Journal of InterDisciplinary Research Applied to Medicine
JDREAM. Journal of interDisciplinary REsearch Applied to Medicine
JDREAM (2019), v. 2 i. 2, 5-25
ISSN 2532-7518
DOI 10.1285/i25327518v2i2p5
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The OMICS role in the early diagnosis of OSA

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Abstract
Obstructive sleep apnea (OSA) syndrome is a condition characterized by the presence of complete or partial collapse of the upper airways during sleep, resulting in fragmentation of sleep associated with rapid episodes of intermittent hypoxia (IH) and activation of the sympathetic nervous system and oxidative stress. (Dempsey et al. 2010, 47–112; Bradley and Floras 2003, 1671–78; Bradley and Floras 2009, 82–93). OSA is associated with a broad spectrum of cardiovascular, metabolic, neurocognitive and comorbidities that appear to be particularly evident in obese patients (Floras 2014, 3–8; Luz Alonso-Álvarez et al. 2011, 0, 2–18; Marcus et al. 2012, e714–55; Sforza and Roche 2016, 99), while affecting both sexes in a different manner and varying in severity according to gender and age (Mokhlesi, Ham and Gozal 2016, 1162–69). In recent years, studies on OSA have increased considerably, but in clinical practice it is still a highly underdiagnosed disease (Costa et al. 2015, 1288–92). To date, the gold standard for the diagnosis of OSA is nocturnal polysomnography (PSG). However, since it is not well suited to a large number of patients, also the Home Sleep Test (HST) is an accepted diagnostic method.
Currently, the major aim of the research is to identify non-invasive methods to achieve a highly predictive, non-invasive screening system for this category of subjects. The most recent reports indicate that research in this field has made significant progress in identifying possible biomarkers in OSA, using -OMIC approaches, particularly in the field of proteomics and metabolomics. In this review, we analyze a list of these OMIC biomarkers found in literature.

Keywords: Obstructive sleep apnea, OMICs Sciences, Proteomics, Metabolomics, Lipidomics

Incidence of OSA

Despite its high prevalence and the high burden of morbidity, Obstructive Sleep Apnea (OSA) remains a significantly underdiagnosed disease worldwide. The Hypnolaus study estimated that the prevalence of moderate-to-severe sleep-disordered breathing (≥15 events per h) was 23.4% (95% CI 20·9–26.0) in women and 49.7% (46.6–52.8) in (Heinzer et al. 2015, 310–8) whereas according to the American Academy of Sleep Medicine (AASM 2016), only 20% of patients are diagnosed (about 6 million out of a total of 24 million) in US. The annual cost for an undiagnosed patient is estimated to be at around $5,500 (considering direct and indirect health costs), while it drops to $2,100 per year for diagnosed patients (Pietzsch et al. 2011, 695–709). On this basis, it is evident that OSA is not only a serious health problem, but also a socio-economic problem.
OSA is also becoming dangerously frequent in children, associated with adenotonsillar hypertrophy (Capdevila et al. 2008, 274–82; Lumeng and Chervin 2008, 242–52) as well as high rates of overweight and obesity in children in western countries. These trends will have disastrous long-term consequences for global health and

life expectancy if solutions are not taken as soon as possible to correct erroneous lifestyles from the earliest age (Bixler et al. 2009, 731–36; L Kheirandish-Gozal and Gozal 2012, 713–14; Li et al. 2010, 991–97; Marcus et al. 2012, e714–55).
These data also suggest that the only way to make sustainable the costs of OSA is the prevention.

