Update on Reversibility of Obstructive Sleep Apnea Consequences

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Abbreviations: OSA = obstructive sleep apnea, CPAP = continuous positive air pressure, MSU = monosodium urate

Abstract
Many medical conditions have been reported to be consequences of obstructive sleep apnea (OSA) in adults. Some reports discuss the reversibility of those conditions just by overcoming the OSA, usually by the patients’ adherence to continuous positive air pressure (CPAP) therapy used during sleep. This article updates a previously reported tabulated list of OSA consequences, now including thirty-one OSA consequences in adults, based on a review of the literature. The OSA consequences are categorized according to whether they have been reported to be reversible (at least partially) just by overcoming the OSA, not reversible, or their reversibility has not yet been reported. There are life-threatening conditions in each category, and the conditions cover a wide range of medical specializations. This updated list could be beneficial to many medical practitioners to support their diagnosis and treatment of OSA’s consequences, and of OSA itself. This approach is a back-up for the better practice of routine screening for sleep apnea, leading to its diagnostic testing and treatment when warranted, with the aim of greatly reducing the risk for development of these OSA consequences.

Keywords: sleep apnea, cardiovascular diseases, kidney disease, liver disease, autoimmune diseases, diabetes, cancer
1. Introduction

Obstructive sleep apnea (OSA) is the repeated cessation of breathing during sleep for at least ten seconds at a time at least five times per hour, resulting from obstruction of the airway. The immediate effects from these periods of self-suffocation are chronic intermittent hypoxia, generation of stress hormones (eg. cortisol and catecholamines), and disturbed sleep. OSA is known to be very common (>20% of US adults affected), to have many very serious consequences, and to be readily treatable, yet it is grossly underdiagnosed (>80% of individuals with OSA never diagnosed).

The usual consequences of OSA which are mentioned in peer-reviewed and public press articles are cardiovascular diseases and falling asleep while driving because of excessive sleepiness during waking hours. This paper presents a list that is far more extensive. The negative impact of OSA on public health and mortality usually occurs from any of the many consequential comorbidities that develop years after the initial development of OSA.

Knowledge of the consequences of OSA can be a great aid in the screening process for this disease when early screening procedures have not been successfully followed. Of particular immediacy is the recognition of OSA’s reversible consequences as screening clues, hopefully before OSA’s life-threatening irreversible consequences develop. Furthermore, prompting OSA patients to adhere to its recommended treatment may be additional therapy for treatment of those comorbidities of OSA which are reversible. Even the presence of irreversible consequences of OSA may be useful screening clues, aimed at reducing the risk of additional serious consequences by overcoming the OSA.

2. Summary Table

Table 1 presents a recent update of a similar table that was previously published by this author1. Table 1 summarizes the OSA consequences in each of those three reversibility categories, based on reports in the published peer-reviewed literature: reversible, irreversible, and degree of reversibility not yet reported. Included with all but one of the entries in Table 1 are superscript numbers2–40 referring to the corresponding numbers in the reference list of this paper which support their inclusion in the particular column of the table. In some cases, the basis for a causal relationship has been hypothesized.
Table 1: Untreated OSA Consequences and Their Reversibility Just by Overcoming OSA

