Disclosure statement:
We have no financial relationships with a commercial interest/interests producing healthcare related products and/or services

“It’s a taser. It’s for your snoring.”
Glucose Intolerance and its Association with Sleep Disordered Breathing

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What is normal human sleep?
Sleep Architecture

**The Stages of Sleep: One Sleep Cycle**

- **Sleep Latency**
  - Time to fall asleep
  - Starts when you close your eyes and ends when you fall asleep
  - Light sleep

- **Stage 1**
  - Brain waves slow down, resting the parts you use while awake

- **Stage 2**
  - Deeper sleep; restorative
  - Delta waves

- **Stage 3**
  - Especially recuperative; restores and recharges the body
  - Delta waves
  - Essential to the sleep process

- **Stage 4**
  - The deepest sleep
  - Characterized by rapid eye movements
  - Body (arms and legs) otherwise motionless
  - Dreaming; active brain waves similar to when thinking

- **REM**
Sleep Cycles

Awake
Low voltage
High frequency

Stage 1
Low voltage
Mixed frequency

Stage 2
Sleep spindles
& K complexes

Stage 3
Mostly slow waves

Stage 4
Slow waves

REM
Low voltage, mixed frequency
+ rapid eye movement & muscle atonia

After Rechtschaffen & Kales, 1968; Kalat, 2005; Weiten 2004
Normal Patterns of Sleep

**Slow wave sleep** is present when delta waves account for more than 20% of the sleep EEG.

- REM sleep follows NREM sleep and occurs 4-5 times during a normal 8-hour sleep period.
- The first REM period of the night may be less than 10 minutes in duration, while the last may exceed 60 minutes.

- The average length of the first NREM-REM sleep cycle is between 70 and 100 minutes.
- The average length of the second and later cycles is about 90 to 120 minutes.
- The reason for such a specific cycling pattern of NREM and REM sleep across the night is unknown.
Changes with Age

- Infancy
- Maturity
- Old Age
Sleep Parameters In Normal Aging

- **Sleep Duration**, current review of literature supports the Total Sleep Time (TST) decreases with age.

- Review of a 3 meta-analysis study reported that age was linearly associated with decreased TST. 10-12 minute reduction per decade of age was noted. TST plateaued after age 60.

- **Sleep Initiation**, sleep onset and ability to fall back to sleep after nocturnal awakenings, show minimal increases after age of 60.

- **Sleep Efficiency**, declines significantly in adulthood however differs from all other sleep parameters in that it continues to decline slowly with advanced age.

- **Sleep Maintenance**, wake after sleep onset (WASO) plateaus after age 60 and remains unchanged. In age range 30 – 60 years, 10 minute increase in WASO is reported.
Daytime Napping and Daytime Sleepiness

• Routine for many people across the lifespan

• More prevalent in older adults

• No clear evidence support nap duration difference between older adults and other adult population

• Number of daytime naps increased with age, older adults napped more in evening, younger adults likely to nap in afternoon

• People choose to take naps for various reasons
  ➢ nighttime sleep loss
  ➢ restore energy
  ➢ reduce daytime sleepiness
  ➢ just to relax

Cultural backgrounds influences nap habits

Older adults nap more frequently because of biological changes and lifestyle changes, due to more opportunities
• Excessive Daytime Sleepiness (EDS):
  - Associated with sleep disorders as well as depression, pain, and nocturia
  - Up to 20 percent of adults reported EDS in epidemiological studies.
  - Coexists with other adverse health problems such as cognitive impairment, CV events, and increased mortality risk
  - Not a part of normal aging but may be symptom of certain diseases.
Other Sleep Changes Noted with Aging

- It is associated with advanced sleep timing, decreased nocturnal sleep time and sleep efficiency.

- Increased daytime nap frequency causes increased nocturnal awakenings and decreased Slow Wave Sleep or deep sleep stage.

- Most sleep parameters are unchanged after age 60 in healthy older adults.

- Less robust Circadian system and sleep homeostasis is noted in aging.

- Multiple factors in aging process from medical and psychiatric problems, environmental, social and lifestyle changes contribute to sleep problems in older adults.
Common Causes of Sleep Disturbances

- **Obstructive Sleep Apnea (OSA)**: insomnia like symptoms 40-60 percent higher in patients with sleep apnea as compared to general population.

- **Nocturia**: common cause of insomnia in older adults, defined as waking up at least one time at night to void. Reduces sleep quality if difficulty falling asleep after awakenings. May be a direct cause of sleep disturbance or be linked to other comorbidities such as OSA.

- **GERD**: sleep disturbances are higher in patients with gastroesophageal reflux disease than those without. 50 percent of patients with GERD report heartburn and reflux symptoms, acid regurgitation and chest pain that awakens them from sleep.

