Over the last two decades there has been increased awareness that sleep disturbances may have an important role in the pathogenesis of metabolic dysfunction. Insufficient sleep has been associated with reductions in insulin sensitivity, glucose intolerance, and increased risk for type 2 diabetes. Laboratory based studies have shown that sleep restriction in health subjects is associated with reduction of insulin sensitivity and impairments in glucose tolerance. Interestingly, the metabolic impairments observed with acute sleep restriction appear to reverse with recovery sleep. Putative mechanisms linking sleep restriction to metabolic impairments include increase in sympathetic nervous system activity, alterations in corticotropic function, abnormalities in adipocyte function, and rise in markers of systemic inflammation. Pooled data from epidemiological longitudinal studies support that notion that short sleep duration is associated with a higher risk for developing type 2 diabetes. In addition to the effects of habitual sleep duration, quality of sleep may have deleterious effects on metabolic function. Disruption of sleep continuity, a hallmark of a number of sleep disorders including RLS, has been shown to impair glucose metabolism. In healthy volunteers, non-specific fragmentation of sleep for two nights decreases insulin sensitivity by 25% and is associated with a shift in sympathovagal balance towards heightened sympathetic nervous system activity. Moreover, selective suppression of slow wave sleep can also lead to a similar level of decrease in insulin sensitivity. Although inferences regarding the implications of sleep quality are limited given the laboratory-based nature of the available studies, prospective data from population-based research does, in fact, show that poor sleep quality increases the risk for incident diabetes independent of other well-established risk factors. Indeed, a meta-analysis of the available literature has shown that difficulty initiating sleep and maintaining sleep are associated with a relative risks of 1.54 and 1.87, respectively, for developing type 2 diabetes. Mechanisms through which poor sleep quality may worsen metabolic function are not known. As with habitual sleep duration, it is certainly possible that corticotropic dysregulation, sympathetic activation, alterations in appetite-regulating hormones including leptin and ghrelin, and increase in inflammatory cytokines may explicate some of the excess metabolic risk. The overarching goal of this presentation will be to review the current evidence linking sleep disturbances to various aspects of glucose metabolism and type 2 diabetes.

References:

3. Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. J Clin Endocrinol Metab 2009;94:3242-50.
Sleep and Diabetes: More than Sleep Apnea

Naresh M Punjabi MD, PhD
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University, School of Medicine
Baltimore, MD, USA

General Outline

• Relevance of sleep for endocrine function
• Sleep deprivation and glucose metabolism / diabetes risk
• Mechanisms relating sleep deprivation to glucose metabolism
• Does recovery sleep improve glucose metabolism?
• Epidemiological data on sleep duration / diabetes risk
• Sleep quality on glucose metabolism and diabetes risk
• Current state of the art on “sleep and diabetes”

Incidence of and risk factors for nodding off at scientific sessions

Kenneth Rockstroh, David B. Hogan, Christopher J. Patteson; for the Nodding at Presentations (NAP) Investigation

Table 1: Risk factors for nodding off at lectures

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental</td>
<td>1.6 (0.8-2.8)</td>
</tr>
<tr>
<td>Dim lighting</td>
<td>1.4 (0.9-2.1)</td>
</tr>
<tr>
<td>Warm room temperature</td>
<td>1.0 (0.7-1.3)</td>
</tr>
<tr>
<td>Comfortable seating</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Auditory</td>
<td>1.0 (1.0-3.5)</td>
</tr>
<tr>
<td>Poor slides</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Failure to speak into microphone</td>
<td>1.7 (0.9-3.2)</td>
</tr>
<tr>
<td>Circadian</td>
<td>1.3 (0.9-1.8)</td>
</tr>
<tr>
<td>Early morning</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td>Post prandial</td>
<td>1.7 (0.9-3.2)</td>
</tr>
<tr>
<td>Speaker related</td>
<td>6.6 (1.4-28.6)</td>
</tr>
<tr>
<td>Monotonous tone</td>
<td>2.1 (1.7-3.3)</td>
</tr>
<tr>
<td>Toned jacket</td>
<td>2.0 (1.5-2.6)</td>
</tr>
</tbody>
</table>

Sleep-wake state and circadian rhythmicity on pituitary secretion

Modified from Van Cauter and Copinschi, Endocrinology, 2006
General Outline

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Impact of sleep debt on metabolic and endocrine function

- 11 healthy volunteers (men)
- Experimental sleep restriction (4 hours/night x 6 nights)
- Recovery period (12 hours/night x 6 nights)

Outcomes assessed:
- Carbohydrate metabolism
- Adrenal function
- Heart rate variability (sympathetic activity)

SLEEP DEBT SLEEP EXTENSION

**Study Protocol**

<table>
<thead>
<tr>
<th>Day</th>
<th>Sleep Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td>09 13 17 21 01 05 09</td>
</tr>
<tr>
<td>21</td>
<td>09 13 17 21 01 05 09</td>
</tr>
<tr>
<td>01</td>
<td>09 13 17 21 01 05 09</td>
</tr>
<tr>
<td>05</td>
<td>09 13 17 21 01 05 09</td>
</tr>
</tbody>
</table>

