OTHER

Review

The cardiovascular risk in paediatrics: the paradigm of the obstructive sleep apnoea syndrome

Marco Zaffanello[1], Giorgio Piacentini[1], Stefania La Grutta[2]

[1]*Department of Surgical Sciences, Dentistry, Gynaecology and Paediatrics, University of Verona, Verona;*
[2]*National Research Council of Italy, Institute for Research and Biomedical Innovation, Palermo, Italy*

Background - Obstructive sleep apnoea syndrome (OSAS) describes a spectrum of abnormal breathing patterns during sleep characterised by snoring, increased upper airway resistance and pharyngeal collapsibility, with alteration of normal oxygenation and ventilation. Intermittent desaturations during sleep have multi-organ implications. Adults with OSAS have an increased risk of developing a dysfunctional endothelium that is characterised by greater adherence of inflammatory mediators to endothelial cells and hypercoagulability. There is increasing evidence to show that risk factors for comorbid cardiovascular disease (CVD) can develop during childhood and adolescence and are likely to continue over time. Risk factors for CVD include both modifiable factors and factors that cannot be changed.

Materials and methods - Using the MEDLINE® electronic database, we reviewed the scientific literature for published studies evaluating the association between sleep-disordered breathing and cardiovascular damage in children.

Results - In this review, we show the role of blood markers in demonstrating the inflammation caused by intermitted oxygen desaturations during sleep in both healthy and obese children. Several instrumental techniques, in addition to serum biomarkers, can be used to assess vascular endothelial damage and its deterioration in the form of a pre-atherosclerotic condition. The confirmation of their role as markers of inflammation and vascular damage is supported by normalisation after resolution or improvement of the sleep-disordered breathing with surgery.

Discussion - Great attention should be given to this condition in infants and children as it will significantly affect their present and future well-being as they grow into adulthood. Healthcare professionals, especially paediatricians, should be trained to recognise the signs and symptoms of the disease in order to send children forward for specialist care in centres dealing with sleep-disordered breathing.

Keywords: *biochemical marker, endothelium, inflammation, obstructive sleep apnoea syndrome, sleep-disordered breathing.*

Arrived: 13 November 2019
Revision accepted: 21 November 2019
Correspondence: Marco Zaffanello
e-mail: marco.zaffanello@univr.it

INTRODUCTION

Obstructive sleep apnoea syndrome (OSAS) is a frequent pathology in children. It has been estimated that the frequency of the disease ranges between 1 and 5% in preschool and school children, respectively[1-4]. OSAS describes a spectrum of abnormal breathing

patterns during sleep characterised by snoring and respiratory effort secondary to increased upper airway resistance and pharyngeal collapsibility[5], with alterations of normal oxygenation, ventilation and sleep architecture. Polysomnography is the gold standard for OSAS diagnosis. The mean number of apnoea plus hypopnoea episodes per hour of sleep time or apnoea-hypopnoea index (AHI) classifies the OSAS as mild, moderate or severe[6,7]. Pulse oximetry measures the blood peripheral SpO_2 and McGill oximetry measures the severity of sleep-disordered breathing (SDB) from 1 to 4[8]. This method is used for screening purposes but is not free from heavy methodological limitations.

Adults with OSAS have an increased risk of developing a dysfunctional endothelium that is characterised by increased adherence of inflammatory mediators to endothelial cells and hypercoagulability[9]. They not only have an increased risk of developing comorbid cardiovascular disease (CVD) but also have worse outcomes related to CVD[10]. A growing body of evidence shows that risk factors for CVDs can develop during childhood and adolescence. When risk factors develop at an early age, they are likely to continue over time, maintaining a high-risk status. Risk factors for CVDs include both modifiable factors (e.g., unhealthy diet, amount of physical inactivity) and factors that cannot be changed (e.g., age, heredity, sex)[11].

Intermittent desaturations during sleep have multi-organ implications. The link between paediatric OSAS and complications of the cardiovascular system is robust and has been the focus of several studies. Obesity and/or severe OSAS have both been associated with cardiovascular alterations from childhood to adulthood[10,12]. The pathogenesis of OSAS-associated CVD is not fully understood. Several factors, such as endothelial dysfunction (ED), arterial stiffening, and systemic inflammation may mediate OSAS-associated CVD[13,14]. Specifically, ED makes a substantial contribution to the pathogenesis of cardiovascular disorders, and arterial stiffening is strongly associated with the development of atherosclerosis[15]. Furthermore, increasing evidence of selective activation of inflammatory pathways, increased oxidative stress, ED and metabolic dysregulation suggest that inflammation plays an important role in the development of cardiovascular complications in patients with OSAS[16,17].

Growing evidence suggests that OSAS is also associated with cardiovascular consequences in children. The relationship between OSAS and major adverse cardiovascular problems in children and adolescents has recently been emphasised. A study reported that after a 15-year follow up, the incidence rate of major adverse cardiovascular events was higher in children and adolescents with OSAS than in controls without OSAS[18].

The present review aims to describe the current knowledge on inflammation and cardiovascular problems correlated to OSAS in a paediatric setting.

MATERIAL AND METHODS

Research method

We reviewed the scientific literature for published studies evaluating the association between SDB/OSAS and cardiovascular damage in children. The MEDLINE® electronic database was searched without temporal limits using only the English Language. The Medical Subject Heading and keywords used were the following: "biochemical marker", "endothelium", "inflammation", "obstructive sleep apnoea syndrome", "sleep-disordered breathing" and "children." We also hand-searched the reference lists of the most relevant items to identify further eligible studies not captured in the initial literature search.