<table>
<thead>
<tr>
<th>Usually Reversible (at least partially)</th>
<th>Reversibility Undetermined</th>
<th>Usually Irreversible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout attacks – immediately²</td>
<td>Residual monosodium urate</td>
<td>Myocardial infarction³²</td>
</tr>
<tr>
<td>Atrial fibrillation – 6 months³</td>
<td>Coronary¹⁷ / peripheral¹⁸ artery disease</td>
<td>Ischemic stroke³³</td>
</tr>
<tr>
<td>Hypercoagulability – 6 months⁴</td>
<td>Dyslipidemia / atherosclerosis¹⁹</td>
<td>Type 2 diabetes³⁴–³⁵</td>
</tr>
<tr>
<td>Chronic kidney disease – 3 months⁵–⁶</td>
<td>Congestive heart failure²⁰</td>
<td>Cancer³⁶–³⁸</td>
</tr>
<tr>
<td>Ventricular mechanical dysfunction – 3 months⁷</td>
<td>Depression²¹</td>
<td>Mitral valve disease³⁹</td>
</tr>
<tr>
<td>Hypertension – 6 months⁸</td>
<td>Autoimmune disease²²–²³</td>
<td>Aortic valve stenosis⁴⁰</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease⁹–¹⁰</td>
<td>Chronic migraine²⁴</td>
<td></td>
</tr>
<tr>
<td>Excessive daytime sleepiness¹¹</td>
<td>Esophageal reflux²⁵ / Barrett’s esophagus²⁶</td>
<td></td>
</tr>
<tr>
<td>Nocturia¹²</td>
<td>Hypothyroidism²⁷</td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment¹³</td>
<td>Systemic inflammation²⁸</td>
<td></td>
</tr>
<tr>
<td>Endothelial dysfunction – 3 months¹⁴</td>
<td>Erythrocytosis / polycythemia²⁹</td>
<td></td>
</tr>
<tr>
<td>Rate of Alzheimer’s progress¹⁵</td>
<td>Insomnia³⁰</td>
<td></td>
</tr>
<tr>
<td>Rate of telomere shortening¹⁶</td>
<td>Keratoconus³¹</td>
<td></td>
</tr>
</tbody>
</table>

2.1. Reversible Entries

All entries in the leftmost column of Table 1 are referenced to previous peer-reviewed medical journal papers which present evidence of their reversibility, some after a particular length of time of OSA resolution. Gout, defined as the formation of monosodium urate (MSU) crystals in body tissues and fluids (not only in synovial fluid as arthritic gout) resulting from hyperuricemia, is listed first because this author considers gout to be a bellwether for the presence of OSA. The hypoxemia of OSA leads to gout by increasing cellular generation of uric acid, reducing its solubility in the blood, and slowing its removal by the kidneys, all of which combine to cause supersaturation of serum uric acid and the resulting precipitation of MSU². The MSU crystals are detectable ultrasonically⁴¹, even before gout symptoms manifest clinically. For gout reversibility, this author has relied on online unsolicited testimonials from former gout sufferers because no formal studies have been published that report on the reversibility of gout by overcoming OSA. Although overcoming sleep apnea can prevent any future gout...
development, it may not lead to the dissolution of previously occurring MSU crystals.

The reasons that gout is a causal consequence of OSA are clearer than reasons for other reversible consequences of OSA, and certainly more clear than for all the other entries on Table 1. Some reasons have been advanced as causal hypotheses as to why the other reversible diseases are consequences of OSA, although not for all of them. Several possible reasons for atrial fibrillation developing as a consequence of OSA include the chronic intermittent hypoxia from OSA leading to cardiac remodeling, and the effect of the elevation of circulating levels of C-reactive protein known to occur with OSA⁴². Cardiac remodeling may also be the reason for ventricular mechanical dysfunction. Chronic kidney disease is hypothesized to be a consequence of OSA because of increased urinary protein excretion and high blood pressure⁶. The reasons for hypertension⁸ are “Recurrent cycles of intermittent hypoxia stemming from obstructive respiratory events cause chemoeceptorial and baroceptorial hypersensitivity, with subsequent sympathetic nervous system hyperactivation, which, together with endothelial dysfunction and systemic inflammation, leads to the activation of peripheral vasoconstriction and impaired vasodilatation.” The hypoxemia of OSA is ascribed to be a cause for nonalcoholic fatty liver disease⁹. Data in Table 3 of a paper by Sahebjami⁴³ appear to show that people with OSA produce more liquid in their urine when they sleep without using continuous positive airway pressure (CPAP) than when they use CPAP, leading to nocturia with untreated OSA. Cognitive impairment with OSA is usually ascribed to poor quality sleep night after night. Endothelial dysfunction is hypothesized to be a result of the systemic hypoxia of OSA¹⁴.

