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Original Article

Biomarkers associated with obstructive sleep apnea and morbidities: a scoping review

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ABSTRACT

Objective: To map potential biomarkers of obstructive sleep apnea (OSA)-associated morbidities in both adults and children, to identify gaps in current evidence, and to determine the value of conducting a full systematic review.
Methods: A scoping review was undertaken of studies in patients with OSA that evaluated the potential value of biological markers in identifying OSA-associated morbidities. Retained articles were only those studies whose main objective was to identify morbidity biomarkers in subjects with OSA, the latter being confirmed with a full overnight polysomnography (PSG) in a laboratory or at-home settings. The methodology of the selected studies was classified using an adaptation of the evidence quality criteria recommended by the American Academy of Pediatrics. Additionally the biomarkers were categorized according to their potential clinical applicability.
Results: 572 citations were identified of which 48 met inclusion criteria. Thirty-four studies were conducted in adults and 14 involved children. Most of the studies evaluated blood biomarkers, and presented 31 potential diagnostic biomarkers.
Conclusion: The majority of studies that performed explored blood-based biomarkers, with most not identifying definitive morbidity biomarkers. Of the potentially promising morbidity biomarkers, plasma IL-6 and high sensitivity C-reactive protein appear to exhibit a favorable profile, and may discriminate OSA patients with and without morbidities in both adults and children. MRP 8/14 was retained in children as well as cardiovascular morbidity-associated biomarker. Urinary neurotransmitters may also provide a good tool for screening OSA cognitive morbidity in children.

1. Introduction

Obstructive sleep apnea (OSA) has now been recognized as a major public health issue with potential society-wide consequences involving car or work-related accidents, cognitive and behavioral deficits impairing work performance, and potentially leading to cardiovascular and metabolic dysfunction [1]. Indeed, OSA has been associated with serious morbidities such as endothelial dysfunction [2,3], hypertension [4], cardiovascular disease (CVD) [5–7], cognitive and behavioral dysfunction [8], metabolic disorders such as insulin resistance [9], diabetes [10], and dyslipidemias [11], erectile dysfunction in men [12], nocturnal enuresis in children [13], and excessive daytime sleepiness (EDS) [14,15]. Consequently, healthcare costs are substantially increased in patients with OSA, accounting either directly or via its associated morbidities for a substantial proportion of all medical-related costs [16–18].

In adults, the prevalence of OSA varies widely, from 14.7% to 36.5%, depending on age, gender, and ethnicity [19]. It is generally higher in males [19], and although the prevalence in Hispanics is similar to white Caucasians, it is significantly higher in African

Abbreviations: OSA, obstructive sleep apnea; CVD, cardiovascular disease; DTA, diagnostic test accuracy; EDS, excessive daytime sleepiness; PSG, polysomnography; EBC, exhaled breath condensate; RR, risk ratio; OR, odds ratio; AHI, apnea hypopnea index; OAI, obstructive apnea index; RDI, respiratory disturbance index; Hr/TST, hour of total sleep time; ROC, receiver operating characteristic; AASM, American Academy of Sleep Medicine; hsCRP, high-sensitivity C-reactive protein; IGF, Insulin-like growth factor; MRP, myeloid-related protein; IL-6, interleukin-6.

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American or Asians [19]. In children, the prevalence of OSA is reported as ranging between 1 and 4% [20,21].

Current diagnostic approaches range from exclusively using clinical presentation and physical examination to the current 'gold standard', the overnight polysomnography (PSG). However, the measures derived from PSG are poor predictors of OSA-associated morbidities [22]. In other words, two patients with similar OSA severity may present with markedly different clinical phenotypes, whereby one will manifest substantial end-organ morbidities related to the presence of OSA, while all such features are absent in the other. The phenotypic variance in the clinical morbidity of OSA has therefore prompted exploration of biomarkers that would enable the identification of the more "vulnerable" patients, who would more likely benefit from timely and targeted therapeutic interventions. In other words, such studies explored the opportunity to enable incorporation of morbidity biomarkers into well-defined and validated clinical algorithms [22]. The search for appropriate biomarkers becomes therefore critical. The discovery of an ideal biomarker for OSA-associated morbidity has the potential to provide information related to prognosis and response to treatment [5]. Ideal biomarkers should be highly sensitive and specific for OSA-induced end-organ dysfunction should be involved in an important causal pathway, so that changes in the biomarker levels in the context of OSA treatment reliably predict improvements in the specific end-organ outcome [23].