Markers of inflammation in paediatric obstructive sleep apnoea syndrome

Biochemical biomarkers in non-obese children

Obstructive sleep apnoea syndrome elicits extensive activation of the inflammatory system, which poses a substantial risk to the integrity of the vascular endothelium[19,20]. In clinical practice, one of the most common inflammatory biomarkers is the C-reactive protein (CRP). CRP is a component of the innate immune system produced by the liver in response to interleukin (IL)-1 and IL-6. Plasma CRP levels are increased in children and adolescents with SDB[21-24].

T-helper 17 cells (Th17) are a subset of pro-inflammatory T-helper cells that produce interleukin 17 (IL-17)[25]. By contrast, regulatory T cells (Tregs) inhibit T-cell proliferation and cytokine production[26]. Th17 cells cause autoimmunity and inflammation, whereas Treg cells inhibit these complications. A prospective study showed that the peripheral Th17/Treg ratio was positively correlated to OSAS severity, serum CRP, and hypoxia-

inducible factor-1α mRNA. Surgery reversed the Th17/Treg imbalance[27]. This result would confirm normalisation of the inflammatory process following improvement of SDB. Intercellular adhesion molecule 1 (ICAM-1), an inflammatory cytokine-induced by TNFα and IL-6[28], contributes to the pathogenesis of atherosclerosis. The levels of ICAM-1 remained stable from evening to morning in children with OSAS[29]. Both ICAM-1 and CRP returned to normal after adenotonsillectomy (A&T)[30]. ICAM-1, vascular cell adhesion molecule-1 (sVCAM-1) and other markers of inflammation (IL-6, and high-sensitive CRP) improved after adenoidectomy[31].

A study investigating the lipid profiles of OSAS children showed increased oxidised LDL-particles (oxLDL)[32]. Another study showed that obstructive sleep apnoea (OSA) children had significantly elevated plasma levels of lipoprotein-associated phospholipase A2 (Lp-PLA2), a cardiovascular risk marker. Treatment of OSA by A&T resulted in reductions in Lp-PLA2 activity[33].

Another molecule involved in the pathophysiology of atherosclerosis is the myeloid-related protein (MRP) 8/14. Elevated plasma levels of the MRP8/14 heterodimer predict increased risk of cardiovascular events[34]. In a study involving OSAS children, plasma MRP8/14 levels increased progressively with OSAS severity[35].

Low basal levels of vitamin D receptor (VDR) induced a state of endothelial activation with increased leukocyte-endothelial cell interactions that may contribute to atherosclerosis[36]. Shin *et al.* reported that children with vitamin D deficiencies had greater adenoidal and/or tonsillar hypertrophy than did those with sufficient vitamin D, pointing to the importance of vitamin D measurement also in children with SDB[37]. Low vitamin D levels in children with primary snoring (PS) and OSAS has been associated with increased mean platelet volume (MPV) and CRP levels, which both corroborate underlying inflammation[23].

The electronic nose (E-nose) is a device that detects odours or flavours. Exhaled biomarkers of OSAS patients were discriminated from controls with 78% sensitivity and 70% specificity[38]. Biochemical biomarkers in non-obese children are shown in **Table I**.

Biochemical biomarkers in obese children

In the context of cardiovascular morbidity associated with OSA, a previous study confirmed the increased frequency of children with abnormal endothelial function, particularly when obesity and OSA are both present at the same time.

Endothelial dysfunction in obese children is one of the major complications[39] with or without OSAS[33]. To our knowledge, one study has found a link between CRP and high Body Mass Index (BMI) (and fat mass) of patients with OSAS, but not between CRP and OSAS itself[40].

Circulating MRP8/14 levels have also been associated with

Table I - *Biomarkers of endothelial dysfunction (ED) after adenotonsillectomy (A&T) in non-obese children*

Author, year[Ref]	Biomarker	ED	Vascular tests	Population study	Main results	After A&T	Comment
Gozal D *et al.*, 2013[53]	Adropin	Yes	Modified hyperemic test after cuff-induced occlusion of the radial and ulnar arteries	OSA+EF+ (n=35) OSA+EF− (n=47) Control (n=35) Age-, sex- and ethnicity-matched children; aged 7.2±1.4 yrs	↓ Adropin levels 2.7±1.1 ng/mL mean morning in OSA+/EF+ *vs* adropin levels 7.4 ng/mL mean morning in controls p<0.001	**N** adropin levels only in OSA+/EF+ (n=14) 2.5±1.4 ng/mL to 6.4±1.9 ng/mL p<0.01	Reliable predicted ED
Gozal D *et al.*, 2007[50]	sCD40 ligand ADMA Nitrotyrosine	Yes	2 iterations of 60'' cuff-occlusion tests	OSA (no.=26) Control (no.=8) 6-11 yrs	↑ sCD40 ligand levels in OSA	↓ sCD40 ligand levels in children with normalised hyperemic responses	sCD40 ligand levels reflects the changes in ED function
Apostolidou MT *et al.*, 2008[30]	CRP cICAM-1 Insulin	Yes	Blood pressure	SDB (no.=58), 6.2±2.5 yrs; Controls (no.=17), 6.5±2 yrs	Patients and controls similar regarding outcomes	↓ CRP in SDB patient with >0.3 mg/dL	Absence of biomarker changes

ADMA: Asymmetric dimethylarginine; cICAM-1: Circulating intercellular adhesion molecule-1; EF: endothelial dysfunction; E-selectin: Endothelial leukocyte adhesion molecule; ICAM-1: intercellular cell adhesion molecule-1; N: normal level; T&A: tonsillectomy and adenoidectomy; SDB: obstructive sleep-disordered breathing.

the degree of ED in both obese and non-obese children[41].

