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CLINICAL REVIEW

Circulating biomarkers to identify cardiometabolic complications in patients with Obstructive Sleep Apnea: A systematic review

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SUMMARY

Untreated Obstructive sleep apnea (OSA) is associated with an increased risk of cardiometabolic diseases such as diabetes and myocardial infarction. However, it is difficult to predict which patients are at particularly high risk. This systematic review aimed to identify potentially useful circulating biomarkers that could predict cardiometabolic complications in OSA. We searched Cochrane (EBM), EMBASE, Medline, PubMed, and Web of Science databases. Search concepts included: "Obstructive Sleep Apnea", "Biomarkers" and "Risk-Stratification". Manuscripts were included if they studied adults with OSA, circulating (blood) markers, and relationships with clinical outcomes. After screening, 10 were included. Studies addressed cardiovascular disease, type 2 diabetes, end-stage renal disease and metabolic syndrome. In general, levels of inflammatory markers, adhesion molecules, and vascular proteins were associated with the presence of cardiometabolic disease in OSA patients. Although studies regarding prognostic circulating biomarkers in OSA are limited, a number of potentially promising biomarkers were identified in our review. However, more research is needed using prospective cohorts to determine which biomarkers are most robustly associated with and useful in predicting future cardiovascular and metabolic sequelae in OSA patients. Identification of such biomarkers could guide more selective and targeted therapy for OSA in an emerging era of precision-based medicine.

Introduction

Obstructive sleep apnea (OSA) is the most common respiratory sleep disorder and is characterized by recurrent closure of the upper airway leading to intermittent hypoxia and arousals. It is considered a substantial public health problem with an estimated prevalence of 13% in adult men and 5.6% in adult women [1]. OSA causes many adverse physiologic and biochemical sequelae including: activation of the sympathetic nervous system, systemic inflammation, oxidative stress, endothelial dysfunction, hypercoagulability, and metabolic dysregulation [2–5]. In addition, patients with OSA are at increased risk of developing cardiometabolic diseases [6] including cardiovascular disease (CVD), atrial fibrillation, hypertension, heart failure, diabetes, stroke, and metabolic syndrome [7–9]. For example, men with severe untreated OSA have approximately a three times greater risk of experiencing a fatal or non-fatal cardiovascular (CV) event compared to healthy controls [10].

One current challenge in the management of OSA is to distinguish which patients are at highest long-term risk of developing these complications. The ability to identify high-risk patients is important both in terms of providing prognostic information, and to provide the opportunity for a more targeted approach to OSA treatment (precision medicine). For example, if a patient could be identified as being at high risk of subsequent myocardial infarction, more aggressive management of OSA and other cardiac risk factors

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List of abbreviations

AASM	American Academy of Sleep Medicine
Adj	Statistical Adjustment
AHI	Apnea Hypoapnea index
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
cTnT	Cardiac troponin T
CV	Cardiovascular
CVD	Cardiovascular Disease
DNA	Deoxyribonucleic acid
EDS	Excessive daytime sleepiness
ESRD	End stage renal disease
HbA1c	Hemoglobin A1c
HDL	High density lipoprotein
HMG CoA	Hydroxymethylglutaryl coenzyme A
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
hs-CRP	High sensitivity c-reactive protein
ICAM	Intercellular adhesion molecule
IHD	Ischemic Heart Disease
IL-1β	Interleukin 1 beta
IL-1Ra	Interleukin 1 receptor antagonist
IL-6	Interleukin 6
IL-8	Interleukin-8
IQR	Interquartile Range
LDL	Low-density lipoprotein
LVEF	Left Ventricle Ejection Fraction
MetS	Metabolic Syndrome
MI	Myocardial Infarction
NFκB	Nuclear factor kappa B
NOS	Newcastle-Scale
NR	Not reported
NS	Not significant
ODI	Oxygen desaturation index
OSA	Obstructive Sleep Apnea
PD	Peroxides
PICO(S)	Population Intervention Control Outcome (Study design)
PON-1	Paraoxonase-1
PRISMA	Preferred reporting items for systematic reviews
PSG	Polysomnography
RANTES	Regulated on Activation Normal T Cell Expressed and Secreted
RDI	Respiratory disturbance index
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SD	Standard deviation
sEng	Soluble Endoglin
sFlt-1	Soluble fms-like tyrosine kinase-1
sICAM	soluble intercellular Adhesion Molecule
T2DM	Type 2 Diabetes Mellitus
TBARS	Thiobarbituric reactive substances
TIA	Transient Ischemic Attack
TNF-α	Tumor Necrosis Factor alpha
VCAM	Vascular cell adhesion molecule

(e.g., hypertension) could be considered. Levels of circulating biomarkers may provide such information.

Many biomarkers have been linked to OSA and may be useful to predict cardiometabolic sequelae: these include inflammatory markers, oxidative stress markers, adhesion molecules, lipids, and catecholamines [11]. The purpose of this systematic review was to identify potentially useful circulating biomarkers that could predict cardiometabolic complications in OSA.

Materials and methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis PRISMA Checklist [12]. Our PICO(S) question was: In adult (>18 y old) patients with diagnosed OSA (P), will the presence or occurrence of a cardiovascular or metabolic complication (I) be associated with elevated levels of circulating biomarkers (O) in comparison with patients with OSA who do not have a cardiometabolic condition (C) within any study design (S)? Appropriate subject headings and keywords with different truncation and word combination were selected for various databases (Appendix I). The concepts included "Obstructive Sleep Apnea" and "Biomarkers." The third concept "Risk Stratification" was not readily accessible as subject headings or keywords; therefore, two authors (BUP and AHA) screened each full-text checking for "risk stratification" concept, which was identified as any paper containing an OSA population, with and without a diagnosable comorbidity. Of note, the purpose of this review was not to identify biomarkers that have been associated with sleep apnea [13], but rather to identify biomarkers that may be useful in predicting future risk of cardiometabolic complications in patients with OSA.

