Endocrine & Metabolic Aspects: Obstructive Sleep Apnoea

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AllMS, New Delhi
Endocrine considerations

- Endocrine disorders and OSA
  - Acromegaly, Hypothyroidism etc

- OSA and Endocrine Disturbances
  - Pituitary-Gonad Axis

- Cause and effect relation not known
  - Obesity, Diabetes, metabolic syndrome
Brain stem regulates breathing during sleep by sending inputs to respiratory muscles.

- These centers are sensitivity
  - Fall in PO2 inhibits respiration
  - Increase in PCO2

Set of 10 striated muscles in Pharynx controlled by brainstem. These muscles have mechanoreceptors and dilatory effect on to prevent UA collapse in normal.

These mechanism are not full proof and up to 5 apnea episodes up can be seen in normal subjects.
Sagittal representation of the pharynx.

Attal P, and Chanson P JCEM 2010;95:483-495
Role of testosterone in pathogenesis of OSA

Supporting points

1. Testosterone Provokes and Estrogen protects
2. Testosterone replacement in males can trigger OSA
3. PCOD have higher AHI matched controls (44% vs 6%)

Point Against:
There are reports also that androgen blockade did not modify the sleep disturbances
Nocturnal melatonin plasma levels in patients with OSA: the effect of CPAP.

Nocturnal Peak of Melatonin at 2.00 am in normal
Primarily due to circadian rhythm
Promotes sleep and decrease wakefulness

OSA: Peak at 6.00 am with level lower than normal

Levels not increased on the night of CPAP treatment

Hypogonadism:

Common males and can lead to Erectile dysfunction

It is independent of increasing age or obesity

CPAP therapy improves total testosterone

Females with higher AHI have lower serum estradiol & progesterone indicating poor ovarian function
The Association of Testosterone Levels with Overall Sleep Quality, Sleep Architecture, and Sleep-Disordered Breathing

| TABLE 3. BMI-adjusted association between total testosterone and sleep outcomes |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Quartile 1, 5–330 ng/dl (n = 328) | Quartile 2, > 330–414 ng/dl (n = 327) | Quartile 3, > 414–513.4 ng/dl (n = 329) | Quartile 4, > 513.4–1345 ng/dl (n = 328) | P for trend |
|                                 | Adjusted mean (95% CI) | Adjusted mean (95% CI) | Adjusted mean (95% CI) | Adjusted mean (95% CI) |           |
| Total sleep time (h)            | 6.48 (6.35–6.61)  | 6.50 (6.38–6.63)  | 6.45 (6.32–6.58)  | 6.47 (6.34–6.60)  | 0.76       |
| Sleep efficiency (%)            | 82.2 (81.2–83.2)  | 84.0 (83.0–85.0)  | 83.0 (82.0–84.0)  | 83.8 (82.8–84.9)  | 0.10       |
| Wake after sleep onset (min)    | 81.5 (77.1–85.9)  | 71.0 (66.7–75.3)  | 76.5 (72.2–80.8)  | 73.4 (69.0–77.8)  | 0.07       |
| Time in stage 3/4 sleep, %      | 11.9 (10.9–12.9)  | 11.1 (10.1–12.1)  | 11.5 (10.6–12.5)  | 11.4 (10.3–12.4)  | 0.62       |
| Time in REM sleep, %            | 19.0 (18.2–19.7)  | 20.0 (19.3–20.7)  | 19.8 (19.0–20.5)  | 19.5 (18.8–20.2)  | 0.45       |
| AHI                             | 16.1 (14.6–17.6)  | 16.1 (14.6–17.6)  | 16.9 (15.4–18.4)  | 15.9 (14.3–17.4)  | 0.97       |
| Arousal index                   | 23.4 (22.2–24.7)  | 22.1 (20.9–23.3)  | 22.9 (21.7–24.1)  | 23.1 (21.9–24.3)  | 0.97       |
| ≥1% sleep time O₂ desaturated < 90% | 1.0                | 1.01 (0.73–1.41)  | 0.88 (0.63–1.23)  | 0.84 (0.60–1.18)  | 0.23       |
| AHI 15+                         | 1.0                | 0.80 (0.58–1.11)  | 1.15 (0.83–1.60)  | 0.98 (0.70–1.37)  | 0.58       |

Models adjusted for age, race, site, and BMI. CI, Confidence interval.
*p < 0.05, compared with the lowest quartile.