The oxidative stress biomarkers involved in artery dysfunction are serum isoprostanes (8-iso-PGF2α) and soluble NOX2-dp (sNOX2-dp); these were increased in OSAS children but decreased after A&T[42].

An improvement in uric acid concentration, unlike changes in other inflammatory markers, such as leukocyte differentiation and high sensitivity CRP, were associated with an improvement of both the oxygen desaturation index and OSA, independently of obesity or weight loss[43].

Biochemical biomarkers in obese children are shown in **Table II.**

Tissue biomarkers

Inflammation of the upper airways in children with SDB was found by nasal cytology analysis, which showed inflammation in 88% of children[44]. In addition, various studies have evaluated serum biomarkers in lymphatic tissues (tonsils, adenoids). IL-1α is a non-secreted pro-inflammatory cytokine produced in a variety of cells, including monocytes, tissue macrophages, keratinocytes, and other epithelial cells. High expression of IL-1α and classical NF-kB subunits p65 and p50 is found in adenoid and tonsillar tissues of children with OSAS[45]. Moreover, activated $CD4^+$ T cells play a major role in the suppression of immune reaction through secretion of specific cytokines[46]. Tonsillar distribution of $CD4^+$ T-lymphocyte subsets proved to be comparable in subjects who underwent tonsillectomy for either OSAS or primary snoring. The inflammation of tonsils of children with snoring and OSAS could be triggered and maintained by recurring upper airway collapse, which promotes soft-tissue damage[27].

Endothelial dysfunction

Chronic inflammation can cause acute and/or chronic damage to various organs and tissues, for example, at endothelial level[47].

Biochemical markers

Biomarkers of endothelial damage/atherosclerosis in patients with SDB have been studied and researched in order to provide indirect monitoring of vascular improvement after adequate treatment. Circulating platelet-derived microparticles (MPs) are increased in children with OSA and vascular dysfunction[48]. Exosomal miRNA-360 in children with ED is reduced in comorbid OSA and/or obesity and normalised after therapy[49]. CD40 ligands, secondary to activation of platelets, are increased in children with OSA and normalised after treatment, suggesting normalisation of endothelial function[50]. Plasma angiopoietins (Ang-2) in children with obesity and OSA are also significantly increased[51]. The triggering receptor expressed on myeloid cells-1 (TREM-1) plays an important role in innate immunity and amplifies inflammatory responses. Pentraxin-3 is released from macrophages and vascular endothelial cells, playing a role in atherogenesis. Increased TREM-1 and pentraxin-3 levels in children with OSAS play a role in modulating systemic inflammation[52]. Adropin is significantly lower in children with OSAS and ED but returns to normal levels after A&T[53,54].

Instrumental markers

Post-occlusive hyperaemic test

Post-occlusive reactive hyperaemia is used to investigate microvascular function (endothelial function). The test involves blood perfusion Doppler measurements

Table II - *Biomarkers of endothelial dysfunction (ED) after adenotonsillectomy (A&T) in obese children*

Author, year[Ref]	Biomarker	ED	Vascular tests	Population study	Main results	After A&T	Comment
Kelishadi R *et al.*, 2011[31]	E-selectin sVCAM-1 IL-6 hsCRP ICAM-1	Yes	None	OSA normal-weight (no.=45) OSA overweight (no.=45) 4-10 yrs	↑ Levels of the ED and inflammation markers	↓ E-Selectin ↓ sVCAM-I ↓ IL-6 ↓ hs-CRP ↓ ICAM-I	Biomarkers of ED reduced in both normal-weight and overweight subjects after 2 weeks and 6 months
Kheirandish-Gozal L *et al.*, 2017[33]	Lp-PLA2	Yes	Post-occlusive reperfusion evaluation	No.=160, age 7.1±2.3 yrs Obese, No OSA (n=40) Obese, OSA (n=40) Nonobese, No OSA (n=40) Nonobese, OSA (n=40)	↑ Plasma Lp-PLA2 in obese and OSA	↓ Lp-PLA2 activity (n=37; p<0.001)	Reliable biomarker for children at risk for atherosclerosis, i.e., when obesity or OSA is present.

E-selectin: leukocyte adhesion molecule; hsCRP: high-sensitive C-reactive protein; ICAM-1: intercellular cell adhesion molecule-1; IL-6: interleukin-6; Lp-PLA2: Lipoprotein-associated phospholipase A2; sVCAM-1: vascular cell adhesion molecule-1.

Blood Transfus 2020; 18: 217-25 DOI 10.2450/2020.0283-19

before, during and after vein occlusion. Post-occlusive hyperaemia is an endothelial nitric oxide synthase (eNOS)-dependent response.