Pathogenic mechanisms associated with OSA

OSA is considered by far the most important form of sleep disturbance in breathing. It is caused by increased collapsibility or insufficiency/loss of muscular dilation capacity of the upper airways, leading to repeated pharyngeal constriction (hypopnea) or closure (apnoea), and therefore resulting in oxyhemoglobin saturation decreasing and partial pressure of carbon dioxide in arterial blood increasing (Jordan, McSharry and Malhotra 2014, 736–47).
To date, the gold standard for the diagnosis of OSA is nocturnal polysomnography (PSG). This sleep examination utilizes electroencephalography, electrooculography in both eyes, sub-mental electromyography, nasal airflow, snoring sounds, electrocardiography, thoracic/abdominal movements, pulse oxygen saturation and body position to measure various parameters. The PSG indices included were the apnoea-hypopnoea index
(AHI) and oxygen desaturation index. However, since it is not well suited to a large number of patients, also the Home Sleep Test (HST) is an accepted diagnostic method.
To restore pharyngeal patency, patients experience recurrent awakenings, resulting in fragmented sleep, followed by reduced cognitive performance and, in some cases, diurnal sleepiness episodes.
High circumference values of the neck, hips and waist, hypertension (HTN), usual nocturnal snoring, as well as presence of a diabetic condition and a high body mass index (BMI) are often coexisting conditions in the OSA patient at the time of diagnosis. Among these comorbidities, obesity is often the worst aggravating factor, leading to the activation of molecular mechanisms that, if not effectively and early identified, may worsen the overall clinical pattern of OSA.
In the literature, substantial evidence suggests that OSA increases oxidative and inflammatory processes on animal models and humans. Notably, chronic hypoxia-reoxygenation cycles due to intermittent hypoxia (IH) have been shown to promote the activation of inflammatory pathways (Lavie 2003, 35–51), such as increased pro-inflammatory cytokine production, metabolic dysregulation and insulin resistance (Christou et al. 2003, 105–9; Ciftci et al. 2004, 87–91). In addition, several markers of reactive oxidative species (ROS) are increased in OSA, amplifying inflammatory cascades and endothelial dysfunctions, such as the development of atherosclerosis, as well as promoting central nervous system dysfunctions (Lavie 2003, 35–51; Wang, Zhang and Gozal 2010, 307–16; Shelley X.L. Zhang, Wang and Gozal 2012, 1767–77; Zhou et al. 2016, 9626831).
Many clinical researches have clearly demonstrated that acute IH, associated with the activation of the sympathetic nervous system and strictly linked to a persistent condition of oxidative stress, represent the pathogenetic modalities for the manifestation of cardiovascular comorbidities in OSA, such as systemic arterial hypertension, left ventricular hypertrophy, cardiac rhythm alterations and, following associated early alterations of the vasal endothelium, with increased risk of cerebral stroke and myocardial infarction. (Alchanatis et al. 2002, 1239–45; Ameli et al. 2007, 729–34; Amin et al. 2002, 1395–99; Brooks et al. 1997, 106–9; Lesske et al. 1997, 1593–1603; Varadharaj et al. 2015, 40–47; Jose M Marin et al. 2005, 1046–53; Mason et al. 2012, 1791–98)
Other studies have shown clear and solid associations between OSA and HTN (Nieto et al. 2000, 1829–36; Peppard et al. 2000, 1378–84; Phillips and O'Driscoll 2013, 43–52; Ren et al. 2016, 1264–70), type II diabetes (Lai et al. 2016, 543–51; Plíhalová, Westlake and Polák 2016, S79-84; Reichmuth et al. 2005, 1590–95), stroke (Arzt et al. 2005, 1447–51; Campos-Rodriguez et al. 2013, 99–105; Ifergane et al. 2016, 1207–12), heart failure (Pearse and Cowie 2016, 353–61; Cowie 2016, 255–65; Shahar and Whitney 2001, 19–25), coronary heart disease (Loo et al. 2014, 631–36; José M. Marin et al. 2012, 2169–76; Selim, Won and Yaggi 2010, 203–20), cardi-

ac arrhythmias (Vizzardi et al. 2017, 490–500), cancer (Campos-Rodriguez et al. 2013, 99–105), metabolic, neurodegenerative and respiratory diseases (Al Lawati, Patel and Ayas 2009, 285–93; Caples, Garcia-Touchard and Somers 2007, 291–303; Tahrani, Ali and Stevens 2013, 631–38; Young et al. 2008, 1071–78).
However, the factors determining the damage in a given OSA patient are not yet well defined, so research is still ongoing (Bhattacharjee et al. 2011, 313–23; Leila Kheirandish-Gozal and Gozal 2013, 338–43; Tan, Kheirandish-Gozal and Gozal 2014, 474–80).