Conner et al JCEM 2008
OSA and Hypothalamic-Pituitary-Adrenal and Thyroid axis

- No clear involvement of Hypothal-PIT-Adrenal impairment.
- Except exaggerated response of ACTH to CRH not explained by obesity alone.
- No dysfunction in Hypothalamic-Pituitary-Thyroid axis
- Increased BMP due to increased pre and after load on heart can give polyuria
Endocrine Hypertension

- Risk of HT increased by 3 fold when AHI of > 15
- Drug resistant hypertension

- Mechanism implicated
  - Sympathetic activity
  - Increased renin angiotensin-aldosterone activity.
  - Hypoxemia induced O2 species, free radicals, endothelial dysfunction & atherosclerosis

- RCT of CPAP showed lowering of HT, improved Left ventricular systolic function, Ventricular premature contractions and reduced sympathetic activity in patients with heart failure
  (Bradley TD, Lancet 2009 373: 82-93)
**Obesity and OSA**

- **Prevalence**
  - OSA is a complication of obesity- and reverse
  - 10% increase in wt leads to 32% increase in AHI.
  - 55-100% candidates for bariatric surgery have OSA

- **Fat Distribution**
  - Besides BMI, fat distribution is important.
  - Neck & waist circumference
  - Narrowed UA and reduced tidal volume with increasing girth and therefore stretching of UA during inspiration is less
Obesity and OSA

- Metabolic syndrome independent of obesity is 9 times more common in OSA
- **Mechanism implicated**
  - IL-6 & TNG-alpha aggravates CV risk independent of obesity
  - Hypoxemia induced O2/free radicals, endothelial dysfunction
  - Increase adipose tissue in OSA patients,
    - Adipose tissues generated hormones: adipocytokines
      - Over/under-expression of many adipokines reported in OSA.
      - Leptin,
      - Adiponectin,
      - Visfatin,
      - Vaspin,
      - Apelin,
      - Chemerin
      - Omentin (sensitizes insulin action but increased in OSA).
Meta analysis: AHI of 54.7/hr to 15.8 after bariatric surgery.

Peri-operative deaths > with OSA.
OSA may recur due to lesser weight reduction around neck.
Diabetes and OSA

- Type 2 DM
- Type 1 DM
- Metabolic syndrome including Fatty liver
- Complications of DM
- Relation with glycemic control
- Effect of treatment on glycemic control
Obstructive sleep apnoea and the risk of type 2 diabetes: A meta-analysis of prospective cohort studies

First Author, Year | RR (95% CI)
--- | ---
Reichmuth et al. 2005 | 0.91 (0.36, 2.33)
Botros et al. 2009 | 1.43 (1.10, 1.86)
Muraki et al. 2010 | 1.69 (1.04, 2.76)
Celen et al. 2010 (F) | 11.80 (1.14, 121.70)
Celen et al. 2010 (M) | 1.58 (0.55, 4.58)
Overall ($I^2 = 41.2\%, P = 0.130$) | 1.53 (1.09, 2.45)

N = 5953

NOTE: Weights are from random effects analysis
**Meta analysis: Risk of T2DM in mild OSA**

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>RR (95% CI)</th>
<th>%Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichmuth et al. 2005</td>
<td>1.00 (0.49, 2.02)</td>
<td>17.34</td>
</tr>
<tr>
<td>Marshall et al. 2009</td>
<td>1.51 (0.25, 9.12)</td>
<td>2.69</td>
</tr>
<tr>
<td>Muraki et al. 2010</td>
<td>1.26 (0.91, 1.76)</td>
<td>79.97</td>
</tr>
<tr>
<td>Overall (I² = 0.0%, P = 0.822)</td>
<td>1.22 (0.91, 1.63)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Figure 3** Association between mild obstructive sleep apnoea and the risk of type 2 diabetes, as identified in prospective cohort studies. CI, confidence interval; RR, relative risk.