In non-obese OSAS children, cuff-occlusion tests showed blunted perfusion kinetics after the release of the occlusion, which normalised after A&T[50]. Soluble platelet CD40 levels, as markers of cardiovascular risk[55], were normalised after treatment[50]. In mild, moderate and severe OSA children, a low reactive hyperaemia index was observed that reverted after A&T[56]. Significant delays to peak capillary perfusion after occlusion release occurred in obese compared to non-obese children, and the degree of ED in all groups was associated with increased circulating myeloid-related protein 8/14 (MRP8/14) levels[57]. Low hyperaemic vascular responses in children with OSAS are predictive of neurocognitive status, and in at least 80% of children these co-existed[58].

A reactive hyperaemia test in children with OSA displayed severity-dependent deterioration of endothelial function[59]. In these children, an altered modified post-occlusive hyperaemic test was correlated with characteristic polymorphisms of the nitric oxide synthase (NOS) and endothelin family gene, showing their contribution in the pathophysiology of cardiovascular morbidity[60]. In addition, a post-occlusive hyperaemia test showed the presence of abnormal eNOS-dependent vascular responses in children with OSA and associated epigenetic modifications in the eNOS gene[61]. In addition, monocytes from the OSAS group exhibited overall reduced NO production[62]. Increasing sleep fragmentation reduced T-regulatory lymphocytes (Tregs) and peak occlusive hyperaemia in OSA children[63]. Stromal cell-derived factor-1 (SDF-1) activates leukocytes, inducing pro-inflammatory stimuli. Endothelial progenitor cells (EPCs) play roles in the regeneration of the endothelial lining of blood vessels. Despite similar OSAS severity, EPC and SDF-1 levels were significantly lower in OSAS children with the longest cuff-induced occlusion but not associated with AHI[64].

Flow-mediated dilation

Flow-mediated dilatation (FMD) refers to the widening of an artery when the blood flow increases in that artery. The diameter of the brachial artery is recorded by external vascular ultrasound at specific time points during flow occlusion and after the release of the blood pressure (BP) cuff to assess flow-mediated changes in diameter. The primary cause of FMD is the release of nitric oxide by endothelial cells.

A negative correlation between FMD and childhood OSA severity compared to controls was reported[65]. The OSA group had lower FMD than the control group. A significant reduction in OSA severity was documented in the A&T group associated with a significant increase in FMD[66].

Primary snoring children had significantly reduced FMD compared to non-snoring controls in both normal weight and overweight subgroups[67]. There was no difference in maximal FMD response between snoring and non-snoring groups, but the estimated time to reach maximal dilation was significantly delayed in children who snored[68]. OSA and PS children had significantly higher sNOX2-dp and serum 8-iso-PGF2α levels, and lower FMD than healthy controls. FMD was significantly lower in OSA children compared with PS. Finally, A&T significantly decreased sNOX2-dp and serum 8-iso-PGF2α levels, and increased FMD after A&T in OSA children[42].

Children with severe obesity and SDB showed higher values of the incremental elastic modulus common carotid artery and glyceryl trinitrate-mediated dilation independently of obesity, induced by intermittent hypoxia[69].

Pulse wave velocity

Pulse wave velocity (PWV) is the velocity at which the BP pulse propagates through the circulatory system. Pulse wave analysis permits the non-invasive assessment of arterial elasticity indices. PWV is considered one of the most important clinical parameters to evaluate cardiovascular risk, vascular adaptation, and therapeutic efficacy. An important part of studies on PWV has focused on the correlation between PWV and BP. The SDB group had increased PWV compared to controls. Overweight/obese children with SDB had higher central systolic blood pressure compared with normal-weight children with SDB and non-snoring controls[70].

Hypertension or some heart diseases also influence the PWV and result in earlier wave reflections[71]. The relationship between nocturnal pulse wave amplitude (PWA) attenuation and office BP is reported. The degree of PWA attenuation during the night is associated with office BP independently of SDB[72].

Carotid intima-media thickness

Maximal carotid intima-media thickness (cIMTmax) and carotid-femoral pulse wave velocity (CFPWV) are a measure

of carotid structural changes and a measure of aortic stiffness. Subjects with OSA demonstrated higher values of aortic stiffness and lower distensibility and FMD than controls[73]. In another study, the AHI was not associated with cIMTmax and carotid diameter[74]. In a further study, OSAS severity in obese adolescents did not predict carotid structural changes or arterial stiffness; it was not associated with maximal carotid intima-media thickness (cIMTmax), carotid diameter, carotid-femoral pulse wave velocity (CFPWV) or the augmentation index (Aix)[74].

Thrombosis risks

The epidemiological evidence on adults supports the hypothesis that OSA may be an independent risk factor for venous thromboembolism[75,76]. In particular, OSAS was found to be an independent risk factor for either deep-vein thrombosis or pulmonary embolism in adults[76]. Deep venous thromboses and seven pulmonary emboli were observed in children aged 10-18 years and, unexpectedly, in children aged 1-5 years. A central venous line was the main risk factor (55% of venous thromboembolic events); surgery (not cardiac) (25%), concomitant infections (23%), and malignancy (22%) were the clinical conditions most often associated with the onset of venous thromboembolism[77].

The clinical case of a 3-year old boy with severe adenotonsillar hypertrophy and OSAS who developed severe thrombosis (pulmonary arterial microemboli, intracardiac organised thrombus and vein thrombosis of the left sigmoid sinus of the brain), despite tests for inherited thrombophilia being negative, led some authors to study this link[78]. A study performed on 152 children with OSAS tested the association between several haemostatic parameters and sleep breathing-related variables. These children had a significantly higher platelet count, plateletcrit and platelet distribution width compared with those without OSA. However, coagulation indices, prothrombin time and activated partial thromboplastin time correlated with mean SaO_2 and oxygen desaturation index, respectively. Thus, paediatric OSAS may induce measurable coagulation disturbances. The authors believe that different OSA-related effects may contribute to enhanced coagulability in paediatric OSAS[79].