Searching for new biomarkers

Given the difficulty of applying Home Sleep Test (HST) to the population as a screening system due to high cost and examination timing, researchers are currently focusing on identifying new biomarkers for the early diagnosis of OSA (Mullington et al. 2016, 727–36).
In 1998, the National Institutes of Health Biomarkers defined a biomarker as an objectively measured feature evaluated as an indicator of normal biological or pathogenic processes, or either pharmacological responses to a therapeutic intervention (Strimbu and Tavel 2010, 463–66). Biomarkers can therefore provide information for diagnosis, prognosis, regression or response to treatment. In this scenario, the -OMIC sciences, such as genomics, transcriptomics, proteomics, and metabolomics, have been widely applied for finding new biomarkers in various disease mechanisms. The identification of such molecules involved in the pathogenesis of OSA patients, can facilitate early diagnosis and help to understand the complex mechanism of this disease.
In the case of sleep disorders and lung diseases, traditional biomarker research techniques have proved to be not particularly performing. Studies based on proteomics (Zheng et al. 2015, 7046; Jurado-Gamez et al. 2012, 139–46; Gozal et al. 2009, 1253–61) and metabolomics (Auffray et al. 2010, 1410–16; Davies et al. 2014, 10761–66; Weljie et al. 2015, 2569–74; Giskeødegård et al. 2015, 14843) techniques instead, have proven to be more sensitive, although, to date, the number of molecules potentially available for clinical application in the OSA context is still limited.. The development of new technologies is therefore necessary, also to provide a greater understanding of the biochemical mechanisms involved in OSA.

Proteomics Approach

The study of the proteome in OSA patients has been largely assessed. Many studies have reported that OSA patients express increased levels of mediators of the systemic inflammatory response. Zhang et al. (Huina Zhang et al. 2018, 97–108) have performed, for the first time, a proteomic approach to detect protein profiles of serum extracellular microvescicle proteins in OSA patients and in a chronic IH rodent model. Extracellular microvescicles are vescicles released from cells into the extracellular fluid environment, including serum. Their potential utility in clinical diagnosis is well documented, since vescicles are reported to reflect the physiological or pathological status of the tissue from which they arise. They found 4 differentially expressed proteins in serum extracellular microvescicles of OSA patients compared to control: C-reactive protein (CRP), Haptoglobin (HP), Fibronectin (FN1), and Platelet factor 4 (PF4). In addition, Nadeem et al., (Nadeem et al. 2013, 1003–12) have confirmed expressed level of CRP and other systemic inflammatory mediators, including intercellular adhesion molecules (ICAM), coagulation factors (factor VIII, tissue factor), and significant increase in serum levels of tumour necrosis factor alpha (TNF-α), interleukin 1β (IL-1β) and interleukin 6 (IL-6) were observed in patients with OSA. The excessive infiltration of inflammatory cells is also highlighted by the formation of subepithelial edema in OSA patients seen by histology. Among these proteins, circulating CRP is an important predictive factor of cardiovascular risk involved in the onset and progression of atherosclerosis. Its pro-inflammatory and proaterogenic properties have been found in endothelial cells, muscle cells, both smooth and striated, and macrophages. Its levels, as well as those of IL-6, are strongly associated with oxidative stress or anoxia (Nena et al. 2012, 181–86; Huina Zhang et al. 2018, 97–108). A similarly important role in the clinical picture of the OSA patient is the high level of TNF-α ob-

served; it is in fact a pro-inflammatory cytokine with an important role in the defence of the host, which at the same time mediates the onset of a series of pathological processes such as atherosclerosis, septic shock and autoimmune diseases. The release of TNF-α is mediated by IL-6, as well as by other pro-inflammatory cytokines such as IL-2, IL-2, IFN-γ and by TNF-α itself through a positive feedback process (Aihara et al. 2013, 597–604; Dyugovskaya et al. 2011, 154–62).