- **Chronic Pain**: sleep plays a protective role against pain, lack of sleep will activate the pain matrix, increasing severity of pain symptoms.
Sleep – Wake Disorders

- **Sleep deprivation** - inadequate opportunity and circumstances for sleep, resulting in similar daytime symptoms as patients with insomnia.

  - Tiredness, loss of concentration, irritability, decreased productivity.

- **Insomnia** - dissatisfaction with sleep (quality, duration, difficulty falling asleep or staying asleep, awakening to early, inability to return to sleep) despite adequate opportunity and circumstances for sleep.

- **Circadian rhythm sleep disorders** - symptoms of difficulty falling asleep or waking too early. Patient goes to bed and wakes at very late times.
Restless Legs Syndrome (RLS)

- Disorder characterized by an irresistible urge to move the legs during rest, usually accompanied by uncomfortable sensations in affected extremity or extremities.

- Often worse at nighttime and can interfere with sleep onset.

- RLS can manifest at any age but prevalence increases with advancing age.
Periodic Leg Movement Syndrome (PLMS)

- Involuntary limb movements seen during Sleep Study (Polysomnogram)
- Different from RLS
- Often associated with OSA. Once OSA is treated - PLMS often improves.
Sleep Arousal/Fragmentation

Sleep Disordered Breathing (SDB)

- Dynamic imbalance between airway patency and collapse during sleep leading to recurrent airways obstruction (partial or complete) resulting in:
  - Gas exchange abnormalities
  - Cortical arousals leading to sleep fragmentation
  - Autonomic arousals leading to systemic fragmentation
- Diagnosed by presenting symptoms (night and day) and sleep study
- Naturally occurring model of sleep fragmentation
Obstructive Sleep Apnea (OSA)

- Most common sleep-related breathing disorder

- Epidemiology
  - It affects 20 to 30% males, 15% females
  - Male-to-Female ratio: Adulthood: 2-3:1
  - African Americans and Hispanics > Caucasians
  - Interestingly, OSA prevalence in Asia is similar to that in the United States, despite lower rates of obesity, possibly because of craniofacial anatomy.
Respiratory Events

• **Apnea**: cessations of airflow for at least 10 seconds

• **Hypopnea**: airflow decreases for at least 30% and lasts for at least 10 secs. This event is associated with either a 4% oxygen desaturation or arousal.

• **Respiratory effort-related arousal (RERA)**: increasing respiratory effort for 10 secs leading to an arousal from sleep that does not fulfill the criteria for an hypopnea or apnea.
Types of apneic events

• **Obstructive event**: partial or complete obstruction of airflow despite continued thoraco-abdominal effort.

• **Central event**: airflow obstruction with in the absence of thoraco-abdominal effort.

• **Mixed events**: both obstructive and central features are present. Events usually begin without thoraco-abdominal effort and end with several thoracoabdominal efforts in breathing.
STOP-Bang Questionnaire

Please answer the following questions by checking “yes” or “no” for each one

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring (Do you snore loudly?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiredness (Do you often feel tired, fatigued, or sleepy during the daytime?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed Apnea (Has anyone observed that you stop breathing, or choke or gasp during your sleep?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Blood Pressure (Do you have or are you being treated for high blood pressure?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (Is your body mass index more than 35 kg per m²?)</td>
<td></td>
<td></td>
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<tr>
<td>Age (Are you older than 50 years?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck Circumference (Is your neck circumference greater than 40 cm [15.75 inches]?)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Are you male?)</td>
<td></td>
<td></td>
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</tbody>
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Score 1 point for each positive response.

Scoring interpretation: 0 to 2 = low risk, 3 or 4 = intermediate risk, ≥ 5 = high risk.
### Clinical features of obstructive sleep apnea (OSA)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Examination findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Daytime sleepiness</td>
<td>- Narrow or &quot;crowded&quot; airway</td>
</tr>
<tr>
<td>- Nonrestorative sleep</td>
<td>- Obesity</td>
</tr>
<tr>
<td>- Loud snoring</td>
<td>- Large neck circumference</td>
</tr>
<tr>
<td>- Witnessed apneas by bed partner</td>
<td>- Systemic hypertension</td>
</tr>
<tr>
<td>- Awakening with choking</td>
<td>- Hypercapnia</td>
</tr>
<tr>
<td>- Nocturnal restlessness</td>
<td>- Cardiovascular disease</td>
</tr>
<tr>
<td>- Insomnia with frequent awakenings</td>
<td>- Cerebrovascular disease</td>
</tr>
<tr>
<td>- Lack of concentration</td>
<td>- Cardiac dysrhythmias</td>
</tr>
<tr>
<td>- Cognitive deficits</td>
<td>- Pulmonary hypertension</td>
</tr>
<tr>
<td>- Changes in mood</td>
<td>- Cor pulmonale</td>
</tr>
<tr>
<td>- Morning headaches</td>
<td>- Polycythemia</td>
</tr>
<tr>
<td>- Vivid, strange, or threatening dreams</td>
<td>- Floppy eyelid syndrome</td>
</tr>
<tr>
<td>- Gastroesophageal reflux</td>
<td></td>
</tr>
<tr>
<td>- Nocturia</td>
<td></td>
</tr>
</tbody>
</table>
Cardiovascular effects of OSA