**Response to breakfast**

<table>
<thead>
<tr>
<th>Glucose (mg/dl)</th>
<th>Insulin Secreted (nmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9772 ± 211</td>
<td>47.6 ± 2.5</td>
</tr>
<tr>
<td>9205 ± 314</td>
<td>43.2 ± 2.4</td>
</tr>
</tbody>
</table>

**Response to intravenous glucose**

<table>
<thead>
<tr>
<th>Glucose Tolerance</th>
<th>Acute Insulin Response</th>
<th>Glucose Effectiveness</th>
<th>Insulin Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>p&lt;0.05</td>
<td>p&lt;0.001</td>
<td>p&lt;0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Impact of sleep debt on metabolic and endocrine function**

- Sleep debt can lead to:
  - Decreased glucose clearance
  - Decrease in acute insulin response to glucose
  - Increased levels of evening cortisol
- Effects similar to those seen in normal aging

**Possible contributors to glucose intolerance with sleep deprivation**

- Decreased brain glucose utilization
- Alterations in sympatho-vagal balance
- Increased evening cortisol levels
- Alterations in leptin/ghrelin with sleep deprivation
- Alterations in systemic inflammation

**General Outline**

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Possible contributors to glucose intolerance with sleep deprivation

- Decreased brain glucose utilization
  - Brain is the major site of non-insulin-dependent glucose utilization
  - PET studies show decrease in brain glucose utilization with sleep deprivation

- Alterations in sympatho-vagal balance
- Increased evening cortisol levels
- Alterations in leptin/ghrelin with sleep deprivation
- Alterations in systemic inflammation

Heart rate variability (rRR)

High rRR = Decreased Heart Rate Variability =
Increased Sympathetic Nervous Activity and/or
Decreased Parasympathetic Nervous Activity

Modified from Spiegel et al., J Clin Endocrinol Metab, 2004

Cortisol after partial or total sleep deprivation

Modified from Leproult et al., Sleep, 1997
Possible contributors to glucose intolerance with sleep deprivation

- Decreased brain glucose utilization
- Alterations in sympatho-vagal balance
- Increased evening cortisol levels
- Alterations in leptin/ghrelin with sleep deprivation
- Alterations in systemic inflammation

Two days of sleep restriction or extension

<table>
<thead>
<tr>
<th>Dinner Time</th>
<th>Glucose Infusion</th>
<th>Hunger and Appetite Questionnaires</th>
<th>Blood Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>22:00</td>
<td>5gKg/24h</td>
<td>Every hour</td>
<td>Every 20 min</td>
</tr>
</tbody>
</table>

Daytime leptin and ghrelin levels

<table>
<thead>
<tr>
<th>CLOCK TIME</th>
<th>9-21 leptin levels (ng/ml)</th>
<th>12-21 ghrelin levels (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00</td>
<td>2.4 ± 0.3</td>
<td>3.3 ± 0.3</td>
</tr>
<tr>
<td>11:00</td>
<td>2.6 ± 0.3</td>
<td>3.5 ± 0.4</td>
</tr>
<tr>
<td>13:00</td>
<td>2.9 ± 0.4</td>
<td>3.6 ± 0.5</td>
</tr>
<tr>
<td>15:00</td>
<td>3.1 ± 0.5</td>
<td>3.8 ± 0.6</td>
</tr>
<tr>
<td>17:00</td>
<td>3.3 ± 0.6</td>
<td>4.0 ± 0.7</td>
</tr>
<tr>
<td>19:00</td>
<td>3.5 ± 0.7</td>
<td>4.2 ± 0.8</td>
</tr>
<tr>
<td>21:00</td>
<td>3.7 ± 0.8</td>
<td>4.4 ± 0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p level</th>
<th>% change</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.041</td>
<td>-37%</td>
</tr>
<tr>
<td>0.018</td>
<td>+24%</td>
</tr>
</tbody>
</table>

Ratings of hunger and appetite

<table>
<thead>
<tr>
<th>CLOCK TIME</th>
<th>HUNGER (cm)</th>
<th>GLOBAL APPETITE (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22:00</td>
<td>6.2 ± 0.5</td>
<td>39.7 ± 3.0</td>
</tr>
<tr>
<td>23:00</td>
<td>7.2 ± 0.4</td>
<td>47.7 ± 3.4</td>
</tr>
<tr>
<td>0.010</td>
<td>+20%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>p level</th>
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<td>+24%</td>
</tr>
</tbody>
</table>

