Bang
- RLS questionnaire
- Sleep Study or Polysomnogram (PSG)
Screening tools: Epworth Sleepiness Scale

- Subjective assessment of daytime sleepiness
- Patient completed questionnaire
- Uses a four point scale (0,1,2,3) to indicate the likelihood of dozing in eight sedentary conditions
- Total score of 10 out of 24 or more suggests excessive daytime sleepiness
- May correlate to a limited extent with the presence or severity of OSA
- Best used as a follow up to assess treatment response or as a screening tool for daytime sleepiness

STOP-BANG

- S **Snoring** Do you snore loudly (louder than talking or loud enough to be heard though closed doors)?
- T **Tired** Do you feel tired, sleepy or fatigued during the daytime?
- O **Observed apneas** Has anyone heard you stop breathing during your sleep?
- P **Blood Pressure** Do you have or have you been treated for high blood pressure?
- B **BMI** BMI greater than 35 kg/m2?
- A **AGE** Age greater than 50?
- N **Neck circumference** Neck circumference greater than 40 cm or 15.75 inches?
- G **Gender** Male?
Screening tools: STOP-BANG Questionnaire

- Sensitive screening tool for OSA, not in DM
- High risk OSA, answering three or more items
- Low risk OSA, answering less than three items

In Lab Polysomnogram
## Home Sleep Testing

### What Should I Order? Testing Options

<table>
<thead>
<tr>
<th>Full night diagnostic</th>
<th>Split night study</th>
<th>Home or portable sleep study</th>
</tr>
</thead>
<tbody>
<tr>
<td>-attended by sleep technologist</td>
<td>-attended by sleep technologist</td>
<td>-unattended study</td>
</tr>
<tr>
<td>-in sleep lab</td>
<td>-in sleep lab</td>
<td>-at home</td>
</tr>
<tr>
<td>-pure diagnostic study</td>
<td>-first several hours are diagnostic</td>
<td>-pure diagnostic for OSA</td>
</tr>
<tr>
<td></td>
<td>-Second part of this study is with positive airway pressure</td>
<td></td>
</tr>
</tbody>
</table>
Sleep Hygiene

- Not exercising either mentally or physically too close to bedtime;
- Taking naps at appropriate times;
- Establishing a regular sleep schedule;
- Reducing worry;
- Getting out of bed if sleep doesn’t come;
- Limiting exposure to light prior to sleep;
- Using bed only for sex and sleep;
- Avoiding stimulant such as alcohol, caffeine and nicotine in the hours before bedtime;
- Creating a dark, comfortable, and peaceful sleep environment.

Cognitive Behavioral Therapy for Insomnia

- Behavioral treatment for insomnia
- Cognitive behavioral therapy for insomnia or CBT-I is more effective than medications in treating insomnia over the long term
- More time-consuming
- Medications may provide stronger short-term results
Cognitive Behavioral Therapy for Insomnia

- Relaxation techniques
- Stimulus control- addresses the learned associations between the bedroom and staying awake
- Sleep restriction- reduce wake hours spent in bed
- Cognitive therapy-combines several therapies
- Sleep hygiene, most patients have tried

FDA approved medications for insomnia

<table>
<thead>
<tr>
<th>Sleep onset</th>
<th>Sleep maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset:</td>
<td>Zolpidem ER</td>
</tr>
<tr>
<td>Zolpidem low dose</td>
<td>Low dose doxepin</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Zolpidem ER</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>Eszopiclone</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Suvorexant</td>
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<tr>
<td></td>
<td>Temazepam</td>
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<tr>
<td></td>
<td>Estazolam</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
</tr>
</tbody>
</table>
Restless Leg Syndrome

- 18% of diabetic patients
- Associated with pregnancy, diabetes, deficiency with ferritin less than or equal to 50 ng/ml, medications (such as antidepressants, Benadryl), hereditary 50%, uremia
- Nearly irresistible urge to move legs, typically in the evening
- Associated with discomfort in the legs
- Occurs while awake

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**Restless Legs Syndrome**

Table 1: Criteria for the Diagnosis of Restless Legs Syndrome

An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. Sometimes the urge to move is present without the uncomfortable sensations, and is occasionally present in the arms or other body parts in addition to the legs.

The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting.

The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.

The urge to move or unpleasant sensations are worse in the evening or night than during the day or occur only in the evening or night. When symptoms are severe, the worsening at night may not be noticeable but must have been previously present.
RLS Treatment

- General measures
- Iron deficiency, ferritin check
- Stop aggravating factors
- Dopamine agonists
- Gabapentin enacarbil, Brand Horizant

CPAP

- CPAP remains the gold standard for OSA treatment
- Education and follow up are key
- CPAP machines are quieter, smaller and more portable.
- CPAP masks are more comfortable.
- There also are more mask options, including “nasal pillows” and special sizes for women
- Heated humidifiers are more advanced
CPAP

TABLE 1. CPAP Treatment and Type 2 Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (n)</th>
<th>Design</th>
<th>Primary Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasad et al. (62)</td>
<td>221</td>
<td>Retrospective cohort; CPAP effects over 2 years</td>
<td>No change in A1C before and after CPAP treatment</td>
</tr>
<tr>
<td>Guest et al. (63)</td>
<td>300</td>
<td>Retrospective case control; CPAP vs. no treatment over 5 years</td>
<td>A1C significantly lower in CPAP group</td>
</tr>
<tr>
<td>Myhill et al. (64)</td>
<td>44</td>
<td>Prospective, randomized; CPAP early (&lt;1 week) or late (&gt;1 month) for 3 months</td>
<td>Decreased insulin resistance in CPAP group by oral GTT</td>
</tr>
<tr>
<td>Guo et al. (65)</td>
<td>40</td>
<td>Prospective; pre-treatment vs. post-CPAP treatment for 1 month</td>
<td>Decreased 24-hour mean blood glucose and nighttime mean blood glucose after CPAP, as determined by continuous glucose monitoring</td>
</tr>
<tr>
<td>Salford et al. (66)</td>
<td>80</td>
<td>Prospective, randomized, controlled trial; CPAP vs. conservative treatment for 3 months</td>
<td>Decreased insulin resistance by oral GTT in CPAP group</td>
</tr>
</tbody>
</table>
Dental Devices For OSA

- Most work as mandibular advancing devices by advancing the mandible
- Studies have documented their effectiveness in mild to moderate OSA
- Effective (defined as acceptance plus an AHI of less than 10-15/hour) in 50%-70%
- Self report of adherence at 4 years is 63%

Mandibular Advancing Device

During sleep, there is restricted airway space  
Mandibular Advance Device (Mouth Guard) increases airway space
Weight Loss and OSA

- Weight loss may result in significant improvement in OSA
- Considered adjunct treatment for OSA
- Not recommended as a primary treatment in patient unless mild and asymptomatic
- Takes time and difficulty with maintenance
- Weight loss may reduce/improve the AHI even if obesity is mild

Hypoglossal Nerve Stimulation

- Upper-airway stimulation with unilateral stimulation of the hypoglossal nerve
- Apnea is accompanied by a reduction in drive to the upper-airway muscles
- Stimulation of the hypoglossal nerve evokes an anterior displacement of the tongue
Management of Sleep Disorders

- Sleep history: shift work
- Review total sleep duration
- Epworth sleepiness scale, may help to tease out sleepiness vs fatigue
- Consider sleep disorders than may exacerbate sleep issues such as RLS, OSA, PLMD
- Consider sleep study
- Review medication for side effects
- Screen depression and anxiety