Eligibility criteria

Inclusion criteria

Studies published in English with a full-text available, including adult subjects (18 y old or older), diagnosed with OSA (not central or mixed sleep apnea), and with blood samples drawn, were eligible for inclusion. Additionally, articles were required to report clinical outcomes associated with OSA (excessive daytime sleepiness and obesity were not considered).

Exclusion criteria

Studies including children, infants or adolescents (less than 18 y old) were excluded from the review. Also, any other source of biological material other than blood (i.e., urine, saliva, exhaled breath condensation) was not considered. Histological and nonhuman studies, reviews, letters, expert opinions/interviews, and studies published as an abstract only were not included. Finally, studies without a control group within the OSA population were not considered.

Search strategy and study screening

EBM Reviews, EMBASE, Medline, PubMed, and Web of Science databases were utilized (Appendix 1). All references were exported using RefWorks (ProQuest, Bethesda, MD). EBM Reviews was included to confirm the existence of previous reviews regarding cardiometabolic biomarkers in OSA. Grey literature search, expert consult and manual search in references from included papers were verified to minimize the possibility of omitting any relevant study. The search process started in July 2nd, 2016 and finished July 26th,

2017. Initially, duplicates were removed through RefWorks, then two independent reviewers (BUP and AHA) applied inclusion and exclusion criteria to screen: first, for titles only, and then abstracts. After the initial screening, the same criteria was applied to full-text manuscripts. In case of any disagreement, a consensus was reached by consulting a third reviewer (NA). The included studies were imported into a second citation management software (Zotero, Virginia, US), and had data extracted by one author (BUP). Variables extracted from all studies included: year of study, first author, country where study was conducted, study design, type of cohort (community vs hospital), criteria for diagnosis of OSA, sample size, sex, mean age, body mass index, mean AHI, mean and standard deviation or median and interquartile range of levels of biomarkers, time of blood collection, p-values comparing the OSA group with the OSA and comorbidity group, the laboratory technique that was used to process the samples, and time to follow-up. A modified Newcastle-Scale (NOS) was used to determine the of risk bias in selecting the studies that were reviewed.

Results

A total of 2733 papers were identified. After duplicates were removed, and application of inclusion and exclusion criteria to titles, 1143 papers remained. After abstract screening, 206 full-text articles were obtained. From these, we were able to identify prognostic markers in 14 studies. As part of grey literature search and manual inclusion of relevant papers, an additional 14 papers were identified; of these, only one study fit the criteria for inclusion in the final review (Appendix 2 and 3). As the primary focus was on cardiovascular and metabolic disorders, a total of 10 articles were included in the final analysis (Fig. 1).

Studies characteristics

Of the 10 papers included in the final review (Tables 1–3), two were from China [14,15] and the remaining countries of origin varied with representation from Japan [16], USA [17], Turkey [18], Israel [19], Germany [20], France [21], Sweden [22] and Bulgaria [23]. The sample size ranged from 18 [20] to 432 [15]. Although one study used a community-based sample [22], the majority collected data from clinic-based samples.

There was substantial variation across the studies regarding sleep diagnostic testing for OSA. Some studies used portable monitors [22], while others used full polysomnography [17–19,21]. Oxygen desaturation criteria for OSA also varied; some used a 4% drop in the oxygen saturation to score hypopneas [17] while others used a 3% desaturation [23]. Some studies considered OSA as an AHI above 5/hr [14,18], while others only included severe cases (AHI > 30) [17]. The modified Newcastle–Ottawa scale (Table 7) indicated that the majority of studies (90%) scored five or more out of nine in this quality assessment tool, which reflects an overall moderate quality of the evidence.

All study designs were either case-control or cross-sectional. In other words, none of the studies examined the use of biomarkers to prospectively identify the development of future complications, but rather studied the presence of concurrent OSA and the cardiac or metabolic outcome.

Biomarkers and cardiovascular complications

Most of the studies (6/10) investigated cardiovascular (CV) complications (Tables 1 and 4). Cardiovascular outcomes had a wide range of definitions; for example, some studies considered hypertension as a cardiovascular event, while others used composite outcomes including ischemic heart disease, heart failure, coronary artery disease, stroke and transient ischemic attack.

Table 4 describes the biomarkers tested in these studies. As can be appreciated, a broad range of markers were studied in this context. These included markers of oxidative stress and inflammation, levels of adhesion molecules, vascular proteins, catecholamines, lipids/lipoproteins, and glucose. Data should be interpreted cautiously given that most of the studies had small sample sizes