2.2 Undetermined Reversibility Entries

The first entry is the residual monosodium urate crystals from previous gout attacks, which may require a period of urate lowering therapy to dissolve them before they can cause significant joint damage. The other entries in the center column of Table 1 reference previous peer-reviewed medical journal papers which present evidence that they are consequences of OSA, but this author has found no medical journal papers that show them to be reversible by overcoming OSA. Autoimmune disease has been hypothesized to be a consequence of long-term untreated OSA because of the nightly up-regulation of the immune system with maturation of dendritic cells and proliferation of T-cells as a reaction to the formation of MSU, an alarm signal that many cells may be dying²³.
2.3 Irreversible Entries

All entries in the rightmost column of Table 1 are referenced to previous peer-reviewed medical journal papers which present evidence that they are consequences of OSA. They are listed in this category because the OSA has led to conditions which cannot be reversed just by overcoming OSA. Myocardial infarction is listed as irreversible because after it occurs a portion of the heart muscle has been irreversibly damaged by interruption of its blood flow for too long a time. Ischemic stroke is listed as irreversible because after it occurs a portion of the brain has been irreversibly damaged by interruption of its blood flow for too long a time. Type 2 diabetes has been reported to be irreversible because the chronic intermittent hypoxemia of sleep apnea has reduced the pancreatic beta cell mass. Cancer is listed as irreversible because treatments other than overcoming OSA are needed to shrink the tumors. The proliferation of cancer cells is thought to be closely tied to the chronic intermittent hypoxia of OSA. Mitral valve disease is listed as irreversible because the demands on the heart during the hypoxemic episodes can be so extreme that some of the cords which control the mitral valve leaflets can become ruptured, repairable only by surgery. If either the mitral valve or aortic valve disease is from stenosis by deposition of calcium, neither would reverse by overcoming OSA.

3. OSA Mortality

The numerous life-threatening conditions in each of the three columns of Table 1 raise the issue of mortality from OSA. Two long-term (18-20 years) studies of all-cause mortality with sleep apnea have been reported\textsuperscript{44-45}. Both conclude that there is significant increase in all-cause mortality among those with sleep apnea, particularly those with the moderate (15-30 apneic events per hour of sleep) and severe (>30 apneic events per hour of sleep) forms of the disease. In an interview with Family Practice News\textsuperscript{46}, the lead author of reference\textsuperscript{45}, Dr. Nathaniel Marshall, synopsized his findings with the statement, “Sleep apnea has about the same effect on mortality as getting eighteen years older.” The impact of that statement is exemplified from US mortality data showing about a 10% death rate for 85-year olds in the general population, applying to 67-year olds with long term untreated sleep apnea.

Relying on the life-threatening OSA consequences of Table 1 to prompt diagnosis and then treatment for OSA risks premature death and declining quality of life for the patient. A much better practice is routine screening for OSA, perhaps by the method proposed in reference\textsuperscript{44}, with the aim of greatly reducing the risk for development of any of these OSA consequences.
4. Conclusion

The tabulated review of OSA consequences has divided known consequences of OSA into three categories: those that are reversible, those that are irreversible, and those whose reversibility has yet to be determined. The reasons that these diseases are consequences of OSA are generally not well-established, but they have been listed in this paper because clinical studies have found that they are indeed OSA consequences. There are life-threatening conditions in each category, and the conditions cover a wide range of medical specializations, including cardiovascular diseases, chronic kidney disease, nonalcoholic fatty liver disease, autoimmune diseases, and cancer. Those who overcome their OSA are fortunate if the only consequences which they have experienced are reversible, because promptly overcoming their OSA may reverse the progress of these diseases, as well as greatly reduce their risks for developing other life-threatening diseases that are consequences of OSA. Those who have experienced irreversible consequences are much less fortunate. The consequences whose reversibility has yet to be determined provide much fodder for future studies aimed at determining their reversibility. This list could be beneficial to many medical practitioners to support their diagnosis and treatment of OSA’s consequences, and of OSA itself. This approach is a back-up for the better practice of routine screening for OSA, leading to its diagnostic testing and treatment when warranted, with the aim of greatly reducing the risk for development of these OSA consequences.
5. References


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