*NOTE: Weights are from random effects analysis*
Disturbed subjective sleep characteristics in adult patients with long-standing type 1 diabetes mellitus

M. van Dijk · E. Donga · J. G. van Dijk ·

Results Of the patients with type 1 diabetes, 35% had subjective poor sleep quality compared with 20% of the control participants ($p=0.021$). A higher proportion of the patients with type 1 diabetes were at increased risk for obstructive sleep apnoea (OSA) (17.2% vs 5.1%, $p=0.012$). There was no significant association between individual sleep characteristics and HbA$_{1c}$ values. On logistic regression analysis, the HADS depression score, presence of peripheral polyneuropathy, habitual snoring and other sleep disturbances (e.g. hypoglycaemia) were independently associated with poor sleep quality.
Sleep apnoea syndrome and 10-year cardiovascular risk in females with type 2 diabetes: relationship with insulin secretion and insulin resistance

Michel P. Hermans

Abstract
<table>
<thead>
<tr>
<th></th>
<th>OSAS[−]</th>
<th>OSAS[+]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>280</td>
<td>25</td>
<td>~</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (12)</td>
<td>65 (9)</td>
<td>0.6848</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>15 (9)</td>
<td>15 (8)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Family history of diabetes (%)</td>
<td>56</td>
<td>44</td>
<td>0.2978</td>
</tr>
<tr>
<td>Family history of premature CHD (%)</td>
<td>15</td>
<td>13</td>
<td>0.3290</td>
</tr>
<tr>
<td>Education (%)</td>
<td>69:31</td>
<td>88:12</td>
<td>0.0645</td>
</tr>
<tr>
<td>Exercise level (none/light/moderate; %)</td>
<td>76/20/4</td>
<td>100/0/0</td>
<td>0.0021</td>
</tr>
<tr>
<td>Smoking (never/former/current; %)</td>
<td>74/18/8</td>
<td>68/20/12</td>
<td>0.4885</td>
</tr>
<tr>
<td>Ethanol (U week⁻¹)</td>
<td>6 (11)</td>
<td>5 (10)</td>
<td>0.6613</td>
</tr>
<tr>
<td>Menopause (%)</td>
<td>84</td>
<td>92</td>
<td>0.3925</td>
</tr>
<tr>
<td>BMI (kg m⁻²)</td>
<td>29.7 (6.1)</td>
<td>38.7 (6.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>40.7 (6.5)</td>
<td>46.4 (5.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>37 (3)</td>
<td>41 (4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Predicted neck circumference (%)</td>
<td>94 (8)</td>
<td>102 (9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>99 (14)</td>
<td>119 (12)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist/hip</td>
<td>0.92 (0.08)</td>
<td>0.98 (0.10)</td>
<td>0.0072</td>
</tr>
<tr>
<td>Conicity index (m² kg⁻¹)</td>
<td>1.32 (0.10)</td>
<td>1.39 (0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist/height</td>
<td>0.62 (0.09)</td>
<td>0.75 (0.08)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Visceral fat (0–30 score)</td>
<td>10 (3)</td>
<td>13 (3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Skeletal muscle (%)</td>
<td>25 (3)</td>
<td>23 (3)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Fat mass/skeletal mass</td>
<td>1.66 (0.42)</td>
<td>2.08 (0.49)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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## Table 2. Cardiometabolic profile