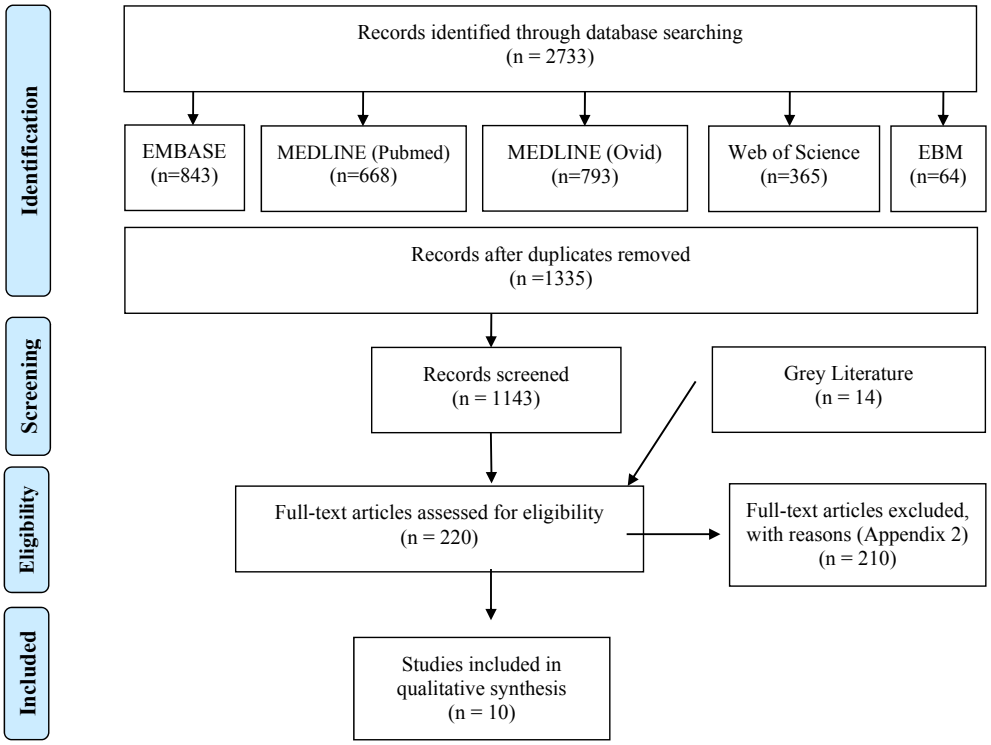

Fig. 1. Flow diagram.

Table 1
Characteristics of cardiovascular studies.

Author (Year)/Country	Study design/	AHI Scoring Criteria	OSA Definition	Sample Size (n)	Age (years)	Male (%)	Mean BMI (kg/m^2)	Mean AHI (SD)	Definition of Outcome
Lavie et al (2004)+ Israel [19]	Case-Control	PSG with no clear oxygen desaturation cutoff	RDI >10+ at least one symptom (EDS, chronic fatigue, restless sleep) was considered OSA+.	**OSA** + **CVD**+ 59	58.5	83	30.6	31.3 (18.5)	**CVD**+ = Either Hypertension or IHD, or history of MI or stroke. Hypertension = BP > 140/90 mmHg or use of antihypertensive. IHD = History of MI or angiographic findings.
				OSA + **CVD**− 55	46.8	85.5	28.4	26.9 (13.8)	
Kokturk et al (2005)+ Turkey [18]	Case-Control	PSG 3%	AHI ≥ 5 was considered OSA+.	**OSA** + **CVD**+ 38	44.5	100	31.7	32.9 (28.7)	**CVD**+ = Hypertension and/or ischemic heart disease. No description on how hypertension or IHD were defined.
				OSA + **CVD**− 56	42.9	100	32.3	44.9 (41.5)	
Mohsenin and Urbano (2011)+ USA [17]	Cross-Sectional	PSG 4%	AHI ≥ 30 was considered OSA+.	**OSA** + **Hypertension**+ 11	48	91	41	81 (11)	**Hypertension**+ = BP ≥ 149/90 mmHg
				OSA + **Hypertension**− 11	45	91	40	76 (9)	
Sui and Gao et al (2013)+ China [14]	Case-Control	PSG with no clear oxygen desaturation cutoff	AHI ≥ 5 was considered OSA+.	**OSA** + **Coronary Artery Disease**+ 134	57	74	26.56	Median (IQR): 24 (17–32)	**CAD**+ = >50% of stenosis in at least one major coronary artery in visual analysis of angiographic results.
				OSA + **Coronary Artery Disease**− 112	56	71	25.9	Median (IQR): 23.5 (17–30)	
Testelmans et al (2013) France [21]	Case-Control	PSG with no clear oxygen desaturation cutoff	AHI ≥ 15 were considered OSA+.	**OSA** + **CVD**+ 15	53	93	25	36 (19)	**CVD**+ = Patients admitted with acute coronary syndrome or cerebrovascular ischemic accident.
				OSA + **CVD**− 15	52	80	25	38 (15)	
Johansson et al (2015)+ Sweden [22]	Case-Control	Type III AASM Portable Monitor 4%	Sleep disordered breathing characterized by ODI and AHI.	**OSA** + **CVD**+ 119	79	67	27.7	Median (IQR): 8.8 (2.8–18)	**CVD**+ = Either ischemic heart disease (history of angina pectoris/myocardial infarction), heart failure (LVEF < 50% from echocardiography) or TIA/stroke.
				OSA + **CVD**− 221	78	40	27.4	Median (IQR): 4.4 (1.8–11.6)	

+**Cardiovascular Outcomes**; **AHI Scoring Criteria**: refers to threshold values for desaturations to score hypopneas. **Abbreviations**: **AASM**: American academy of sleep medicine; **AHI**: Apnea hypopnea index; **BMI**: Body mass index; **CAD**: Coronary artery disease; **CVD**: Cardiovascular disease; EDS: Excessive daytime sleepiness; **IHD**: Ischemic heart disease; **IQR**: Interquartile range; **LVEF**: Left ventricle ejection fraction; **MI:** Myocardial infarction; **ODI**: Oxygen desaturation index; **OSA:** Obstructive sleep apnea; **PSG**: Polysomnography; **RDI:** Respiratory disturbance index; **SD:** Standard deviation; **TIA**: Transient ischemic attack.

Table 2
Characteristics of metabolic studies.