Several different morbidity biomarkers have been proposed for OSA over the last 12 years. However, to the best of our knowledge, no scoping review has thus far been conducted to understand what we know about the use of biomarkers in the identification and management of OSA-associated morbidities. Therefore, the purpose of this scoping review was to map our current understanding regarding any of the putative biomarkers that have been thus far investigated regarding their potential association or predictive ability of OSA-associated morbidities in both adults and children, to identify gaps in the research, and to determine the value of conducting a full systematic review related to this topic.

2. Methods

This scoping review was performed while adhering to Arksey and O'Malley's scoping review proposed reporting framework [24].

2.1. Research question

A scoping review of studies in subjects with OSA that evaluated the potential diagnostic value of biological markers (blood, exhaled breath condensate or EBC, salivary, and urinary) in the identification of those patients with morbidities associated with the underlying disease was undertaken.

2.2. Identifying relevant studies

2.2.1. Inclusion criteria

Retained articles were only those studies which objective was to identify morbidity-related biomarkers in patients with OSA (cognitive, excessive sleepiness, cardiovascular, and/or metabolic), with the diagnosis being confirmed with a full overnight PSG in either the laboratory or home setting. Only studies that performed PSG in all subjects were included. Studies that assessed the impact of treatment were also included. Lack of a control group was accepted. Only studies in English, Spanish and Portuguese were considered.

2.2.2. Exclusion criteria

Studies using daytime PSG or respiratory polygraphy were not considered. Studies in which the cohort included syndromic patients (eg, Down syndrome, craniofacial anomalies, neuromuscular disorders, etc.) or patients with a primary disease for which OSA prevalence is being investigated (eg, patients with kidney disease, and/or rheumatologic conditions), were discarded. Reviews, letters, conference abstracts, and personal opinions were not considered. Studies about central apnea were not included.

In phase 2, we excluded studies that explored OSA only, but did not assess OSA-associated morbidities.

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 references that could have been missed during the electronic database searches. Additional studies that were already known by the authors but were not identified in the searches were also included.

Appropriate truncation and word combinations were selected and were adapted for each database search. (Appendix: Supplementary Table S1) All references were managed by reference manager software (RefWorks –COS, a business unit of ProQuest, LLC. ©7200 Wisconsin Avenue, Suite 601 Bethesda, MD 20866 USA) and duplicate hits were removed.

2.3. 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 included articles was revised by one examiner (GDL). The articles selected were read by both examiners (GDL and CPP). Any disagreement in either phase was resolved by discussion and mutual agreement between the three reviewers (GDL, CPP, SA). A fourth author, an expert in sleep medicine (DG), was involved when controversy arose before making a final decision. Final selection was always based on the full-text of the publication.

2.4. Charting the data

For the included studies the following information was recorded: year of publication, author, country, sample characteristics, name and type of OSA-related morbidity biomarkers, OSA diagnostic cut-off value at PSG, results, and main conclusion. Authors of potentially eligible full-articles were contacted as necessary to provide further details about their studies.

One author (GDL) collected the required information from the selected articles. A second author (CPP) crosschecked all the collected information. Again, any disagreement in either phase was resolved by discussion and mutual agreement between the three reviewers (GDL, CPP, SA). A fourth author (DG) was involved, when required, to reach the final decision.

2.5. Level of evidence

The methodology of selected studies was classified using a non-validated adaptation of the evidence quality criteria from American Academy of Pediatrics [25]. Two reviewers (GDL and CPP) independently classified the studies as A (well-designed prognostic or diagnostic studies on relevant population), B (prognostic or diagnostic studies with minor limitations, overwhelmingly consistent evidence from observational studies), C (observational studies;