<table>
<thead>
<tr>
<th></th>
<th>OSAS[–]</th>
<th>OSAS[+]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>280</td>
<td>25</td>
<td>~</td>
</tr>
<tr>
<td>Epworth score</td>
<td>6 (4)</td>
<td>9 (5)</td>
<td>0.0072</td>
</tr>
<tr>
<td>Epworth score &gt;9 (%)</td>
<td>14</td>
<td>43</td>
<td>0.0007</td>
</tr>
<tr>
<td>HOMA S (%)</td>
<td>59 (44)</td>
<td>37 (20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HOMA B (%)</td>
<td>67 (50)</td>
<td>59 (28)</td>
<td>0.2150</td>
</tr>
<tr>
<td>Hyperbolic product [B × S] (%)</td>
<td>30.0 (18.8)</td>
<td>19.8 (12.3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>[B × S] loss rate (% yr⁻¹)</td>
<td>1.22 (0.41)</td>
<td>1.39 (0.31)</td>
<td>0.0442</td>
</tr>
<tr>
<td>Fasting plasma insulin (pmol L⁻¹)</td>
<td>110 (73)</td>
<td>147 (83)</td>
<td>0.0170</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>85</td>
<td>100</td>
<td>0.0327</td>
</tr>
<tr>
<td>Metabolic syndrome score (0/5 to 5/5)</td>
<td>3.69 (1.13)</td>
<td>4.36 (0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hepatic steatosis (%)</td>
<td>65</td>
<td>92</td>
<td>0.0063</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>83</td>
<td>96</td>
<td>0.1468</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>139 (20)</td>
<td>136 (24)</td>
<td>0.4805</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>78 (10)</td>
<td>76 (12)</td>
<td>0.3470</td>
</tr>
<tr>
<td>UKPDS 10-year risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD (%)</td>
<td>12 (10)</td>
<td>18 (11)</td>
<td>0.0136</td>
</tr>
<tr>
<td>Fatal CAD (%)</td>
<td>9 (9)</td>
<td>13 (10)</td>
<td>0.0671</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>10 (15)</td>
<td>8 (7)</td>
<td>0.3011</td>
</tr>
<tr>
<td>Fatal stroke (%)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>0.1503</td>
</tr>
<tr>
<td></td>
<td>OSAS[−]</td>
<td>OSAS[+]/p</td>
<td></td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>280</td>
<td>25/0.0099</td>
<td></td>
</tr>
<tr>
<td>HbA1c (mmol mol⁻¹)</td>
<td>62 (13)</td>
<td>69 (12)</td>
<td></td>
</tr>
<tr>
<td>eGFR a (mL min⁻¹ 1.73 m²)</td>
<td>79 (28)</td>
<td>74 (26)</td>
<td></td>
</tr>
<tr>
<td>eCrCl b (mL min⁻¹ 1.73 m²)</td>
<td>86 (39)</td>
<td>109 (42)</td>
<td></td>
</tr>
<tr>
<td>Albuminuria (µg mg creatinine⁻¹)</td>
<td>49 (94)</td>
<td>95 (163)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg dL⁻¹)</td>
<td>182 (41)</td>
<td>175 (45)</td>
<td></td>
</tr>
<tr>
<td>LDL-C (mg dL⁻¹)</td>
<td>99 (36)</td>
<td>92 (29)</td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C (mg dL⁻¹)</td>
<td>130 (40)</td>
<td>132 (45)</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg dL⁻¹)</td>
<td>53 (15)</td>
<td>43 (13)</td>
<td></td>
</tr>
<tr>
<td>apoA-I (mg dL⁻¹)</td>
<td>165 (29)</td>
<td>147 (29)</td>
<td></td>
</tr>
<tr>
<td>apoB₁₀₀ (mg dL⁻¹)</td>
<td>90 (26)</td>
<td>105 (34)</td>
<td></td>
</tr>
<tr>
<td>apoB₁₀₀/apoA-I</td>
<td>0.53 (0.18)</td>
<td>0.68 (0.24)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg dL⁻¹)</td>
<td>155 (93)</td>
<td>185 (111)</td>
<td></td>
</tr>
<tr>
<td>Atherogenic dyslipidaemia (%)</td>
<td>35</td>
<td>48/0.1999</td>
<td></td>
</tr>
<tr>
<td>log(TG)/HDL-C</td>
<td>0.044 (0.016)</td>
<td>0.058 (0.025)</td>
<td></td>
</tr>
<tr>
<td>LDL-C/apoB₁₀₀</td>
<td>1.07 (0.30)</td>
<td>0.95 (0.18)</td>
<td></td>
</tr>
<tr>
<td>hscCRP (mg dL⁻¹)</td>
<td>0.44 (0.53)</td>
<td>0.92 (1.10)</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (mg dL⁻¹)</td>
<td>337 (76)</td>
<td>380 (100)</td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg dL⁻¹)</td>
<td>5.2 (1.6)</td>
<td>5.9 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Testosterone (nmol L⁻¹)</td>
<td>0.93 (0.54)</td>
<td>0.91 (0.57)</td>
<td></td>
</tr>
<tr>
<td>Free testosterone (nmol L⁻¹)</td>
<td>0.014 (0.008)</td>
<td>0.024 (0.024)</td>
<td></td>
</tr>
<tr>
<td>SHBG (nmol L⁻¹)</td>
<td>49 (30)</td>
<td>35 (31)</td>
<td></td>
</tr>
</tbody>
</table>