Modified from Spiegel et al., J Clin Endocrinol Metab, 2004

Leptin, cortisol, HOMA and sleep duration

<table>
<thead>
<tr>
<th>LEPTIN (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
</tr>
<tr>
<td>1.5</td>
</tr>
<tr>
<td>2.0</td>
</tr>
<tr>
<td>2.5</td>
</tr>
<tr>
<td>3.0</td>
</tr>
<tr>
<td>3.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CORTISOL (µg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HOMA (INSULIN (mU/L) * GLUCOSE(mmol/L) / 22.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>20</td>
</tr>
</tbody>
</table>

Modified from Spiegel et al., Ann Int Med, 2004
LABORATORY STUDY
Spiegel et al
Within subject comparison
2 days of 4-h bedtimes versus
2 days of 10-h bedtimes
n = 12
age: 22 ± 2 years
100% men

CHANGE IN LEPTIN
(Satiety hormone)
-18 % *

CHANGE IN GHRELIN
(Appetite hormone)
+28 % *

* Body mass index unchanged; * After controlling for Body mass index

Spiegel et al., J Appl Physiol, 2005

Impact of sleep loss on leptin and ghrelin

Longer sleep associated with lower ghrelin levels

Adjusted Ghrelin (ng/ml), sqrt scale

Total Sleep Time (hrs)

Spiegel et al., J Appl Physiol, 2005

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• Current state of the art on “sleep and diabetes”
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Association of Sleep Time with Diabetes Mellitus and Impaired Glucose Tolerance

- Participants from the multi-center Sleep Heart Health Study
  - A community based study of sleep, sleep apnea, and CVD
  - Sub-sample of 1,486 subjects (722 men and 764 women)
  - Usual sleep time obtained by self-report
  - Impaired glucose tolerance and diabetes mellitus based on serum glucose measurements (fasting and 2-hour)
  - Statistical adjustments made for numerous covariates including age, gender, race, sleep apnea severity, and waist

Data from Nutrition and Health Survey (Taiwan)
- Stratified three-staged probability sampling method
- Cross-sectional design
- 1533 participants (733 men, 800 women)
- Age 19-64 years of age
- Sleep duration related to prevalent type 2 diabetes

Current state of the art on “sleep and diabetes”
Sleep Disturbance as a Predictor of Type 2 Diabetes Mellitus in Men and Women from the General Population

- MONICA (monitoring trends and determinants of cardiovascular disease) sample from population registry in Germany

- Sleep disturbance ascertained as difficulty initiating or maintaining sleep (3-point Likert scale)

- Sample size 8,269 non-diabetic participants (4,140 men and 4,129 women) followed up over a 10-year period

- Assessment of incident diabetes (self-reported or hospital-physician records)

Meisinger et al. Diabetologia 48, 2005

Incidence of Diabetes in Middle-Aged Men is Related to Sleep Disturbances

- Prospective population-based study in Sweden
- Male cohort (n = 6,599) examined over a 15-year period
- Self-reported difficulty in falling asleep or use of hypnotics
- Diabetes defined based on fasting glucose measurements

Nilsson et al. Diabetes Care 27, 2004

Conclusion:
Difficulty maintaining sleep is associated with an increased risk of type 2 diabetes in men and women from the general population

Meisinger et al. Diabetologia 48, 2005

Sleep disturbance in middle-aged men is associated with increased risk of diabetes.

Nilsson et al. Diabetes Care 27, 2004

The Effect of Sleep Quality on the Development of Type 2 Diabetes in Primary Care Patients

- Outpatient clinic patients in general hospitals (Korea)
- 563 patients without diabetes
- Pittsburgh Sleep Quality Index to determine sleep quality
- Score of ≥ 5 was considered to define poor sleep quality

Nilsson et al. Diabetes Care 27, 2004
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  • MECHANISMS?
• Current state of the art on “sleep and diabetes”

Sleep Fragmentation in Normal Subjects

Effects of Sleep Fragmentation on Glucose Metabolism in Normal Subjects

• Sleep fragmentation (non-specific) for two nights
  • Decreases insulin sensitivity (Si)
  • Increases insulin secretion to compensate for lower Si
  • Decrease glucose effectiveness
  • Increases sympathetic nervous system activity
  • Increase morning cortisol levels

Stamatakis and Punjabi (Chest - 2010)
General Outline

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- Current state of the art on “sleep and diabetes”
Pooled adjusted RRs of sleep disturbances relative to traditional risk factors. None of the studies of traditional risk factors adjusted for sleep disturbances while a majority of sleep disturbances studies adjusted for traditional risk factors.

General Conclusions

- Sleep is integral for endocrine function
- Sleep deprivation impairs glucose metabolism / diabetes risk
- Several mechanisms relate sleep deprivation to glucose metabolism
- Recovery sleep improves glucose metabolism
- Epidemiological link sleep duration to diabetes risk
- Sleep quality is vital for normal glucose metabolism and impairments in sleep quality increases diabetes risk

“Sleep is the golden chain that ties health and our bodies together”

Thomas Dekker (1572 – 1632)  
English Poet and Playwright