Diabetes, hypertension, obesity, and sleep disorders are among the most costly and intractable public health problems. A number of syndromes have been described — cardiometabolic syndrome, Syndrome X, and the Insulin Dysmetabolic Syndrome — to characterize the overlap of these three diseases (see Table 1). A common denominator would be welcome that could effectively aid the management of this constellation of dysfunctions. This factor has now been discovered: disturbed sleep. In particular, obstructive sleep apnoea (OSA) is known to contribute to the morbidity of diabetes, hypertension, and obesity. Treatment of OSA may limit the cardiovascular (CV) effects and end-organ damage resulting from the other three members of the syndrome.

Recent work suggests that disordered breathing during sleep exerts its multi-organ, pathological effects through the mechanism of sympathetic stimulation caused by arousal from sleep. Thus, in the link between OSA and hypertension, the emphasis is on the repeated arousals rather than the breathing abnormality.

Repeated arousals from sleep cause bursts of sympathetic activation and increases in heart rate as well as in both systolic and diastolic blood pressure. Animal models and human studies also suggest that heart failure is reduced and preload is increased with every apnoeic event, providing another likely mechanism for CV morbidity. Hyperinsulinemia, a consequence of diabetes and obesity, also leads to increased sympathetic activity and hypertension (see Figure 1). An examination of the mechanisms reveals how treating OSA can ameliorate the course of diabetes and reduce blood pressure.

Two decades ago, observers noted the comorbidity of hypertension and lack of breathing during sleep. The prevalence of OSA in hypertensives is between 30% and 50%. More than half of sleep apneics are hypertensive, compared with a prevalence of 24% in the general adult population.

OSA shares many of the features of the cardiometabolic syndrome (see Table 1). The causal relationships between OSA, CV disease, and related metabolic disorders are complex and may be multidirectional. Two recent large research projects have reported a dose-response relationship between OSA and hypertension. One elegant study (N=1060) revealed a dose-response association between the severity of OSA and the magnitude of blood pressure elevation. Even mildly sleep-disordered breathing was associated with elevated blood pressure. The investigators adjusted for age, gender, body mass index (BMI – the weight in kilograms divided by the square of the height in meters), smoking, alcohol, education, physical activity, and antihypertensive medication.

Supporting these results is another study (N=2677) in which both blood pressure and the number of patients with hypertension increased linearly with the severity of OSA. Each additional apnoea event per hour of sleep added 1% to the risk of hypertension and each 10% decrease in the oxygen saturation nadir increased the risk of hypertension by 13%. Lavie also adjusted for confounding variables (age, level of obesity, and sex) and hypertensive medication. The chronic effects of obstructive sleep apnoea may include an increase in sympathetic tone and an elevation of nocturnal, daytime, and pulmonary blood pressure. Also associated with OSA are alterations in chemoreceptor function and morphologic changes in vessel walls.

The prevalence of obesity, diabetes, and OSA in the US is alarming – estimated at 9% of women and 24% of men. The prevalence of insulin resistance in a supposedly normal, healthy middle-aged population was found to be 37%. OSA, obesity, and hypertension are all risk factors for diabetes. Half of hypertensive patients display insulin resistance, as do the majority of patients with non-insulin-dependent diabetes. The fact that obesity contributes to OSA is not news. Obesity exacerbates OSA through upper airway obstruction and alteration of the breathing drive. BMI is the best predictor of OSA.

The humoral links between OSA, obesity, and diabetes are still being elucidated, but several clear relationships have been shown between sleep deprivation and metabolic abnormalities. Sleep debt strongly affects glucose utilization as well as circadian cycles of thyrotropin, cortisol, growth hormone, and other
Sleep debt alone is reported to result in impaired glucose effectiveness similar to that found in non-insulin-dependent diabetics. Severe OSA significantly influences plasma insulin and glycemia and may increase the risk of diabetes independently of obesity.

Not all OSA patients are obese; however, insulin resistance is found in both obese and non-obese OSA patients. Blood pressure and fasting insulin correlate closely with both BMI and the severity of OSA. Thus, both the sleep debt and the sympathetic activation that accompany OSA may speed the deterioration of glucose tolerance. Insulin resistance and hyperinsulinemia lead to further sympathetic activation, thus completing the circle of obesity, diabetes, hypertension, and the related metabolic abnormalities.

Clearly, it is important to manage all the risk factors for diabetes and hypertension. Patients with diabetes, obesity, and hypertension have about a 70% chance of having significant OSA. Thus, OSA must be included in the differential diagnosis for hypertension. Treatment of OSA in the obese, diabetics, and hypertensives may improve insulin responsiveness (~32%), reduce blood pressure, and normalize the abnormal growth hormone cycle – and may possibly improve the impaired lipid metabolism seen in OSA.

Patients with hypertension and diabetes should be asked specific questions that can reveal undiagnosed OSA. A positive answer to the following two questions provides a 90% predictability for identifying a sleep disorder:

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**Table 1. Diabetes, Hypertension, and Obesity Syndromes and OSA**

<table>
<thead>
<tr>
<th></th>
<th>Cardio-metabolic syndrome</th>
<th>Insulin dysmetabolic syndrome</th>
<th>Syndrome X (metabolic)</th>
<th>Common in OSA</th>
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<tr>
<td>Hypertension</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Diabetes (type 2)</td>
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</tr>
<tr>
<td>Obesity (abdominal)</td>
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<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Glucose intolerance</td>
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<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Insulin resistance</td>
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<tr>
<td>Hyperinsulinemia</td>
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<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Dyslipidemia</td>
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<td>Microalbuminuria</td>
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<td>x</td>
<td>~</td>
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<tr>
<td>Coagulation abnormalities</td>
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<td>x</td>
<td>~</td>
</tr>
<tr>
<td>Accelerated CV disease</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

**Plus...**

- Endothelial dysfunction, diabetic cardiomyopathy, renin-angiotensin abnormalities
- Hyperuricemia
- Endothelial dysfunction, hyperuricemia
- Renin-angiotensin abnormalities

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Diabetes, Hypertension, Obesity, and Sleep Disorders

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Figure 1: Sympathetic Activation is the Common Denominator among Obstructive Sleep Apnoea, Hypertension, Diabetes, and Obesity
• Do you snore?
• Have you ever been told that you stop breathing during sleep?

Physicians who ask these questions can expect an eightfold increase in OSA patients in their office. After treatment of OSA, they can also expect improvement in the management of both hypertension and diabetes.

References
Diabetes, Hypertension, Obesity, and Sleep Disorders