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Obstructive Sleep Apnea and Diabetic Neuropathy
A Novel Association in Patients with Type 2 Diabetes

Abd A. Tahrani¹,², Asad Ali³,⁴, Neil T. Raymond⁵, Safia Begum³, Kiran Dubb¹, Shanaz Mughal³, Biju Jose³, Milan K. Piya⁵,⁶, Anthony H. Barnett¹,²,³, and Martin J. Stevens¹,²
### TABLE 1. PARTICIPANT CHARACTERISTICS IN RELATION TO OBSTRUCTIVE SLEEP APNEA STATUS

<table>
<thead>
<tr>
<th></th>
<th>OSA− (n = 83)</th>
<th>OSA+ (n = 151)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>34 (41%)</td>
<td>101 (67%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>32 (39%)</td>
<td>97 (64%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, yr</td>
<td>54.7 (11.9)</td>
<td>58.5 (11.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes duration, yr</td>
<td>9 (5–15)</td>
<td>11 (7–17)</td>
<td>0.02</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.2 (27.3–35.0)</td>
<td>34.4 (30.9–39.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>105.5 (96.0–115.0)</td>
<td>116.0 (107.5–125.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hip, cm</td>
<td>106.0 (98.0–117.0)</td>
<td>114.0 (105.0–125.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>0.97 (0.93–1.02)</td>
<td>1.01 (0.96–1.05)</td>
<td>0.002</td>
</tr>
<tr>
<td>Neck circumference, cm</td>
<td>38.0 (36.5–41.3)</td>
<td>43.0 (39.0–46.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163.5 (8.3)</td>
<td>167.8 (10.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>125.5 (115.0–135.5.0)</td>
<td>130.0 (123.5–140.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>78.50 (71.0–85.00)</td>
<td>78.00 (71.00–84.50)</td>
<td>0.88</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.7 (7.0–8.7)</td>
<td>8.3 (7.3–9.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.7 (3.4–4.5)</td>
<td>3.7 (3.3–4.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.5 (1.0–2.1)</td>
<td>1.8 (1.3–2.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.2 (0.9–1.4)</td>
<td>1.1 (0.9–1.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Estimated GFR, ml/min/1.73 m²</td>
<td>92.92 (25.16)</td>
<td>82.41 (26.41)</td>
<td>0.003</td>
</tr>
<tr>
<td>TSH</td>
<td>1.6 (1.0–2.2)</td>
<td>1.7 (1.2–2.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>Epworth sleepiness score</td>
<td>5.0 (2.0–12.0)</td>
<td>8.0 (4.0–13.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Smoking (current or ex-smoker)</td>
<td>32 (39%)</td>
<td>62 (41%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Alcohol (drinks alcohol)</td>
<td>12 (15%)</td>
<td>12 (35%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Oral antidiabetes treatment</td>
<td>81 (98%)</td>
<td>137 (91%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Insulin</td>
<td>34 (41%)</td>
<td>91 (60%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Insulin dose, units</td>
<td>61 (35–88)</td>
<td>80 (56–118)</td>
<td>0.007</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>40 (48%)</td>
<td>69 (46%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Angiotensinconverting enzyme</td>
<td>48 (74%)</td>
<td>129 (85%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>61 (74%)</td>
<td>125 (83%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Lipid-lowering treatment</td>
<td>81 (86%)</td>
<td>137 (91%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>14 (17%)</td>
<td>33 (22%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1 (1%)</td>
<td>10 (7%)</td>
<td>0.06</td>
</tr>
<tr>
<td>PVD</td>
<td>20 (24%)</td>
<td>65 (43%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Sight-threatening retinopathy</td>
<td>17 (21%)</td>
<td>72 (48%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Experimental studies

Intermittent hypoxia in animals leads to sympathetic activation, reduced insulin sensitivity, oxidative stress, lipid peroxidation, upregulation of nuclear factor κB. Hypoxia inducible factor 1 are the main determinants.

Spiegel et al Nat Rev Endocrinol 5: 253-261
Treatment of OSA and Diabetes

- RCT with CPAP/Sham Rx for 3 months in patients with T2DM and OSA had no effect on HbA1c and insulin resistance. West et al, Thorax 2007; 62:969-974.