A whole-genomic microarrays recently carried out by Yung-Che et al., has shown angiomotin (AMOT), pleckstrin homology, MyTH4 and FERM domain containing H3 (PLEKHH3), adenosine deaminase RNA specific (ADAR), baculoviral IAP repeat containing 3 (BIRC3), and galectin 3 (LGALS3) proteins over-expressions in the treatment-naïve OSA patients (Chen et al. 2017). LGALS3 has shown to be involved in cancer, inflammation and fibrosis, heart disease, and stroke. Studies have also proved that the expression of galectin-3 is implicated in a variety of processes associated with heart failure, including myofibroblast proliferation, fibrogenesis, tissue repair, inflammation, and ventricular remodelling (Henderson and Sethi 2009, 160–71; Sharma et al. 2004, 3121–28; Liu et al. 2009, H404–12).

Expression of AMOT in endothelial cells and its level is associated with proliferation and invasion of breast tumours (Lv, Lv and Chen 2015, 1938–46).

ADAR are double chain RNA editing enzymes responsible for post-transcriptional modification of mRNA transcripts by changing the nucleotide content of the RNA. The conversion from A to I in the RNA disrupt the normal A:U pairing which makes the RNA unstable (Samuel 2011, 180–93). ADAR is considered to be involved in the insurgence of cancer (9). Studies in sleep field, revealed also that the ADA G22A polymorphism (c.22G>A, rs73598374) is associated with fewer awakenings throughout the night, and a higher duration of slow wave sleep (SWS), as compared to the normal ADA G22G genotype (Milrad et al. 2014).

BIRC3 is a downstream effector of the ubiquitous hypoxia-inducible factor (HIF-1α) that is involved in pro-survival and inflammatory responses induced by the docosahexaenoic acid/neuroprotectin D1 pathway under oxidative stress in an ischemia-reperfusion stroke model. HIF-1 α functions as a principle regulator activity of cellular and systemic homeostatic response to hypoxia. This heterodimer composed of an alpha and a beta subunit can activate the transcription of many genes, including those involved in energy metabolism, apoptosis, angiogenesis, and other genes whose protein products increase oxygen delivery and facilitate metabolic adaptation to hypoxia. Since many studies have shown that OSA is associated with an imbalance between oxidant production and antioxidant activity, this fact, combined with an overabundance of oxidants can be linked to the multifactorial aetiology of metabolic disorders, including insulin resistance (Henriksen, Diamond-Stanic and Marchionne 2011, 993–99).

Almendros et al. (Almendros et al. 2018, 272) examined the correlation between HIF-1α factor and vascular endothelial growth factor (VEGF) expression in patients with cutaneous melanoma. Interestingly, they found that in a large prospective study, the expression of HIF-1α was an independently factor associated with nocturnal IH measures of respiratory disturbance during sleep in patients affected by cutaneous melanoma (Almendros et al. 2018, 272), this means that it has a significant contribution to the disease. Notably, the risk of melanoma was significantly higher in patients with OSA (HR = 1.14, 95% CI 1.10-1.18), along with pancreatic and kidney cancer (Gozal, Ham and Mokhlesi 2016, 1493–1500).

In the recent years, other potential association between OSA and cancer have been reported, principally ascribed to IH effect on tumour biology (Gozal, Farré and Nieto 2016, 43–55; Gozal, Ham and Mokhlesi 2016, 1493–1500; Martínez-García, Campos-Rodriguez and Barbé 2016, 451–63; Almendros et al. 2014, 593–601).

A significant correlation between OSA and increased cardiovascular risk and HTN is strongly reported in literature (Sjöström et al. 2002, 602–7; Drager et al. 2010, 1135–39; Gami et al. 2004, 364–67; Sin et al. 1999, 1101–6). Mass-spectrometry was performed on salivary samples of OSA patients with cardiovascular diseases (CVD) compared to non-CVD OSA patients (Zheng and Li 2014, 7046). A panel of 11 biomarkers were identified to be differentially expressed between the two groups. They found that the alpha-2-HS-glycoprotein (AHSG) pep-

tide level was significantly lower in OSA-CVD group compared to non-CVD group. Reduced level of AHSG was already found in severe OSA patients (Barceló et al. 2012, 1046–48) and at metabolic level (Dyugovskaya et al. 2011, 154–62) (see next chapter). AHSG protein is synthesized by hepatocytes and it is involved in severel process such as brain and bone formation and endocytosis. Interestingly, lack of this protein is involved in leanness.