Author (Year)/Country	Study design/	AHI Scoring Criteria	OSA Definition	Sample Size	Age (years)	Male %	Mean BMI (kg/m^2)	Mean AHI (SD)	Definition of Outcome
Shiina et al (2006)++ Japan [16]	Cross-Sectional	PSG 4%	AHI ≥ 15 was considered OSA+	**OSA + MetS+** 41	51	95	30.8	51.9 (3.3)	**MetS**+ = HDL (mmol/l) < 1.036 (male), <1.295 (female); Triglycerides ≥ 1.695 mmol/l; BP ≥ 130/85 mmHg or BP drugs; Fasting glucose ≥ 6.105 mmol/l BMI ≥ 27.5
				OSA + MetS– 53	52	92	26.1	43.6 (2.5)	
Cherneva et al (2013)++ Bulgaria [23]	Cross-sectional	PSG 3%	AHI 5-30events/h = mild to moderate and AHI > 30 severe.	**OSA + T2DM+** 23	57	74	43	58.8 (34.2)	**T2DM** + = Fasting blood glucose >7 mmol/l at least twice or random blood glucose >11.1 mmol/l
				OSA + T2DM– 17	42.6	100	43	62.3 (30.6)	
Sun et al (2015)++ China [15]	Cross-sectional	PSG with no clear oxygen desaturation cutoff	AHI > 5 was considered OSA+	**OSA + T2DM+** 234	55	NR	26	NR	**T2DM**+ = Fasting glucose ≥7 mM or 2-h postprandial ≥11.1 mM.
				OSA + T2DM– 198	54	NR	25	NR	

++**Metabolic Disorders. AHI Scoring Criteria**: refers to threshold values for desaturations to score hypopneas. **Abbreviations**: **AHI**: Apnea hypopnea index; **BMI**: Body mass index; **BP**: Blood pressure; **MetS**: Metabolic syndrome; **NR**: Not reported; **OSA**: Obstructive sleep apnea; **PSG**: Polysomnography; **SD**: Standard deviation; **T2DM**: Type 2 diabetes mellitus.

and were not prospective in design. In addition, none of the studies (6/6) reported levels of biomarkers after adjustment for possible confounding factors.

Nevertheless, inflammatory markers may be the most promising biomarkers to risk-stratify OSA patients, as in general, levels were elevated in patients with CVD. The most frequently studied molecule was C-reactive protein (CRP), which is produced by the liver with an important role in immune and inflammatory responses [24]. The other potentially important marker was YKL-40, also known as human cartilage glycoprotein 39 or chitinase-3-like protein 1. It is also involved in immune and inflammatory responses, and elevated YKL-40 levels are related to cell migration and remodeling after endothelial disruption [25]. YKL-40 was significantly elevated in 134 OSA patients with coronary artery disease [14]. Finally, several other biomarkers such as hs-CRP, IL-1Ra, IL-8, RANTES and TNF-α were higher in fifteen OSA patients who had an acute cardiovascular event, compared to fifteen non-obese OSA with similar age, BMI and OSA severity [21].

Vascular proteins and adhesion molecules are also well-established markers for atherosclerosis and subsequent CVD in non-OSA cohorts. We identified two studies that examined these markers in OSA patients; both these studies were small. One of these molecules, intercellular adhesion molecule, is a glycoprotein that plays a role in leukocyte adhesion to injured endothelium and could be useful for risk stratification in OSA populations [31]. In our review, soluble intercellular adhesion molecule (sICAM) was positively associated with CVD in 15 OSA patients with acute coronary syndrome or cerebrovascular ischemic accidents [21]. Also, endoglin (a marker of angiogenesis that is involved in the progression of CVD) [32] and fms-like tyrosine kinase-1 (a regulatory marker of vascular endothelial growth) [33] were significantly elevated in eleven (n = 11) hypertensive OSA patients [19].

Oxidative stress can occur because of an imbalance between oxidants and antioxidants. Oxidative stress plays a pivotal role in the initiation and progression of atherosclerosis in non-OSA populations [3,26,27]. OSA, which is categorized by intermittent hypoxia, can result in the development of oxidative stress, analogous to what happens with ischemic/reperfusion injury. In this review, oxidative stress markers such as thiobarbituric reactive substances (TBARS), peroxides, paraoxonase-1 [19] and nitrite/nitrate [17] were not increased in OSA patients with CVD. However, it must be noted that only two studies examined these markers.

In terms of lipids and lipoproteins, there is a single report linking low-density lipoproteins (LDL) levels to OSA and coronary artery disease [14]. Cholesterol, high-density lipoprotein (HDL), LDL and triglycerides were no further elevated if a cardiovascular condition was accompanied by OSA [14,19].

Finally, the repetitive arousals and hypoxemia characteristic of OSA activate the sympathetic nervous system, which may also contribute to the development of hypertension and other cardiometabolic disease. However, we only identified one study that examined the utility of catecholamines such as epinephrine and norepinephrine as a prognostic marker. In this 22 patient study, catecholamine levels were not significantly elevated in OSA patients with hypertension compared to those without hypertension [17].

Biomarkers and metabolic outcomes

There were only three papers that assessed metabolic outcomes in patients with OSA (Tables 2 and 5) and their association with circulating biomarkers. In general, inflammatory markers were elevated more than other circulating biomarkers in patients with the metabolic outcome. However, lipid levels were not significantly elevated.

The most recent study [15] aimed to determine whether inflammatory markers such as YKL-40 and C-reactive protein were

Table 3
Characteristics of renal diseases studies.

