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CLINICAL REVIEW

Biomarkers associated with obstructive sleep apnea: A scoping review

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SUMMARY

The overall validity of biomarkers in the diagnosis of obstructive sleep apnea (OSA) remains unclear. We conducted a scoping review to provide assessments of biomarkers characteristics in the context of obstructive sleep apnea (OSA) and to identify gaps in the literature. A scoping review of studies in humans without age restriction that evaluated the potential diagnostic value of biological markers (blood, exhaled breath condensate, salivary, and urinary) in the OSA diagnosis was undertaken. Retained articles were those focused on the identification of biomarkers in subjects with OSA, the latter being confirmed with a full overnight or home-based polysomnography (PSG). Search strategies for six different databases were developed. The methodology of selected studies was classified using an adaptation of the evidence quality criteria from the American Academy of Pediatrics. Additionally the biomarkers were classified according to their potential clinical application. We identified 572 relevant studies, of which 117 met the inclusion criteria. Eighty-two studies were conducted in adults, 34 studies involved children, and one study had a sample composed of both adults and children. Most of the studies evaluated blood biomarkers. Potential diagnostic biomarkers were found in nine pediatric studies and in 58 adults studies. Only nine studies reported sensitivity and specificity, which varied substantially from 43% to 100%, and from 45% to 100%, respectively. Studies in adults have focused on the investigation of IL-6, TNF-α and hsCRP. There was no specific biomarker that was tested by a majority of authors in pediatric studies, and combinatorial urine biomarker approaches have shown preliminary promising results. In adults IL-6 and IL-10 seem to have a favorable potential to become a good biomarker to identify OSA.

Introduction

Obstructive sleep apnea (OSA) has now been widely recognized as a major public health concern with numerous and widespread societal consequences that include among others, motor vehicle accidents, increased cardiovascular morbidity, heightened risk for metabolic dysfunction, and mood, behavioral and cognitive deficits leading to impaired work performance and productivity [1]. Although healthcare costs are not normally distributed, i.e., the costliest and the sickest tertile of patients consume 65–82% of all medical-related costs, it has now become apparent that OSA significantly adds to the healthcare cost burden, in addition to its adverse impact on the economy [2,3]. It is notable that sleep disorders have been assigned as playing a causative role in an estimated 9.1% of work-related injuries [4].

The prevalence of OSA varies widely, ranging from 14.7% to 36.5%, depending on gender and nationality [5]. It is higher in males (34.2%) than in females (14.7%) [5]. Although the prevalence of OSA in Hispanics (36.5%) is similar to American Whites (33.3%), increased risk of OSA occurs in both African American and Asian ethnic groups [5–8]. In contrast, the prevalence of pediatric OSA is

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Abbreviation

AAP	American Academy of Pediatrics
AHI	apnea/hypopnea index
AI	apnea index
CRP	C-reactive protein
EBC	exhaled breath condensate
EPISONO	Epidemiologic sleep study
hr/TST	hour total sleep time
hs-CRP	high sensitivity C-reactive protein
IL-6	interleukin-6
OAHI	obstructive apnea–hypopnea index
OAI	obstructive apnea index
OSA	obstructive sleep apnea
OR	odds ratio
PSG	polysomnography
RR	risk ratio
sIL-6R	soluble interleukin-6 receptor
TNF-α	tumor necrosis factor α

reported to be between 1 and 4%, with the caveat that prospective community-based studies using overnight polysomnography (PSG) are lacking [9,10].

The standard diagnostic procedure for establishing the presence of OSA is the overnight polysomnography [11]. Except for the *a priori* reported consensus [11], an original publication or study that provided definitive validation on the use of overnight PSG as the gold standard in OSA diagnosis could not be found even after an extensive literature search. However, notwithstanding the great progress in our understanding of sleep disorders that PSG have afforded over the years, it has also become apparent that overnight PSG are onerous and labor-intensive tests that impose substantial inconvenience to the patients, and are relatively inaccessible. Indeed, waiting times between referral for evaluation to diagnosis commonly take 3–6 mo across the United States and around the world [12].