Another studied association between OSA and HTN was performed by Koyama et al. (Koyama et al. 2009, 1107–11). They studied 266 OSA patients on respect to the Angiotensin converting enzyme (ACE) gene. This gene contains an insertion/deletion polymorphism on the intron 16 characterized by a 287-bp DNA sequence (Alhenc-Gelas et al. 1991, 33–39). They showed that ACE II homozygote genotype protects from severe OSA in HTN patients.

Metabolomics Approach

The field of metabolomics, and the consequent search for potential biomarkers in OSA patients, is beginning to be explored only in recent years. The lipidomic profile in OSA patients reported in literature, mainly reveals alteration in the phospholipid biosynthesis and fatty acids expression. One of the major study through mass-spectrometry technique has allowed to identify, both at a serum and urinery level, as many as 103 proteins differently expressed in adult OSA patients compared to controls, all potentially associated with imbalances in lipid metabolism and alterations in the vascular system (Jurado-Gamez et al. 2012, 139–46). Among phospholipids, glycerophosphocholines (PC), lysophosphatidylcholines (LPE), glycerophosphoethanolamines (PE), lysophosphatidylethanolamine (LPA), phosphoserine (PS), and lysophosphatidic acids, along with glycerophosphates (PA), monoacylglycerophosphocholines, lyso-phosphocolyne (LPC) and sphingomyelin (SM) classes were found to be up regulated in patients with OSA compared to control (Ferrarini et al. 2013; Lebkuchen et al. 2018, 11270). Increased PC expression at salivary level was also reported through a LC-MS/MS methods (Kawai et al. 2013; Engeli et al. 2012, 2345–51).

Fatty acids alteration was also detected in OSA. Among those that significantly increased among OSA group compared to normal subjects, circulating anandamide (AEA), 2,4-dihydroxybutyric acid, 2-hydroxy-3-methylbutyric acid, 3,4-dihydrxoybutyric acid, 6-aminocaproic acid, pentanoic acid, and glyceraldehyde, 3-methyl-3-hydroxybutyric acid, and 4-hydroxypentenoic acid were up-regulatetd, whereas the bile acid and glycochenodeoxycholate-3-sulfate (GCDCA-3-sulfate) decreased (Papandreou 2013, 569–72, Kawai et al. 2013; Engeli et al. 2012, 2345–51). Other groups, through GC-LC techniques, found that palmitoleic and oleic acid levels were lower, while stearic acid levels were higher in the tonsillitis tissue of infant control subjects, compared to the hyperplastic tissue typical of the diseased counterpart (Ezzedini et al. 2013, 1008–12).

Other research groups observed that in OSA patients, levels of 1/2-arachidonoylglycerols (AG), and oleoyl ethanolamide (OEA) in plasma where higher when compared to controls. It was interesting to note that also AA arachidonic acid (AA) concentrations and eicosanoids (Ferrarini et al. 2013; Lebkuchen et al. 2018, 11270) were up-regulated in OSA patients, suggesting a role for the endocannabinoid system in regulating blood pressure in patients with high risk OSA for HTN and CVD (Kawai et al. 2013; Engeli et al. 2012, 2345–51).

The endocannabinoid system is, in fact, based on lipid molecules produced by the body in response to various stimuli that bind specific membrane receptors associated with the protein G and called cannabinoid receptors type 1 and 2 (CB1 and CB2) (Pagotto, Vicennati and Pasquali 2008, 74S-82S). The endocannabinoid system represents a neuromodulation system, playing an action in the control of pain at the level of the central nervous system, in the regulation of cell proliferation processes and in the modulation of the immune response. Interestingly, it also seems to play a role in the mechanisms that modulate appetite and therefore obesity (Di Marzo et al. 2001, 822–25; Croxford and Yamamura; Marsicano et al. 2002, 448–56; Engeli et al. 2012, 2345–51; Salzet et al.

