The Challenges of Precision Medicine in Obstructive Sleep Apnea

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KEYWORDS

• Biomarkers • Sleep apnea • Gene arrays • Proteomics • Epigenetics

KEY POINTS

- Obstructive sleep apnea (OSA) is highly prevalent, but its diagnosis requires an onerous and not always readily available approach.
- OSA is associated with a very variable phenotype and with increased risk for end-organ morbidities that are difficult to detect unless specifically sought out.
- Biomarkers for OSA are unlikely to perform well if identified in isolation, and therefore, biomarker signatures are preferable.
- Biomarker signatures should explore (i) diagnostic approaches; (ii) morbidity; (iii) treatment monitoring and outcomes.

SLEEP-DISORDERED BREATHING AND OBSTRUCTIVE SLEEP APNEA

Sleep is an essential biological function with major roles in energy, recovery, conservation, and survival. Good quality of sleep is therefore critical for good health and overall quality of life. Nevertheless, millions of people do not get enough sleep, and many suffer from lack of sleep. Furthermore, sleep disorders are extremely common and lead to substantial morbidity, high health care costs, and reduced quality of life. Disrupted sleep in general, and more particularly, the highly prevalent condition of obstructive sleep apnea (OSA) have emerged as major risk factors for other diseases, such as obesity, high blood pressure, cardiovascular and metabolic disease, cognitive dysfunction, and depression.[1] Untreated patients with OSA suffer up to a 7-fold increased risk of motor vehicle collisions. The negative impacts of sleep apnea and sleepiness on work performance are also being increasingly recognized. Multiple studies have also demonstrated that treatment of OSA is an extremely cost-effective use of health care resources.[2–4]

Sleep patterns and duration vary both among species and within species,[5] and such variability may be due to in part to segregating genetic variation,[6] implying that sleep and risk factors for sleep disorders are at least partly under genetic control. However, the genes accounting for genetic variation in sleep are not known. Similarly, the genes underlying the risk for OSA have only been partially explored, and to date, in-depth exploration of the contribution and mechanisms underlying the role of selected genes that emerged from genome wide scans are lacking.[7–13]

Disclosure Statement: No conflicts of interest to declare.
Funding Sources: D. Gozal is supported by the Herbert T. Abelson Endowed Chair in Pediatrics.
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Sleep Med Clin 11 (2016) 213–226
http://dx.doi.org/10.1016/j.jsmc.2016.01.003
1556-407X/16/$ – see front matter

Based on the aforementioned genetic studies, it has been suggested that OSA is unlikely to represent a simple condition associated with a few genes or proteins; instead, it is likely a manifestation of multiple interconnected pathways and numerous molecular abnormalities.[14] In addition, OSA is a strong risk factor for many other diseases, and conversely, many other diseases increase the risk of OSA. For example, OSA is associated with inflammatory states and oxidative stress,[15–17] and obesity, one of the prominent risk factors for OSA, coenhances the presence other morbidities, such as insulin resistance, hypertension, cardiovascular disease, and neurocognitive dysfunction[18–21] (**Fig. 1**).

PEDIATRIC OBSTRUCTIVE SLEEP APNEA

Similar to adults, pediatric obstructive sleep apnea (P-OSA) is characterized by episodic events associated with either partial or complete obstruction of the airway during sleep, leading to intermittent oxygen desaturations, recurrent and often sustained increases in carbon dioxide, increases in the magnitude of intrathoracic inspiratory pressures, and in many instances, the occurrence of arousals from sleep with resultant sleep fragmentation.[22] P-OSA is a common condition affecting 2% to 4% of the childhood population,[23] and similar to adult patients, can result in significant end-organ morbidities, particularly involving the central nervous, cardiovascular, and metabolic systems.[22,24–28] These end-organ morbidities not only can be immediate but also can affect patients long term,[29] while also incurring higher health care costs, thereby further indicating the pressing need for timely diagnosis and treatment.[30,31]

However, even a thorough clinical history and physical examination are remarkably poor at differentiating between OSA and habitual primary snoring,[32] such that current diagnostic approaches require implementation of in-laboratory or home-based polysomnography (PSG) or similar diagnostic multichannel recording tests.[33–37] Indeed, PSG is labor intensive, inconvenient, and expensive, resulting in long waiting periods and unnecessary delays in diagnosis and treatment. From this perspective, the identification of surrogate biomarkers that reliably diagnose OSA would substantially overcome these problems and enable early detection and intervention for this important medical problem.

ADULT OBSTRUCTIVE SLEEP APNEA

Similar to the pediatric age range, the prevalence of adult obstructive sleep apnea (A-OSA) is high and rather variable (4% to 15%), with major contributions of age, gender, and ethnicity.[38,39] OSA has emerged in the last decades as a major public health issue with society-wide adverse consequences involving car- or work-related accidents, cognitive and behavioral deficits impairing work performance, in addition to increasing the risk cardiovascular and metabolic dysfunction.[40] More recent studies further suggest that there is a link between sleep apnea and diabetes, depression, as well as cancer,[41–43] such that OSA accounts either directly or via its associated morbidities for a substantial proportion of all medical-related costs.[44,45]

TREATMENT OF OBSTRUCTIVE SLEEP APNEA

In adults, continuous positive airway pressure (CPAP) is the gold-standard treatment for patients with symptomatic OSA. CPAP has few major side effects, and for most patients, an initial trial with CPAP is recommended. Some patients have transformative benefits from CPAP,[46,47] but new therapies or improvements in existing therapies for OSA are needed in view of the large number

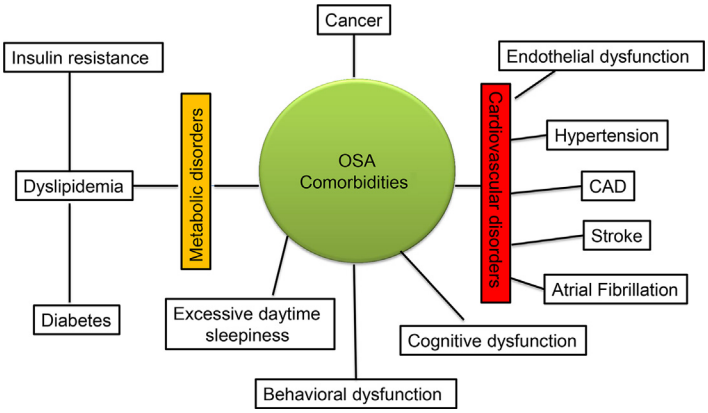

Fig. 1. The multifaceted aspects of OSA. CAD, coronary artery disease.