- Systematic evaluation of OSA in T2DM is recommended in view of increased risk of T2DM
PCOD and OSA

- Patients with PCOD have higher AHI values than age and BMI matched controls (44% vs 6%)

- OSAS and insulin resistance based on HOMA index more common in PCOD with > AHI on polysomnography

- Similarly PCOD with OSA were found to have more impaired glucose intolerance than those without PCOS
Acromegaly & OSA

- 70% of patients with active acromegaly have OSA

- **Mechanism**
  - Facial skeletal: Opening of the angle leads to back protrusion of the tongue & UA obstruction
  - Enlarged Tongue
  - Pharynx tissue thickness, edema & narrowing
  - Odema is because of Sodium retaining effect of GH
  - Obesity and Hypothyroidism are additional factors
  - Myopathy of sternohyoid muscle dilator
Sagittal T1-weighted MRI sequences of the neck before (A) and after (B) effective treatment of acromegaly in a male patient with OSA. The treatment of acromegaly allowed a clear decrease in thickness of the tongue (black star), soft palate (white star), and...

Attal P, and Chanson P JCEM 2010;95:483-495
Acromegaly and OSA

- Effective treatment improves OSA to a substantial extent.
- But may persist in 40% of the patients cured of acromegaly. Therefore patients need to be reassessed after surgery for treatment.
GH deficiency, therapy and OSA

- GH deficiency can also lead to OSA
- Up to 60% adult patients with panhypopituitary receiving all replacement hormones except GH have OSA.
- GH therapy improved SWS and shift from OSA to hypopnea.
- May worsen OSA following GH replacement: depends on BMI
Hypothyroidism and OSA

- OSA is present 25-35% patients with hypothyroidism
  Hypothyroidism in up to 10% patients with OSA

- **Causes**
  - Pharynx narrowing with soft tissue infiltration by mucoploysaccharides & protein as in skin
  - Central apnea
  - Neuropathy giving altered function of dilator muscle
  - Macroglossea
  - Goiter
Treatment reverses OSA in most patients with Hypothyroidism especially if there is no obesity.

Hence, attempt should be made to screen and treat hypothyroidism before CPAP therapy.
Summary

- Testosterone, Melatonin, Obesity, adipokines may have role
- Hypogonadism can be seen in both males and females
- Increased CRH cortisol response to ACTH but with resistance
- OSA prevalence in Acromegaly is high and partially reversible
- Hypothyroidism is a reversible cause of OSA and need to be looked in all patients before CPAP treatment
Summary

- HT, Metabolic syndrome, T2DM, are increased
- T1 DM also can have metabolic syndrome
- Micro vascular & macrovascular complication are increased
- Effect of treatment CPAP on HbA1c: sufficient data not Available
- DM patients need to be assessed for OSA
Thank You
Sleep-Endocrinology

Dr R Goswami MD, DM FASc, FNASc
Professor Endocrinology & Metabolism,
AllMS, New Delhi
There is endogenous rhythm which optimally synchronizes with body physiology (rest/activity or biological day/night)

Suprachiasmatic nuclei: Master circadian clock, Bilateral, in Ant. hypothalamus near 3rd ventrical

Its neuron has autorythmicity of ~ 25-24 hr.

But it requires constant entrainment
Entrainment of Circadian clock

- **Retinohyopthalamic tract**: Projections to the SCN
- Photopigment in rods, cones & retinal ganglion cells are sensors
- Light is the most potent time cue to the master circadian oscillator.
- Body temperature, exercise, feeding can modify this to some extent
Entrainment of Circadian clock

- SCN projections to the
- Hypothalamus: determines circadian rhythm of hormones
- Cerebral cortex: Arousal
- Pineal gland: Multisynaptic pathway to PVN---IML column of upper thoracic spinal cord----cervical ganglion -----pineal
- Autonomic nervous system: Maximum epinephrine secretion between 6.0 am to 9.0 am is independent of behavior.
  - Explains the peak time for the MI/Stroke in the morning.
  - Can be relevant for development of novel therapeutic strategy
General aspects of sleep

- Sleep is important & humans spends at least 1/3 of life in this activity. Reduction of motor output & consciousness.

- Sleep has cycles of NREM and REM. Phase 2 - 4 of NREM correlates with slow wave EEG activity & sleep intensity.
Thus, in simplistic term both sleep & hormone changes are part of circadian system determined by SCN.