2000, 4917–27). The endocannabinoid system also plays an important role in the release of adipokines. Recent research has shown that the pharmacological blockade of CB1 by an antagonist, named Rimonabant, stimulates the release of adiponectin, that is normally inhibited. Adiponectin is a circulating hormone secreted by adipose tissue, with antiaterogenic and antidiabetic properties that can reduce liver glucose production, as well as suppress lipogenesis and activate the oxidation of fatty acids (Matias et al. 2006, 3171–80; Jbilo et al. 2005, 1567–69). The endocannabinoid ways of regulating metabolism are still only partially understood, despite the fact that their role in controlling hunger and satiety acts mainly in hypothalamic structures through the activation of neurons capable of producing neuropeptides with pressizing and anorexic action (Park and Bloom 2005, 228–33). Alterations to the endocannabinoid system therefore affect and alter the energy metabolism of the body and the homeostasis of lipids, as suggested by Di Marzo and Matias, the first to formulate the increasingly true hypothesis that obesity can be associated with a pathological hyperactivation of the endocannabinoid system (Di Marzo and Matias 2005, 585–89). All these conditions can be associated with an increased risk of cardiometabolic diseases such as type 2 diabetes, dyslipidaemia, arterial hypertension, myocardial infarction and stroke, conditions normally found in OSA patients.

Mediators involved in systemic inflammatory response and oxidative stress were also reported in OSA. Among the metabolites associated with oxidative stress, the 15-F2t-urinary isoprostane, one of the most sensitive metabolites correlated to lipid peroxidation, is positively linked to the thickness of the intimo-media carotid tunic (Paci et al. 2000, S87-91). These molecules were shown to be a specific, chemically stable, quantitative marker of oxidative stress in vivo. In particular, F2t-isoprostanes are prostaglandin isomers synthesised in vivo through the free radical catalysed peroxidation of AA in biological membranes, independently of the activity of cyclo-oxygenase (Morrow et al. 1990, 9383–87). Increased urinary excretion or plasma concentrations of 15-F2t-isoprostane has been observed in many conditions including smoking, diabetes, and cardiovascular diseases (Nonaka-Sarukawa et al.).
Another important biomarker of oxidative stress, Malondialdehyde (MDA), is significantly higher in concentrations detected in patients with OSA than in controls (Denis Monneret et al. 2010, 619–25; Dikmenoğlu et al. 2006, 255–61). MDA is the result of lipid peroxidation of polyunsaturated fatty acids. It is an important product in the synthesis of thromboxane A2 in which cyclooxygenase 1 or cyclooxygenase 2 metabolizes AA into prostaglandin H2. ROS degrade polyunsaturated lipids, forming MDA (Gawel et al. 2004, 453–55). This compound is a reactive aldehyde and is one of many reactive electrophilic species that cause toxic stress in cells, reacts with deoxyadenosine and deoxyguanosine in DNA, forming DNA adducts and can be used as a biomarker to measure the level of oxidative stress in an organism (Pryor and Stanley 1975, 3615–17; Marnett 1999, 83–95).
Arguably, the tricarboxylic acid cycle (TCA) and its mediators, tend to increase in OSA (Xu et al. 2016, 30958), suggesting augmenting of the oxidative stress.

Among Metabolites that find space as pro-inflammatory markers, Stanke-Labesque et al. have found Leucotriene E4 (U-LTE4), an inflammatory molecule associated with cysteinyl leukotriene production, whose elevation in urinary concentration has been demonstrated in patients with OSA. Recently, Gautier-Veyret and his group have shown that this pathway activation contributes to OSA-induced atherogenesis and its blockade could represent a new therapeutic target for reducing CVD (Gautier-Veyret et al. 2018, 311–19). It is also interesting to note that Continuous Positive Airway Pressure (CPAP) treatment, a respiratory ventilation method mainly used in the treatment of sleep apnea, reduces the urinary concentration of U-LTE4 by up to 22%, but only if the treatment is carried out in patients with a normal BMI (Stanke-Labesque et al. 2009, 364-370.e2).
Arguably, CPAP treatment reduces also serum levels of Homocysteine (Hcy) by almost 30%, that, along with plasma levels, were found to be significantly higher in patients with OSA compared to those of the controls (Ezzedini et al. 2013, 1008–12; Papandreou 2013, 569–72, Fletcher et al. 1987, 35–44; Findley et al. 1988,