Author (Year)/Country	Study design/	AHI Scoring Criteria	OSA Definition	Sample Size	Age (years)	Male %	Mean BMI (kg/m^2)	Mean AHI (SD)	Definition of Outcome
Kohnlein et al+++ (2009) Germany [20]	Cross-sectional	PSG 4%.	AHI>10 was considered OSA+	**OSA + ESRD+** 10	NR	NR	NR	25	ESRD + = Patients on maintenance hemodialysis treatment
				OSA + ESRD− 8	NR	NR	NR	32	

+++**Other Comorbidities**. **AHI Scoring Criteria**: refers to threshold values for desaturations to score hypopneas. **Abbreviations**: **AHI**: Apnea hypopnea index; **BMI**: Body mass index; **ESRD**: End stage renal disease; **NR**: Not reported; **OSA:** Obstructive sleep apnea; **PSG**: Polysomnography; **SD:** Standard deviation.

useful to predict the development of Type 2 diabetes (T2DM) in OSA patients. The relatively robust sample size yielded a modest statistical signal in a multivariate logistic regression model. The odds ratio (95% confidence interval) was 1.012 (1.003–1.019) for CRP and 1.023 (1.018–1.028) for YKL-40. The other study that investigated T2DM was identified by reviewing grey literature [23]. Resistin, a hormone that links obesity to diabetes, was significantly elevated in severe OSA patients with T2DM, after adjusting for age, BMI and homeostasis model assessment of insulin resistance. Finally, Shiina et al. [16] included 41 patients with an AHI above 15 (using a 4% oxygen desaturation to score respiratory events). After adjusting CRP levels for age, gender, smoking status, cholesterol levels, antihypertensive drugs, statins, BMI and mean blood pressure there was no significant difference between OSA patients with and without metabolic syndrome.

Biomarkers and renal outcomes

Finally, one paper investigated kidney disease associated with OSA (Tables 3 and 6). End stage renal disease (ESRD) [20] was studied in a small sample (n = 18) of OSA patients (AHI > 10). CRP, and troponin levels were significantly higher in OSA patients with ESRD than OSA patients with normal renal function suggesting these may be reasonable markers of poor kidney outcomes to study in the future.

Discussion

The search for biomarkers in patients with OSA has been emphasized recently [11]. Most efforts have been directed towards biomarkers that could be used to screen for OSA [13,28]; however,

Table 4
Characteristics of cardiovascular markers.

Biomarkers	Authors	Mean	SD	Mean	SD	Adj	Significance (p-value)
Inflammation		CVD+		CVD−			
CRP (mg/l)	Kokturk et al. (2005) [18]	4.7	8.0	2.4	5.1	⊥	**<0.05**
	Testelmans et al. (2013) [21]	7*	2.6–9.6	0.7	0.4–1.2	⊥	**<0.001**
	Johansson et al. (2015) [22]	2.7	1.2–4.7	2.2	1.1–4.8	⊥	NS
YKL-40 (ng/ml)	Sui and Gao et al. (2013) [14]	136.1*	107.2–157.2	115.2	87.43–143.13	⊥	**<0.001**
IL-8 (pg/ml)	Testelmans et al. (2013) [21]	17.8*	6.9–141.7	5.9	4–7.9	⊥	**<0.01**
RANTES (ng/ml)	Testelmans et al. (2013) [21]	48.1*	37.6–65.1	35.3	28.2–44.1	⊥	**<0.05**
TNF-α (pg/ml)	Testelmans et al. (2013) [21]	2.5*	2–3.1	1.6	1–2.1	⊥	**<0.05**
IL-1Ra (pg/mL)	Testelmans et al. (2013) [21]	1939*	1149–2360	600	406–695	⊥	**<0.001**
Oxidative Stress							
TBARS (nmol/ml)	Lavie et al. (2004) [19]	18.6	7.3	17.2	6.3	⊥	NS
PD (nmol/ml)	Lavie et al. (2004) [19]	906.5	132.1	901.2	103.9	⊥	NS
PON1 (U.min/ml)	Lavie et al. (2004) [19]	79.5	13.6	86.7	17.6	⊥	NS
Nitrite Nitrate (uM)	Mohsenin and Urbano (2011) [17]	39	13	30	11	⊥	NS
Adhesion Molecules							
sICAM (ng/ml)	Testelmans et al. (2013) [21]	219*	208–252	185	169–204	⊥	**<0.05**
Vascular Proteins							
Creatinine (mg/dl)	Lavie et al. (2004) [19]	1	0.4	0.9	0.1	⊥	NS
Endothelin − 1 (pg/ml)	Mohsenin and Urbano (2011) [17]	0.7	0.1	1.4	0.3	⊥	NS
sFlt-1 (pg/ml)	Mohsenin and Urbano (2011) [17]	90	4.6	74	4.4	⊥	**0.018**
sEng (ng/ml)	Mohsenin and Urbano (2011) [17]	4.9	0.3	3.5	0.4	⊥	**0.016**
Lipids/Lipoproteins							
Cholesterol (mmol/l)	Lavie et al. (2004) [19]	5.1	1	5.3	0.9	⊥	NS
	Sui and Gao et al. (2013) [14]	5.4	1.3	5.2	1.03	⊥	NS
HDL (mmol/l)	Lavie et al. (2004) [19]	1.2	0.3	1.1	0.2	⊥	NS
	Sui and Gao et al. (2013) [14]	1.9	0.6	1.8	0.52	⊥	NS
LDL (mmol/l)	Lavie et al. (2004) [19]	3.1	0.8	3.3	0.84	⊥	NS
	Sui and Gao et al. (2013) [14]	3.7	1.0	3.3	0.95	⊥	**0.002**
Triglycerides (mmol/l)	Lavie et al. (2004) [19]	1.9	1	2.0	0.85	⊥	NS
Glucose (mmol/l)	Lavie et al. (2004) [19]	6	1.4	5.5	0.7	⊥	**0.04**
	Sui and Gao et al. (2013) [14]	1.9	0.6	1.8	0.52	⊥	NS
Cathecholamines							
Norepinephrine (pg/ml)	Mohsenin and Urbano (2011) [17]	840	92	790	110	⊥	NS
Epinephrine (pg/ml)	Mohsenin and Urbano (2011) [17]	38	5.9	54	11	⊥	NS

Cardiovascular Outcomes; *Median and Interquartile range; ⊥: Unadjusted analysis. **Abbreviations**: **Adj:** Statistical adjustment; **CRP**: C-reactive protein; **CVD**: Cardiovascular disease; **HDL**: High density lipoprotein; **IL-1Ra**: Interleukin 1 receptor antagonist; **IL-8**: Interleukin-8; **LDL:** Low-density lipoprotein; **NS**: Not significant ($p > 0.05$); **PD**: Peroxides; **PON-1**: Paraoxonase-1; **RANTES:** Regulated on Activation Normal T Cell Expressed and Secreted; **sICAM**: soluble intercellular adhesion molecule; **SD:** Standard deviation; **sEng**: Soluble endoglin; **sFlt-1**: Soluble fms-like tyrosine kinase-1; **TBARS**: Thiobarbituric reactive substances; **TNF-α:** Tumor necrosis factor alpha; **NOTE**: Significant association between biomarkers and outcomes are in bold.