- Increased negative inspiratory pressure
  - Increased afterload
  - Impaired LV relaxation

- Intermittent hypoxia leads to activation of the endothelial system, results in vasoconstriction

- OSA leads to state of elevated adrenergic tone, contributing to resistant hypertension
Cardiovascular effects of OSA

• Hypoxemia - results from apneas and hypopneas

• Arousal from sleep - less time spent in restorative slow wave sleep

• Don’t see normal fall in HR and BP due to apneas and body’s response

• Heart rate can vary, increasing risk of arrhythmia
Common Clinical Conditions Associated with Insulin Resistance

- Metabolic syndrome
- Hypertension
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease
- Obstructive sleep apnea

Insulin sensitivity as secondary cause:

- Acute illness
- Cushing’s syndrome
- Pregnancy
## Factors for Insulin Sensitivity

<table>
<thead>
<tr>
<th>Well established factors</th>
<th>Possible factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiposity</td>
<td>Sleep</td>
</tr>
<tr>
<td>Diet</td>
<td>Sleep deprivation</td>
</tr>
<tr>
<td>Exercise and physical activity</td>
<td>Sleep-related disorders</td>
</tr>
<tr>
<td>Stress</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
</tr>
</tbody>
</table>
Sleep is a significant and modifiable lifestyle behavior
Sleep Optimization and Diabetes Control: A Review of the Literature

Diabetes Ther 2015 Dec 6(4) 425-426
Teresa Arora and Sharard Taheri
Department of Medicine, Weill Cornell Medical College, New York, USA

Pre-diabetes and diabetes occur secondary to a course of events of pathophysiologic abnormalities resulting in insulin resistance.

- Strong genetic basis but also largely driven by lifestyle factors

- Traditional lifestyle factors of diet and physical activity alone do not fully explain dramatic rise in prevalence and incidence of Diabetes Mellitus (T2DM)

• Sleep has emerged as an additional lifestyle behavior.

Sleep is important for metabolic and energy homeostasis
Two Process Model of Sleep Regulation
Sleep Drive (Process S & C)

**Process S**
- Instinctive desire for sleep
- Sleep debt occurs during the day
- Sleep debt is repaid once sleep occurs
- If not adequately repaid, it accumulates resulting in poor daytime function and potential metabolic abnormalities

**Process C**
- Determines the timing of sleep
- Regulated by light exposure, thus light exposure near bedtime delays sleep
- Circadian regulation occurs via the hypothalamic suprachiasmatic nucleus and is synchronized by light via the retino-hypothalamic tract. (thus light exposure near bedtime delays sleep)
Process S and Process C Interaction
Sleep Hormones

Many hormones are released in circadian manner.

- Cortisol, higher in morning and low in evening.

- Desynchronized Process S and C (as in jet lag or night shift work) results in metabolic abnormalities secondary to hormonal alterations.

Once sleep occurs, several hormones are released, specifically linked to sleep stages.

- Example: Growth hormone and prolactin are released during the deep stages of sleep.

Therefore, sleep loss can also impact the release of hormones that regulate metabolic function.
Highly Complex Physiological Processes Occur During Sleep

- Hormone release, information processing, cellular restoration and more.

- Sleep was previously believed to be only phenomenon for and by the brain.

- Evidence now indicates clear peripheral effects on metabolic outcomes.

- Represented by gradual sleep alterations that have occurred within current societal norms along with the rising prevalence of metabolic diseases.

- Much of the research focus has been on sleep quantity; however, there are many other significant sleep characteristics that have been linked to T2DM.
Shortened Sleep Duration

Shortened sleep duration is widespread and has consequences. Contributing factors include:

- busy lifestyles
- increasing use of technology
- underlying sleep disorders

In short, a number of studies have shown that short total sleep time (< 5 hours) results in significant increase in prevalence of Type 2 Diabetes and Pre-diabetes.
OSA and Diabetes Link

- OSA is strongly linked to diabetes, although which develops first is to be determined.
- Several studies have reported an association between OSA, glycemic control and diabetes microvascular complications.
- OSA appears to be more common in ethnicities where T2DM is more common.
- Snoring may also be a risk factor for T2DM - possibly as a consequence of Obstructive Sleep Apnea (OSA).