There is some pattern in hormonal changes with sleep. Difficult to say hormones modifies sleep or sleep modifies hormone.

**Forced protocol:** Subjects sitting in dim light, relaxed, reclining, equal calories snacks distributed equally in 24 hour which allows study of circadian component.

Repeated Hormonal sampling and EEG are inherent part of this forced protocol.
Sleep & Hormones

- GHRH-GH
- CRH-Cortisol
- Melatonin
- Others
- Ghrelin
- Somatostatin
- Sex hormones  Testosterone and osteorgen and DHEAS
- Neuropeptides
- Increased BMP in night: poluria
1st half of Sleep
GHRH-GH Predominates

2nd half
CRH-Cortisol predominates
Morning normal 08.00 hr plasma cortisol higher than evening
Sleep & Hormone

1st half of Sleep GH and 2nd half Cortisol

Sexual dimorphism
Males show a single peak
Females multiple peak during sleep (Bioadaptation)
Sleep & Hypothalamic-Growth Hormone axis

- GH-Rise after sleep irrespective of sleep time
- GH releasing hormone (GHRH) is the best endogenous substance with sleep promoting activity
- After central and systemic & central administration of GHRH, SWS activity is increased in animals.
- I.V & intranasal boluses of GHRH during first few hr of sleep in normal young and elderly males lead to
  
  Increased GH secretion and SWS
  Decreased cortisol and ACTH levels
  Prolonged first NREM & reduced awakenings
However, in females there was sexual dimorphism and opposite changes were with increased ACTH and cortisol in females.

This indicate that that there is reciprocal anatgonism between GHRH and CRH in males and

Synergism between these two hormones in females

This might explain the increased prevalence of depression and Cushing’s in females
**Sleep, GH analogues & Somatostatin**

- **Ghrelin:** An endogenous ligand of GH scretagogues receptor.
  - Released from stomach to increase the appetite
  - In young males effects of IV Ghrelin & synthetic scertagogues and GHRH are similar with increased GH and enhanced SWS
  - Unlike GHRH, ACTH and cortisol secretion is increased

- **Somatostatin:**
  - In young/elderly males SWS is reduced after IV somatostatin & SC octreotide.
  - Sleep is more impaired in elderly at a lesser dose
  - After arginine (a somatostatin antagonist) SWS is increased
CRH

Pulsatile IV CRH in young males (4 x 50 ug) led to **increased cortisol** during first half of night, 

**GH surge bunted & decreased SWS**

Changes were more with ageing including wakefulness
In stressed rats after CRH antagonist (Astressin) RMES sleep decreased. This preclinical work indicates CRH promotes wakefulness.

RX of patients with CRH receptor antagonist NBI 30775 induced normalization of sleep changes in EEG.

A 4 wk trial of the compound in depressed patients led to increased SWS with decrease in REM density & awakenings.

Thus CRH-I receptor I antagonist is a possible way to counteract sleep changes.
Sleep & CRH-ACTH-Cortisol Axis

- ACTH
  - Administration of synthetic ACTH analogue to volunteers led to general CNS activation but REMS, GH & cortisol remain unchanged
  - It seems unlikely that it has an effect on Sleep disturbances
Sleep & CRH-ACTH-Cortisol Axis

- Steroids
  - Continuous/hrly cortisol infusion from 11.00 pm-7.0 am led to increased SWS and decreased REM in young/elder
  - Thus CRH mediated decrease in sleep density is unlikely to be because of cortisol
  - Long term methylprednisolone in females with multiple sclerosis: REM latency was shortened and SWS density shifted to late phases of sleep. These changes are similar to that of depression
Sleep & Aging & Depression

Controls 25 years

65 years

EEG

Wake

REM

I

II

III

IV

REM
Sleep & Aging & Depression

Controls 25 years

Patients with depression 25 years

65 years
Sleep, Aging & Depression

Controls 25 years

Patients with depression 25 years

65 years
Sleep, Depression, Aging & Hormone

Controls
25 years

Patients with depression
25 years

65 years

Comparison of EEG and hormone levels for controls and patients with depression at ages 25 and 65 years.
Disorders of sleep due to the misalignment in sleep cycle with circadian rhythm as in night shift workers

Jet lag due to time differences in two countries

Patients with depression and senior citizens with sleep disturbances

Cushing’s disease and patients requiring subchronic steroids as in Multiple sclerosis

Common drugs like betablockers are known to increase wake time
Adverse consequences of Misalignment in Day and night sleep

Rotating Night Shift Work and Risk of Type 2 Diabetes: Two Prospective Cohort Studies in Women

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Abstract

Background: Rotating night shift work disrupts circadian rhythms and has been associated with obesity, metabolic syndrome, and glucose dysregulation. However, its association with type 2 diabetes remains unclear. Therefore, we aimed to evaluate this association in two cohorts of US women.