DISCUSSION

Understanding, preventing, mitigating and treating SDB in children can reduce cardiovascular morbidity and mortality. Moreover, defining appropriate therapeutic targets is cost effective[80]. Surgical treatment for OSA has been shown to be at least partially effective in normalising ED, reducing levels of inflammatory markers, and improving lipid profile and SDB severity[81]. The increasing numbers of overweight and obese children play an important role in the development of OSA in this population and the interplay of these two conditions may be an additional risk for cardiovascular morbidities associated with OSA. Indeed, both obesity and OSAS have a common complication in the area of cardiovascular events. Studies have highlighted the pathophysiological mechanisms, including increased oxidative stress, ED, and inflammation, as shown above in this review. It has now been verified that childhood OSAS from adenotonsillar hypertrophy, without any comorbidity, may lead to cardiovascular complications that are based on the degree of severity. In the case of severe OSAS, other conditions that regard the oral cavity (e.g. maxilla development) must be clinically evaluated. It is currently being ascertained whether OSAS may involve a cardiovascular complication independently of obesity, and obesity independently of OSAS. It seems that obesity and OSAS interact with each other to increase cardiovascular morbidity and, consequently, we cannot treat either without the other.

In this review, we show the role of blood markers in demonstrating inflammation caused by intermittent oxygen desaturation during sleep, which poses a substantial risk to the integrity of the vascular endothelium in healthy and obese children[19,20]. Confirmation of their role as markers of the condition is supported by the different concentration in a control population and normalisation after surgery (**Tables I** and **II**)[27,30,31,33,42]. For this reason, physicians should recognise and treat SDB disorders because of the potential consequences for children in the short and long term. Unfortunately, in most cases, these markers cannot be used in clinical practice and therefore have an exclusively research orientated role.

Tissue markers of inflammation limited to the lymphatic tissue of the neck were also detected in children with SDB[45,46]. The role of these markers could be a predisposing SDB condition or an independent inflammatory situation; both are valid assumptions. To our knowledge, there have been no studies to show that resolution of lymphatic tissue

inflammation of the neck, through appropriate therapy and with the normalisation of these markers, confirms the positive contribution of improving SDBs; though this is plausible in mild or moderate cases, it cannot be the case in severe disorders.

Vascular ED is one of the consequences of systemic inflammation. This condition was indirectly investigated by measuring blood markers in subjects suffering from vascular dysfunction who normalise after treatment[49,50,53,54]. In a few cases, some markers are known to be related to atherosclerosis. It is, however, difficult to demonstrate with the single measurement of blood markers that vascular dysfunction presents an improvement in such a short study period. Therefore, some authors have studied vascular damage using direct techniques (post-occlusive hyperaemic test, FMD, PWV and carotid intima-media thickness). All these studies evaluate vascular changes with these techniques and some markers at the same time. Few studies evaluate the improvement of vascular damage[42,50,56,66]. In addition, the normalisation of these markers could itself testify its future improvement. Even in these studies, it would be easy to presume that SDB resolution[42,55,57] can lead to long-term vascular improvement, particularly in obese children[57,69,70,74].

The study of thrombotic risk in children with SDB has received much attention[78,79]. However, one study in particular was well executed and appears quite convincing[79]. However, the incidence of this complication in the paediatric age is not known. Thus, it seems that it is either extremely rare or inconsistent at this age but could become significant in adulthood. Further studies are needed to confirm this relationship.

Unexplored and unmet needs in the assessment of cardiovascular disease associated to obstructive sleep apnoea syndrome in children.

Sleep-disordered breathing is a multifaceted disease both in terms of pathogenesis and complications. There is a large bibliography and related keywords which testify a growing interest in the paediatric setting.

Although OSAS-associated CVD assessment is relevant for a more comprehensive description of the disease and its treatment, some evidence has been found in previous studies. The following areas, which have as yet remained unexplored or not explored in sufficient depth, should be further investigated:

- extensive assessment of the interaction between OSAS and obesity;
- development of integrated tools evaluating obesity and OSAS interaction in the short and long term;
- comprehensive assessment of ED markers in clinical practice;
- advanced assessment of tissue markers of inflammation to evaluate whether their normalisation is linked to SDB improvement in severe disorders;
- broad assessment of the relationship between blood markers and vascular dysfunction;
- thorough assessment of future long-term vascular damage improvement after SDB resolution;
- far-reaching assessment of thrombotic risk in children with SDB.

CONCLUSIONS

Nowadays there is a large amount of data showing that, through activation of a state of systemic inflammation, paediatric SDBs cause significant but likely reversible cardiovascular damage. Great attention should be given to this condition in infants and children as it can significantly affect their present and future well-being as they grow into adulthood. In the current global condition of economic hardship, particularly in health, the prompt treatment of this pathology would have important economic advantages. Healthcare professionals, especially paediatricians, should be trained to recognise the signs and symptoms of the disease in order to send children forward for specialist care. In this context, early diagnosis of OSAS is very important for encouraging primary prevention interventions to correct the risk factors responsible for disease progression and the occurrence of CVDs. Future studies should be aimed at unravelling other reliable and specific biomarker panels as well as instrumental and easy-to-apply clinical methods that can identify those children at higher risk for OSAS-induced morbidities. This would also facilitate the implementation of precision medicine interventions among OSAS patients.