Table 5
Characteristics of metabolic markers.

Biomarkers	Authors	Mean MetD+	SD	Mean MetD-	SD	Adj	Significance (p-value)
Inflammation							
CRP (mg/l)	Shiina et al. (2006) [16]	1.8	0.2	1.2	0.1	⊥⊥	NS
	Sun et al. (2015) [15]	2.6	1.7–4.7	2.2	1.2–3.5	⊥	**0.017**
YKL-40 (ng/ml)	Sun et al. (2015) [15]	205*	146–272	135.7	114–163	⊥	**<0.001**
Lipids/Lipoproteins							
Cholesterol (mmol/l)	Shiina et al. (2006) [16]	5.6	0.2	5.5	0.1	⊥⊥	NS
	Cherneva et al. (2013) [23]	5.0	1.0	5.2	1.04	⊥⊥⊥⊥	NS
HDL (mmol/l)	Shiina et al. (2006) [16]	1.1	0.03	1.3	0.04	⊥⊥	**<0.05**
	Cherneva et al. (2013) [23]	1.3	0.3	1.3	0.26	⊥⊥⊥⊥	NS
	Sun et al. (2015) [15]	1.3	0.3	1.3	0.3	⊥	NS
LDL (mmol/l)	Cherneva et al. (2013) [23]	2.9	0.07	3.2	1.03	⊥⊥⊥⊥	NS
	Sun et al. (2015) [15]	3.5	1.1	3.4	1.02	⊥	NS
Triglycerides (mmol/l)	Shiina et al. (2006) [16]	2.6	0.2	2.0	0.1	⊥⊥	**<0.05**
	Cherneva et al. (2013) [23]	1.7	0.8	2.1	0.82	⊥⊥⊥⊥	NS
	Sun et al. (2015) [15]	1.9	0.6	1.9	0.6	⊥	NS
Fatty acids (mmol/l)	Cherneva et al. (2013) [23]	0.3	0.15	0.2	0.07	⊥⊥⊥⊥	NS
Other							
Glucose (mmol/l)	Shiina et al. (2006) [16]	6.1	0.3	5.2	0.2	⊥⊥	**<0.05**
	Cherneva et al. (2013) [23]	7.0	1.3	4.9	0.71	⊥⊥⊥⊥	NR
Insulin (mU/l)	Cherneva et al. (2013) [23]	18.9	16.6	22.6	12.4	⊥⊥⊥⊥	NS
HbA1C	Cherneva et al. (2013) [23]	6.7	1.1	5.6	0.44	⊥⊥⊥⊥	**<0.001**
Resistin (ng/ml)	Cherneva et al. (2013) [23]	6.1	5.9	3.8	3.23	⊥⊥⊥⊥	**0.043**

Metabolic Disorders: **Metabolic Syndrome**** (Shiina 2006) and **T2DM** (Cherneva 2013 and Sun 2015). *Median and Interquartile range; **Metabolic syndrome characterized by HDL (mmol/l) < 1.036 (male), <1.295 (female); Triglycerides ≥ 1.695 mmol/l; BP ≥ 130/85 mmHg or BP drugs; Fasting glucose ≥ 6.105 mmol/l BMI ≥ 27.5; ⊥: Unadjusted analysis; ⊥⊥: Adjusted for age, gender, smoking status, total cholesterol, antihypertensive drugs, statins, BMI and mean blood pressure; ⊥⊥⊥⊥: Adjusted for Age, BMI and HOMA-IR. **Abbreviations**: **Adj:** Statistical adjustment**; BMI**: Body mass index; **CRP**: C-reactive protein; **HbA1c:** Hemoglobin A1c; **HDL**: High density lipoprotein; **HOMA-IR**: Homeostasis model assessment of insulin resistance; **LDL:** Low-density lipoprotein; **NR**: Not reported; **NS**: Not significant ($p > 0.05$); **SD:** Standard deviation; **T2DM**: Type 2 Diabetes Mellitus; **NOTE:** Significant associations are in bold.

Table 6
Characteristics of renal diseases markers.

Biomarkers	Authors	Mean	SD	Mean	SD	Adj	Significance (p-value)
Inflammation							
CRP (mg/l)	Kohnlein et al. (2009) [20]	**ESRD**+		**ESRD**−			
		11.6	0.02	5.1	4.9	⊥	**<0.01**
cTnT (ug/L)	Kohnlein et al. (2009) [20]	**ESRD**+		**ESRD**−			
		0.38	0.3	0.01	NR	⊥	**<0.001**

Other Comorbidities; ⊥: Unadjusted analysis; **Abbreviations**: **Adj:** Statistical adjustment; **CRP**: C-reactive protein; ***c*TnT**: Cardiac troponin T; **ESRD**: End stage renal disease; **NR**: Not reported; **SD:** Standard deviation; NOTE: Significant associations between biomarkers and outcomes are in bold.

the identification of markers that could predict adverse clinical outcomes is also of fundamental importance. The recent negative results from the SAVE trial [29], where CPAP prescription did not prevent cardiovascular events in unselected patients with OSA, support the initiative to develop novel strategies to treat patients with OSA to prevent future complications. The identification of robust circulating biomarkers that would help to risk stratify patients could help substantially in this regard. For example, we

Table 7
Quality assessment.