The relative complexity and high costs associated with overnight PSG as the gold standard approach employed for diagnosing the vast majority of sleep disorders has spurred the quest for alternative diagnostic methods [12]. The development of simple, cheap, and reliable screening tools that permit precise screening of at-risk populations is paramount. If accurate identification of those subjects with or without definitive disease is accomplished using such simplified and less onerous tools, then timely access to clinical care would be possible to a large sector of the population [12].

During the search for this elusive screening tool, special interest has centered around potential OSA biomarkers. The ideal biomarker should be highly sensitive and specific for OSA, should be dose-responsive and correlate to severity of disease, and should be involved in an important causal pathway, so that changes in the biomarker levels reliably predict improvements in the outcome [13]. Several different OSA biomarkers have been proposed over the last 14 y. However, to the best of our knowledge, no scoping review has been conducted thus far to critically examine what we currently know on the potential viability and use of biomarkers in OSA diagnosis and management. Therefore, the purpose of this study was to map our current understanding regarding biomarkers, and provide assessments of their characteristics in the context of OSA in both adults and children, to identify gaps in the research and help with the dissemination of the findings, and to determine the value of conducting a full systematic review related to this topic.

Methods

This scoping review was done adhering to Arksey and O'Malley's scoping review proposed reporting framework [14].

Research question

A scoping review of studies in humans without age restriction that evaluated the potential diagnostic value of biological markers (blood, exhaled breath condensate (EBC), salivary, and urinary) in the diagnostic process of OSA syndrome was undertaken.

Identification of relevant studies

Inclusion criteria

Retained articles were only those studies whose objective was to identify associated biomarkers in subjects with OSA, the latter being confirmed with a full overnight PSG or home-based PSG. Only studies that performed PSG in all subjects were included. The selected studies could include studies in obese and cardiac patients. Studies that assessed the impact of treatment were also included. Studies with and without a control group were selected. Only studies in English, Spanish and Portuguese language were considered.

Exclusion criteria

Studies using day PSG or multichannel polygraphy as the reference diagnostic standard were not included. Studies using biomarkers only to detect the presence of OSA-associated morbidities (cognitive, excessive sleepiness, cardiovascular, metabolic) and/or in which the sample included genetic syndromic patients (e.g., Down syndrome, craniofacial anomalies, neuromuscular disorders, etc.), or a cohort of patients with a primary disease for which OSA prevalence is being investigated (e.g., patients with kidney disease, and/or rheumatologic conditions) were omitted. Reviews, letters, conference abstracts and personal opinions were not considered.

Detailed individual search strategies for each of the following bibliographic databases were developed: Cochrane, Embase, MEDLINE, PubMed, and LILACS. A partial grey literature search was undertaken using Google Scholar. The end search date for all database searches was March 20, 2014. The references cited in the selected articles were also checked for any citation that could have been missed during the electronic database searches. Additional studies were obtained from a well-published expert in sleep medicine.

Appropriate truncation and word combinations were selected and were adapted for each database search (Appendix 1). All references were managed by reference manager software (RefWorks-COS is a business unit of ProQuest, LLC. ©7200 Wisconsin Avenue, Suite 601 Bethesda, MD 20866 USA) and duplicate hits were removed.

Study selection

The selection was completed in two phases. In phase 1, two reviewers independently reviewed the titles and abstracts of all identified electronic database citations (GDL and CPP). A third author was involved when required to make a final decision (SA). Any studies that appeared not to fulfill the inclusion criteria were discarded. In phase 2, the same selection criteria were applied to the full articles to confirm their eligibility. The same two reviewers (GDL and CPP) independently participated in phase 2. The reference list of all included articles was reviewed by one examiner (GDL). The articles selected were read by both examiners (GDL and CPP).