The Authors declare no conflict of interest.

REFERENCES

1. Overland B, Berdal H, Akre H. Obstructive sleep apnea in 2-6 year old children referred for adenotonsillectomy. Eur Arch Otorhinolaryngol 2019; **276**: 2097-104.

2. Brunetti L, Rana S, Lospalluti ML, et al. Prevalence of obstructive sleep apnea syndrome in a cohort of 1,207 children of southern Italy. Chest 2001; **120**: 1930-5.
3. Bin-Hasan S, Katz S, Nugent Z, et al. Prevalence of obstructive sleep apnea among obese toddlers and preschool children. Sleep Breath 2018; **22**: 511-5.
4. Jennum P, Ibsen R, Kjellberg J. Morbidity and mortality in children with obstructive sleep apnoea: a controlled national study. Thorax 2013; **68**: 949-54.
5. Kaditis A, Kheirandish-Gozal L, Gozal D. Algorithm for the diagnosis and treatment of pediatric OSA: a proposal of two pediatric sleep centers. Sleep Med 2012; **13**: 217-27.
6. Goodwin JL, Kaemingk KL, Mulvaney SA, et al. Clinical screening of school children for polysomnography to detect sleep-disordered breathing--the Tucson Children's Assessment of Sleep Apnea study (TuCASA). J Clin Sleep Med 2005; **1**: 247-54.
7. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012; **8**: 597-619.
8. Kaditis A, Kheirandish-Gozal L, Gozal D. Pediatric OSAS: Oximetry can provide answers when polysomnography is not available. Sleep Med Rev 2016; **27**: 96-105.
9. Budhiraja R, Parthasarathy S, Quan SF. Endothelial dysfunction in obstructive sleep apnea. J Clin Sleep Med 2007; **3**: 409-15.
10. Tietjens JR, Claman D, Kezirian EJ, et al. Obstructive sleep apnea in cardiovascular disease: a review of the literature and proposed multidisciplinary clinical management strategy. J Am Heart Assoc 2019; **8**: e010440.
11. Shrestha R, Copenhaver M. Long-term effects of childhood risk factors on cardiovascular health during adulthood. Clin Med Rev Vasc Health 2015; **7**: 1-5.
12. Umer A, Kelley GA, Cottrell LE, et al. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC Public Health 2017; **17**: 683.
13. Bhattacharjee R, Kheirandish-Gozal L, Pillar G, Gozal D. Cardiovascular complications of obstructive sleep apnea syndrome: evidence from children. Prog Cardiovasc Dis 2009; **51**: 416-33.
14. Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. Chest 2012; **141**: 1601-10.
15. Wada T, Kodaira K, Fujishiro K, et al. Correlation of ultrasound-measured common carotid artery stiffness with pathological findings. Arterioscler Thromb 1994; **14**: 479-82.
16. McNicholas WT, Bonsigore MR. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 2007; **29**: 156-78.
17. Bhattacharjee R, Gozal D. Cardiovascular disease and sleep disordered breathing: are children vulnerable? Sleep 2009; **32**: 1251-2.
18. Tzeng NS, Chung CH, Chang HA, et al. Obstructive sleep apnea in children and adolescents and the risk of major adverse cardiovascular events: a nationwide cohort study in Taiwan. J Clin Sleep Med 2019; **15**: 275-83.
19. Kheirandish-Gozal L. The endothelium as a target in pediatric OSA. Front Neurol 2012; **3**: 92.
20. Kheirandish-Gozal L, Bhattacharjee R, Gozal D. Autonomic alterations and endothelial dysfunction in pediatric obstructive sleep apnea. Sleep Med 2010; **11**: 714-20.
21. Iannuzzi A, Licenziati MR, De Michele F, et al. C-reactive protein and carotid intima-media thickness in children with sleep disordered breathing. J Clin Sleep Med 2013; **9**: 493-8.
22. Tauman R, Ivanenko A, O'Brien LM, Gozal D. Plasma C-reactive protein levels among children with sleep-disordered breathing. Pediatrics 2004; **113**: e564-9.
23. Zicari AM, Occasi F, Di Mauro F, et al. Mean platelet volume, vitamin D and C reactive protein levels in normal weight children with primary snoring and obstructive sleep apnea syndrome. PLoS One 2016; **11**: e0152497.
24. Larkin EK, Rosen CL, Kirchner HL, et al. Variation of C-reactive protein levels in adolescents: association with sleep-disordered breathing and sleep duration. Circulation 2005; **111**: 1978-84.
25. Huang Y-S, Guilleminault C, Hwang F-M, et al. Inflammatory cytokines in pediatric obstructive sleep apnea. Medicine (Baltimore) 2016; **95**: e4944-e.