Quality Assessment (The Newcastle–Ottawa Scale – NOS for Case Control Studies)	Selection (★★★★)	Comparability (★★)	Outcome/Exposure (★★★)
Lavie et al. 2004 [19]	★★	★	★★
Kortuk et al. 2005 [18]	★	★★	★
Shiina et al. 2006 [16]	★★	★★	★★
Kohnlein et al. 2009 [20]	★★	★	★★
Mohesin and Urbano et al. 2011 [17]	★★★	★	★
Sui and Gao et al. 2013 [14]	★★	★	★★★
Testelmans et al. 2013 [21]	★★	★★	★★★
Johansson et al. 2015 [22]	★★★	★	★★
Sun et al. 2015 [15]	★★	★★	★★
Cherneva et al. 2013 [23]	★★	★	★★

Star ratings were given based on manual for scoring the Newcastle–Ottawa Quality Assessment Scale. A study can be awarded a maximum one star for each item within selection and exposure categories, and a maximum of two stars can be given for comparability. Selection: a star is awarded if case is defined with independent validation, if cases are representative, if there are community controls and if controls have no history of disease. Comparability: a start is award if study controlled for confounding at the design or analysis stage, an extra star if controlled for any additional factor. Exposure: a star is awarded if exposure is ascertained by records or blinded structured interviews, another star if cases and controls had the same method of ascertainment, and a final star if the non-response rate is the same for both groups.

would envision that an OSA patient at high risk of subsequent myocardial infarction may have more aggressive treatment of OSA and cardiovascular risk factors, especially given the improved outcomes in patients in the SAVE study adherent to CPAP therapy. In addition, in the future, elevation of certain biomarkers may help to target therapy more precisely. For example, though speculative, patients with higher levels of oxidative stress may benefit with anti-oxidant therapy, while anti-inflammatory agents may be more beneficial in patients with higher degrees of systemic inflammation. In this review, we have summarized the current knowledge of circulating biomarkers associated with cardiometabolic outcomes in patients with OSA.

Cardiovascular outcomes

From our review, markers of inflammation may be a promising biomarker in this regard. In general, circulating levels of these biomarkers are elevated in OSA patients and concomitant CVD. Inflammatory processes play a fundamental role in the development of CVD. The oxidative and inflammatory events at the endothelium level (triggered by risk factors, such as smoking, obesity and hypertension) contribute to fatty-fibrotic vascular lesions. The persistence of such plaques can cause physical trauma and further propagate the inflammatory process [30]. In non-OSA cohorts, substantial data have demonstrated the independent predictive value of CRP, a marker of systemic inflammation, in predicting cardiovascular death, such that CRP levels are used to risk stratify the use of HMG CoA reductase inhibitors [31]. For example, data from the Framingham Heart Study shows that patients with elevated CRP levels (above 3 mg/l) have a significantly increased hazard rate (95% CI: 1.16–2.15) for cardiovascular events, after adjusting for age, sex, systolic blood pressure, anti-hypertensive therapy, cholesterol, smoking and diabetes [32]. A recent study also showed that the administration of monoclonal antibodies to interleukin-1-B reduces rates of CV events in high risk patients, supporting the pivotal role of inflammation in the pathogenesis of CVD [33].

Furthermore, animals exposed to intermittent hypoxia consistently develop elevated circulating levels of inflammatory biomarkers. The inflammation is likely caused by intermittent hypoxia and re-oxygenation, resulting in oxidative stress, and activation of NFkB pathways. Biomarker levels that are elevated in animal models include IL-1β, IL-6, TNF-α, protein carbonyls, 8-hydroxylguanosine, and CRP [34,35]. Interestingly, the impact of CPAP therapy on levels of inflammatory markers in OSA patients is inconsistent, with some randomized controlled trials showing little benefit of treatment in this regard [36]. We suspect that this may reflect differences in adherence with CPAP therapy rather than the fact that OSA per se does not contribute to systemic inflammation.

Adhesion molecules may also be promising biomarkers in the risk stratification of OSA patients. Adhesion molecules including E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular adhesion molecule-1 (VCAM-1) modulate the binding of leukocytes to vascular endothelium. They are present in atherosclerotic plaques and contribute to disease progression. In prospective non-OSA cohorts, circulating levels of these molecules are associated with incident cardiovascular disease [10–13]. To illustrate, one study demonstrated that circulating levels of ICAM-1 were independently associated with incident CVD and carotid artery atherosclerosis (odds ratios of 5.53 and 2.64, respectively) [10]. Furthermore, patients with OSA have increased serum levels of adhesion molecules [14–16]. In our review, we identified one small study that examined the association between ICAM-1 levels and coronary/cerebrovascular ischemic events [21]. Although this study showed a significant difference in sICAM levels between OSA patients with and without these events, larger studies with a broader array of these molecules are clearly needed.

Circulating angiogenic proteins were investigated in a relatively small sample (n = 11) of severe OSA patients (AHI > 30) [19]. Soluble fms-like tyrokinase-1 (sFlt-1) and soluble endoglin (sEng) were elevated in the hypertensive group, compared to the normotensive group. Interestingly, both of these molecules are well-known markers for preeclampsia in women, which is also considered to be a disease of endothelial dysfunction. Consequently, they may also reflect potentially useful molecules of CVD risk in patients with OSA.