Many studies have not been able to address the confounding effect of OSA in the relationship between sleep and metabolism.
Sleep Disordered Breathing disrupts metabolic regulation and extensive data has emerged in relation to insulin resistance and other features of diabetes.

Improving sleep can in turn improve metabolic profiles.

*Continuous positive airway pressure (CPAP), used to treat OSA, has been shown to improve glycemic control prospectively.*
Emerging Effect of Sleep-Wake Misalignment Upon Insulin Resistance and Diabetes

Majority of focus has been on sleep quantity and quality.

- There is now emerging evidence that circadian rhythms, chronotype and sleep-wake timings play important role in diabetes onset, development and management.

It is well established that shift workers have a higher prevalence of metabolic disorders.

- In particular, night-shift workers and rotating shift workers are among those worst affected as they not only experience circadian disruption but also sleep loss.

These extreme patterns are in conflict with human evolution and challenge our internal circadian pacemakers

- regulated by the master circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus
Sleep – Wake Misalignment Effects

Buxton and colleagues

- Effect of sleep restriction combined with gradual circadian misalignment (simulating shift-work patterns)
- 21 healthy participants examined across 39 consecutive day/night period in a strictly controlled laboratory setting.
  - 32% reduction in insulin response to a standardized meal, resulting in inadequate glucose regulation.
  - The resting metabolic rate was reduced following experimental manipulation of sleep restriction and circadian desynchrony, although levels reverted back to baseline subsequent to 9 days/nights of recovery sleep.
Sleep – Wake Misalignment Effects

Leproult et al.

- 26 healthy population of young (21–39 years) individuals
- Wrist actigraphy was used for 1 week prior to the study.
- Sleep was monitored using PSG and volunteers underwent 3 baseline days/nights, then 8 days/nights of 5 h TIB (centered around 03:00: circadian alignment).
  - For 4 of the 8 nights, 13 of the 26 participants had a 8.5-h delay in bedtimes (09:00–14:00) followed by 3 nights of sleep recovery.
  - All participants had the same amount of sleep opportunity per 24 hours, ensuring the effect of circadian misalignment per se was examined.

An IVGTT was performed following an overnight fast on the 2nd baseline day as well as on the 2nd to last day of the intervention

- Insulin sensitivity decreased in 96% of the sample (unaccompanied by an increase in responsiveness of β-cell function)
- The decrease was almost double in the misaligned sleep group (−58%) versus the controls (−32%), \( p = 0.011 \).
- C-reactive protein (an indicator of systemic inflammation) increased by 146% from baseline in the experimental compared to the control group (+64%).
Other Studied Mechanisms

Effects of sleep loss may contribute to unhealthy behaviors through metabolic disruption.

Changes in the appetite-regulating hormones **leptin** (related to satiety) and **ghrelin** (related to hunger) have been observed in response to short/insufficient sleep duration.

- These have been linked to an increased appetite for carbohydrate-dense foods and intake of calories from sweet foods (snacks).

Sleep deprivation results in:
- activation of the hypothalamic orexin (hypocretin) neuropeptide system. Orexin (hypocretin) neurons are located in the lateral hypothalamus and project throughout the central nervous system and particularly to areas important in wakefulness.

Orexin activation is associated with increased sympathetic nervous system activation, increased cortisol and suppressed growth hormone secretion, which can all predispose to hyperglycemia.

Orexin receptor antagonists are currently under investigation for use in insomnia, and it would be of interest to study their impact on metabolism.
Metabolic Syndrome and OSA
Conclusions

- Current evidence suggests that sleep is instrumental to metabolic regulation and disease management.

- Sleep imbalance may promote diabetes onset or hinder glucose control and insulin sensitivity in those with pre-existing diabetes.

- Cross-sectional studies as well as prospective cohort findings demonstrate reasonably consistent findings and implicate a role for sleep in the management of diabetes.

- Furthermore, acute sleep disruption under controlled laboratory conditions has shown significant and negative effects upon glucose control in healthy adults.
Further Study

Exposure to persistent sleep imbalance is likely to be detrimental to metabolic health/disease status

- While the evidence is convincing, a number of limitations are present, including the possibility of uncontrolled major confounders, which restrict robust conclusions.

Further investigation in ‘at risk’ populations as well as those with T2DM is needed incorporating objective and prospective sleep measures.

It may be possible to prevent incident diabetes and smooth the current epidemic by improving diabetes control through sleep optimization in combination with other lifestyle advice, particularly in newly diagnosed cases.

- Promoting the importance of sleep for improving diabetes control/management is unlikely to result in any harmful consequences.

Awareness of an additional, and easily modifiable, lifestyle behavior among healthcare professionals is therefore recommended.
Sleep is a significant and modifiable lifestyle behavior.
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