26. Meng X, Yang J, Dong M, et al. Regulatory T cells in cardiovascular diseases. Nat Rev Cardiol 2016; **13**: 167-79.
27. Ye J, Liu H, Li P, et al. CD4(+)T-lymphocyte subsets in nonobese children with obstructive sleep apnea syndrome. Pediatr Res 2015; **78**: 165-73.
28. Fotis L, Agrogiannis G, Vlachos IS, et al. Intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 at the early stages of atherosclerosis in a rat model. In Vivo 2012; **26**: 243-50.
29. Kaditis AG, Alexopoulos EI, Kalampouka E, et al. Nocturnal change of circulating intercellular adhesion molecule 1 levels in children with snoring. Sleep Breath 2007; **11**: 267-74.
30. Apostolidou MT, Alexopoulos EI, Damani E, et al. Absence of blood pressure, metabolic, and inflammatory marker changes after adenotonsillectomy for sleep apnea in Greek children. Pediatr Pulmonol 2008; **43**: 550-60.
31. Kelishadi R, Nilforoushan N, Okhovat A, et al. Effects of adenoidectomy on markers of endothelial function and inflammation in normal-weight and overweight prepubescent children with sleep apnea. J Res Med Sci 2011; **16** (Suppl 1): S387-94.
32. Tauman R, Lavie L, Greenfeld M, Sivan Y. Oxidative stress in children with obstructive sleep apnea syndrome. J Clin Sleep Med 2014; **10**: 677-81.
33. Kheirandish-Gozal L, Philby MF, Qiao Z, et al. Endothelial dysfunction in children with obstructive sleep apnea is associated with elevated lipoprotein-associated phospholipase A2 plasma activity levels. J Am Heart Assoc 2017; **6**: pii: e004923
34. Croce K, Gao H, Wang Y, et al. Myeloid-related protein-8/14 is critical for the biological response to vascular injury. Circulation 2009; **120**: 427-36.
35. Kim J, Bhattacharjee R, Snow AB, et al. Myeloid-related protein 8/14 levels in children with obstructive sleep apnoea. Eur Respir J 2010; **35**: 843-50.
36. Bozic M, Alvarez A, de Pablo C, et al. Impaired vitamin D signaling in endothelial cell leads to an enhanced leukocyte-endothelium interplay: implications for atherosclerosis development. PLoS One 2015; **10**: e0136863.
37. Shin JH, Kim BG, Kim BY, et al. Is there an association between vitamin D deficiency and adenotonsillar hypertrophy in children with sleep-disordered breathing? BMC Pediatr 2018; **18**: 196.
38. Benedek P, Lazar Z, Bikov A, et al. Exhaled biomarker pattern is altered in children with obstructive sleep apnoea syndrome. Int J Pediatr Otorhinolaryngol 2013; **77**: 1244-7.
39. Bruyndonckx L, Hoymans VY, Lemmens K, et al. Childhood obesity-related endothelial dysfunction: an update on pathophysiological mechanisms and diagnostic advancements. Pediatr Res 2016; **79**: 831-7.
40. Van Eyck A, Van Hoorenbeeck K, De Winter BY, et al. Sleep-disordered breathing and C-reactive protein in obese children and adolescents. Sleep Breath 2014; **18**: 335-40.
41. Bhattacharjee R, Kim J, Alotaibi WH, et al. Endothelial dysfunction in children without hypertension: potential contributions of obesity and obstructive sleep apnea. Chest 2012; **141**: 682-91.
42. Loffredo L, Zicari AM, Occasi F, et al. Endothelial dysfunction and oxidative stress in children with sleep disordered breathing: role of NADPH oxidase. Atherosclerosis 2015; **240**: 222-7.
43. Van Hoorenbeeck K, Franckx H, Debode P, et al. Weight loss and sleep-disordered breathing in childhood obesity: effects on inflammation and uric acid. Obesity (Silver Spring) 2012; **20**: 172-7.
44. Nosetti L, Piacentini G, Macchi A, et al. Nasal cytology in children with primary snoring and obstructive sleep apnoea syndrome. Int J Pediatr Otorhinolaryngol 2019; **122**: 133-7.
45. Israel LP, Benharoch D, Gopas J, Goldbart AD. A pro-inflammatory role for nuclear factor kappa B in childhood obstructive sleep apnea syndrome. Sleep 2013; **36**: 1947-55.
46. Luckheeram RV, Zhou R, Verma AD, Xia B. CD4+T cells: differentiation and functions. Clin Dev Immunol. 2012; **2012**: 12.
47. Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 2018; **9**: 7204-18.
48. Kim J, Bhattacharjee R, Kheirandish-Gozal L, et al. Circulating microparticles in children with sleep disordered breathing. Chest 2011; **140**: 408-17.