Oxidative stress also plays a key role in the development of CVD. Reactive oxygen species (ROS) are chemically reactive molecules such as superoxide, hydroxyl radical, and peroxides characterized by an unpaired electron in their outer atomic shell. Under conditions of stress, levels of ROS can increase dramatically, and can overwhelm the antioxidant capacity for detoxification leading to a state of oxidative stress. These ROS can damage a variety of cellular molecules including DNA, RNA, and proteins, which in turn can cause membrane damage, cell death, apoptosis, and activation of inflammation. Oxidative stress is recognized increasingly as a fundamental contributor to the pathogenesis of CVD; indeed, ROS play a role in mediating the adverse effects of many CV risk factors including diabetes, obesity, smoking, and air pollution. Ischemia reperfusion injury, which is the tissue damage that results due to reestablishment of oxygen supply to ischemic tissue, is also thought to be largely mediated by oxidative stress [37]. The similarity between ischemic/reperfusion injury and intermittent hypoxia leads to a unifying paradigm linking oxidative stress to CVD and OSA [26]. Indeed, many animal studies have shown robust activation of oxidative stress when they are exposed to intermittent hypoxia as reflected by increased levels of 8-isoprostane, protein carbonyls, and other markers [38,39].

However, the studies we identified in our review did not demonstrate increased oxidative stress markers in OSA patients with CVD. It must be noted, that we only found two studies in this regard and the sample sizes were small. In addition, only four markers were tested and the temporal relationship between oxidative stress and clinical symptoms of OSA and CVD was also unclear. Given the theoretical links between OSA, oxidative stress, and CVD, future studies of oxidative stress biomarkers should be considered despite these negative studies.

Metabolic disorders

Intermittent hypoxia and sleep fragmentation are linked to metabolic dysfunction in OSA. Increased sympathetic activation, oxidative stress, systemic inflammation, and alteration of adipokines can predispose OSA patients to hypertension, insulin resistance and β-cell dysfunction. These conditions can lead to type 2 diabetes mellitus, potentially causing vascular complications in OSA patients. Indeed, OSA is an independent risk factor for T2DM. Evidence from prospective cohort studies indicate a relative risk of 1.35 with a 95% confidence interval from 1.24 to 1.47 [40]. Additionally, CPAP treatment seems to improve glycemic control and insulin resistance [41], especially if done in a well-controlled, supervised settings [42]. A bidirectional relationship between OSA and T2DM has been suggested, since diabetes can affect respiratory control, leading to sleep-disordered breathing [40]. In our review, inflammatory and vascular proteins (resistin and endoglin) were significantly associated with the presence of diabetes and metabolic syndrome in OSA patients. However, it must be noted that these studies were not prospective in nature, and we cannot exclude the possibility that the

metabolic comorbidities caused elevations in these markers as opposed to the other way around.

Renal outcomes

It well recognized that renal failure can contribute to OSA, and that more frequent dialysis and ultrafiltration can improve OSA severity in them [43,44]. However, it is becoming increasingly recognized that OSA may contribute to kidney injury through a variety of mechanisms including oxidative stress, sympathetic activation, and renin-angiotensin-aldosterone system activation [45,46]. In our review, we identified one cross sectional study that showed significant increases in levels of C-reactive protein and troponin levels in OSA patients with end-stage renal disease [20]. However, prospective studies are required to determine if other markers are associated with risk of accelerated renal dysfunction.

An ideal prognostic OSA biomarker should be disease-specific, treatment-sensitive, exist in a causal pathway, and predict improvements in outcome [47]. Previous reviews focused on identifying unique OSA signatures that highlighted inflammatory, metabolic, and oxidative stress molecules as potential markers [11], however prognostic biomarkers haven't been systematically explored [13,48]. Our review identified that inflammatory markers (CRP, YKL-40), vascular proteins (resistin, endoglin) and adhesion molecules (ICAM) are biologically linked with OSA and potential cardiometabolic consequences and thus may be useful prognostic markers in patients with OSA. Also, the limited number of studies on oxidative stress markers and catecholamines justify future investigations to clarify their potential role in risk stratifying individuals with OSA.

This is the first report attempting to identify prognostic markers for cardiometabolic complications in the OSA population. A number of limitations of our analysis need to be acknowledged. First, there was significant heterogeneity among the studies that limited the possibility of pooling the data using meta-analysis. Second, the surprising lack of prospective studies makes interpretation of prognostic markers difficult. Specifically, it is possible that the cardiometabolic comorbidities may have at least partially caused the elevation in markers, which would limit their utility as potential prognostic variables. Third, in our review we focused on circulating markers and did not include studies of other biologic fluids (e.g., saliva, urine). Because of the frequency, ease, consistency, and availability of blood collection in clinical laboratories, we believed that blood tests would be more useful as a future clinical test which is the reason, we focused on this. Finally, there is a risk of publication bias, in that negative studies may be less likely to be published.

Conclusions

In this comprehensive systematic review, we identified ten studies that examined the potential utility of prognostic biomarkers in patients with OSA. In general, inflammatory markers, vascular proteins, and adhesion molecules seem to be associated with adverse cardiometabolic outcomes. Although oxidative stress and catecholamine levels were not predictive of cardiometabolic disease, the number of studies were limited. Further research using prospective cohorts with the ability to control for relevant confounders is required to identify whether these and other biomarkers may be potentially useful to manage patients with OSA.

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Conflicts of interest

All authors certify that they have no conflict of interest with any organization or entity.

Practice points

1) There is a need to identify which OSA patients are at greater risk to develop cardiometabolic complications;
2) Circulating biomarkers may be useful prognostic biomarkers;
3) However, there are no robust prospective studies that associate levels of biomarkers and incidence of undesirable cardiometabolic consequences in patients with OSA;
4) Identification of prognostic biomarkers may help to deliver more personalized care to OSA patients;
5) Potentially useful markers include markers of inflammation and oxidative stress, vascular proteins, adhesion molecules, and catecholamines

Research agenda

1) Oxidative stress and sympathetic markers need to be further explored in human studies in the OSA populations
2) Prospective studies addressing the potential utility of circulating molecules as prognostic tools to risk stratify OSA patients are needed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2018.12.004.

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