Methods and Findings: We followed 69,269 women aged 42–67 in Nurses’ Health Study I (NHS I, 1988–2008), and 107,915 women aged 25–42 in NHS II (1989–2007) without diabetes, cardiovascular disease, and cancer at baseline. Participants were asked how long they had worked rotating night shifts (defined as at least three nights/month in addition to days and evenings in that month) at baseline. This information was updated every 2–4 years in NHS II. Self-reported type 2 diabetes was confirmed by a validated supplementary questionnaire. We documented 6,165 (NHS I) and 3,961 (NHS II) incident type 2 diabetes cases during the 18–20 years of follow-up. In the Cox proportional models adjusted for diabetes risk factors, duration of shift work was monotonically associated with an increased risk of type 2 diabetes in both cohorts. Compared with women who reported no shift work, the pooled hazard ratios (95% confidence intervals) for participants with 1–2, 3–9, 10–19, and ≥20 years of shift work were 1.05 (1.00–1.11), 1.20 (1.14–1.26), 1.40 (1.30–1.51), and 1.58 (1.43–1.74, p-value for trend <0.001), respectively. Further adjustment for updated body mass index attenuated the association, and the pooled hazard ratios were 1.03 (0.98–1.08), 1.06 (1.01–1.11), 1.10 (1.02–1.18), and 1.24 (1.13–1.37, p-value for trend <0.001).

Conclusions: Our results suggest that an extended period of rotating night shift work is associated with a modestly increased risk of type 2 diabetes in women, which appears to be partly mediated through body weight. Proper screening and intervention strategies in rotating night shift workers are needed for prevention of diabetes.
Molecules with potential role in Disorders of Sleep

Nocturnal Peak of Melatonin at 2.00 am in normal
Primarily a circadian rhythm and very little change in day
Promotes sleep and decrease wakefulness

Use of Melatonin particularly sustained release might be of help to Night shift workers

GHRH for obvious reasons is not a viable option but GH secretagogues need evaluation

CRG antagonist (astressin) and CRG receptor antagonist
Thank You
**Different phase of Airway obstruction**

- **Phase I:** Increased collapse of airway, turbulent flow & fluttering of soft palate leading to snoring

- **Phase II:** Increased airway resistance, respiratory efforts & short arousals noticed in sleep analyses

- **Phase III:** Apnoea/Hyponea episodes > 5/hr
  - Apnea = Interruption of breathing > 10 sec
  - Hypopnea = (a) fall in inspiratory flow to 50% for 10 sec
  - (b) 4% fall in O2 saturation
Diagnostic Procedures for OSA

- Gold standard: polysomography in sleep Laboratory
- History of snoring, disturbances in sleep
- Nocturnal oximetry during sleep
- Assessment of airway by optic procedure
- Video-endoscopy under sedation
- Measurement of pharyngeal pressure in sleep
Neurocognitive consequences of OSA

- **Neurocognitive**
  Day time sleep slow reactions, oor memory, irritability and quality of life, road accidents
CVS- consequences

- HT risk increased by 3 fold in AHI of > 15
- Drug resistant hypertension.
- Higher sympathetic tone & plasma aldosterone

- Higher CVS mortality. Cardiac pre & after load increased due to –ve intrathoracic pressure during breathing with narrow UA.

- Hypoxemia induced reactive O2 species, free radicals, endothelial dysfunction & atheraosclerosis
OSA is an independent risk for arrhythmia, heart failure & stroke in epidemiological studies.

RCT of CPAP showed lowering of HT, improved Left ventricular systolic function, Ventricular premature contractions and reduced sympathetic activity in patients with heart failure

(Bradley TD, Lancet 2009 373: 82-93)