49. Khalyfa A, Kheirandish-Gozal L, Khalyfa AA, et al. Circulating plasma extracellular microvesicle microrna cargo and endothelial dysfunction in children with obstructive sleep apnea. Am J Respir Crit Care Med 2016; **194**: 1116-26.
50. Gozal D, Kheirandish-Gozal L, Serpero LD, et al. Obstructive sleep apnea and endothelial function in school-aged nonobese children: effect of adenotonsillectomy. Circulation 2007; **116**: 2307-14.
51. Gozal D, Khalyfa A, Qiao Z, et al. Angiopoietin-2 and soluble Tie-2 receptor plasma levels in children with obstructive sleep apnea and obesity. Obesity (Silver Spring) 2017; **25**: 1083-90.
52. Kim J, Gozal D, Bhattacharjee R, Kheirandish-Gozal L. TREM-1 and pentraxin-3 plasma levels and their association with obstructive sleep apnea, obesity, and endothelial function in children. Sleep 2013; **36**: 923-31.
53. Gozal D, Kheirandish-Gozal L, Bhattacharjee R, et al. Circulating adropin concentrations in pediatric obstructive sleep apnea: potential relevance to endothelial function. J Pediatr 2013; **163**: 1122-6.
54. Kheirandish-Gozal L, Gileles-Hillel A, Alonso-Alvarez ML, et al. Effects of adenotonsillectomy on plasma inflammatory biomarkers in obese children with obstructive sleep apnea: A community-based study. Int J Obes (Lond) 2015; **39**: 1094-100.
55. Heeschen C, Dimmeler S, Hamm CW, et al. Soluble CD40 ligand in acute coronary syndromes. N Engl J Med 2003; **348**: 1104-11.
56. Zhang F, Wu Y, Feng G, et al. Polysomnographic correlates of endothelial function in children with obstructive sleep apnea. Sleep Med 2018; **52**: 45-50.
57. Bhattacharjee R, Alotaibi WH, Kheirandish-Gozal L, et al. Endothelial dysfunction in obese non-hypertensive children without evidence of sleep disordered breathing. BMC Pediatr 2010; **10**: 8.
58. Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Spruyt K. Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea. Pediatrics 2010; **126**: e1161-7.
59. Kheirandish-Gozal L, Etzioni T, Bhattacharjee R, et al. Obstructive sleep apnea in children is associated with severity-dependent deterioration in overnight endothelial function. Sleep Med 2013; **14**: 526-31.
60. Chatsuriyawong S, Gozal D, Kheirandish-Gozal L, et al. Polymorphisms in nitric oxide synthase and endothelin genes among children with obstructive sleep apnea. BMC Med Genomics 2013; **6**: 29.
61. Kheirandish-Gozal L, Khalyfa A, Gozal D, et al. Endothelial dysfunction in children with obstructive sleep apnea is associated with epigenetic changes in the eNOS gene. Chest 2013; **143**: 971-7.
62. Kheirandish-Gozal L, Wang Y, Duggan RC, et al. Nitric oxide production by monocytes in children with OSA and endothelial dysfunction. Clin Sci (Lond) 2014; **127**: 323-30.
63. Tan HL, Gozal D, Samiei A, et al. T regulatory lymphocytes and endothelial function in pediatric obstructive sleep apnea. PLoS One 2013; **8**: e69710.
64. Kheirandish-Gozal L, Bhattacharjee R, Kim J, et al. Endothelial progenitor cells and vascular dysfunction in children with obstructive sleep apnea. Am J Respir Crit Care Med 2010; **182**: 92-7.
65. Brunetti L, Francavilla R, Scicchitano P, et al. Impact of sleep respiratory disorders on endothelial function in children. ScientificWorldJournal 2013; **2013**: 719456.
66. Chan KCC, Au CT, Chook P, et al. Endothelial function in children with OSA and the effects of adenotonsillectomy. Chest 2015; **147**: 132-9.
67. Li AM, Au CT, Chook P, et al. Reduced flow-mediated vasodilation of brachial artery in children with primary snoring. Int J Cardiol 2013; **167**: 2092-6.
68. Kontos A, van den Heuvel C, Pamula Y, et al. Delayed brachial artery dilation response and increased resting blood flow velocity in young children with mild sleep-disordered breathing. Sleep Med 2015; **16**: 1451-6.
69. Dubern B, Aggoun Y, Boule M, et al. Arterial alterations in severely obese children with obstructive sleep apnoea. Int J Pediatr Obes 2010; **5**: 230-6.
70. Walter LM, Tamanyan K, Limawan AP, et al. Overweight and obese children with sleep disordered breathing have elevated arterial stiffness. Sleep Med 2018; **48**: 187-93.
71. Korpas D, Halek J, Dolezal L. Parameters describing the pulse wave. Physiol Res 2009; **58**: 473-9.
72. Zou D, Grote L, Radlinski J, et al. Nocturnal pulse wave attenuation is associated with office blood pressure in a population based cohort. Sleep Med 2009; **10**: 836-43.
73. Tanriverdi H, Evrengul H, Kara CO, et al. Aortic stiffness, flow-mediated dilatation and carotid intima-media thickness in obstructive sleep apnea: non-invasive indicators of atherosclerosis. Respiration 2006; **73**: 741-50.
74. Koren D, Chirinos JA, Katz LE, et al. Interrelationships between obesity, obstructive sleep apnea syndrome and cardiovascular risk in obese adolescents. Int J Obes (Lond) 2015; **39**: 1086-93.
75. Peng YH, Liao WC, Chung WS, et al. Association between obstructive sleep apnea and deep vein thrombosis / pulmonary embolism: a population-based retrospective cohort study. Thromb Res 2014; **134**: 340-5.
76. Lippi G, Mattiuzzi C, Franchini M. Sleep apnea and venous thromboembolism. A systematic review. Thromb Haemost 2015; **114**: 958-63.
77. Giordano P, Grassi M, Saracco P, et al. Paediatric venous thromboembolism: a report from the Italian Registry of Thrombosis in Children (RITI). Blood Transfus 2018; **16**: 363-70.
78. Cohen S, Springer C, Perles Z, et al. Cardiac, lung, and brain thrombosis in a child with obstructive sleep apnea. Pediatr Pulmonol 2010; **45**: 836-9.
79. Barcelo A, Morell-Garcia D, Sanchis P, et al. Prothrombotic state in children with obstructive sleep apnea. Sleep Med 2019; **53**: 101-5.
80. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008; **118**: 1080-111.
81. Gozal D. Sleep, sleep disorders and inflammation in children. Sleep Med 2009; **10** (Suppl 1): S12-6.