556–61). In addition, neural-like cell exposure to Hcy for a period of 5 days resulted in a 4.4-fold increase in ROS production (Currò et al. 2014, 1485–95). Hcy is known to mediate adverse effects on cardiovascular endothelium and smooth muscle cells with resultant alterations in subclinical arterial structure and function (Ganguly and Alam 2015, 6), leading to CVD and its complications, such as heart attacks and strokes (Baszczuk and Kopczyński 2014, 579–89). Moreover, hyperhomocysteinemia leads to enhancement of the adverse effects of risk factors like HTN, smoking, lipid and lipoprotein metabolism, as well as promotion of the development of inflammation (Baszczuk and Kopczyński 2014, 579–89). Another study demonstrated that Hcy is capable of initiating an inflammatory response in vascular smooth muscle cells by stimulating CRP production, which is mediated through NMDAr-ROS-ERK1/2/p38-NF-κB signal pathway (Pang et al. 2014, 73–81). CRP expression was also found to be altered in the proteome of OSA patients (see previous chapter).

Some studies also suggest that elevated Hcy levels may be associated with alterations in mental health such as cognitive impairment, dementia, depression, Alzheimer's and Parkinson's disease (Faeh, Chiolero and Paccaud 2006, 745–56; Carmel and Jacobsen 2001) through its capacity to act as a neurotransmitter. In particular, Hcy may act either as a partial agonist at glutamate receptors or as a partial antagonist of glycine co-agonist site of the NMDA receptor, therefore in the presence of normal glycine levels and normal physiological conditions, Hcy does not cause toxicity but in case of a head trauma or stroke, there is an elevation in glycine levels in which instance the neurotoxic effect of Hcy as an agonist outweighs its neuroprotective antagonist effect. This neuronal damage following a stroke has been attributed to the over stimulation of excitatory amino acids such as glutamate and aspartate through activation of NMDA receptors (Ganguly and Alam 2015, 6; Carmel and Jacobsen 2001). Ganguly et al. (Ganguly and Alam 2015, 6) have investigated how Hcy is able to selectively stimulate the release of these excitatory amino acids in stroke and they concluded that they may trigger the release of catecholamine, resulting into detrimental effect in brain and cardiovascular system. Interestingly, in OSA patients, glutamate metabolites were also found to be significantly altered (Xu et al. 2016, 30958).

The study of catecholamine metabolites and derivatives as potential predictors of the onset of the pathological process seems particularly promising. Fletcher et al. (Fletcher et al. 1987, 35–44), for example, observed that norepinephrine (NE) and normethanephrine levels were significantly higher in the urine of patients with OSA than those found in obese HTN controls, as well as epinephrine (E) levels, at the plasma level (Findley et al. 1988, 556–61). Data subsequently confirmed by Paci et al. (Paci et al. 2000, S87-91), who also found higher levels of dopamine (DA) in the comparison of 10 male patients with OSA and 11 controls. HPLC observations revealed a significant increase in all urinary catecholamine in OSA children, and that the levels of NE and E during the night are strongly related to the severity with which they manifest the altered phenotype. Paik et al (Paik et al. 2014, 517–23), after studies carried out using GC-MS to detect metabolites of urinary neurotransmitters, demonstrated that homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC), both dopamine metabolites, were increased in sleepy patients with OSA, suggesting that excessive daytime sleepiness in these subjects is probably caused by an increase in night-time activity of the dopaminergic and sympathetic systems (O'Driscoll et al. 2011, 483–88). Although this theory seems intriguing, the results of several other studies question it. Paci et al. have reported that E and DA levels did not vary significantly between OSA patients and controls. In addition, the results of the studies of Gislason et al, found 5-hydroxyindo-lacetic acid (5-HIAA), HVA and 3-methoxy-4-hydroxypheglicolenyl glycol (MHPG) in the cerebrospinal fluid of 15 patients with OSA and 18 controls; however, even in this case, the levels of all these biomarkers were similar in patients with OSA and control subjects (Paci et al. 2000, S87-91; Gislason et al. 1992, 784–86).

The inconsistency of the results obtained from the studies on catecholamine metabolites in patients with OSA may be due to various factors

such as the heterogeneity of the analytical platforms used by the various research groups, the different biological matrices taken into account, the small size of the samples, and the different protocols used for sample collection. Elements that may also affect the reproducibility of studies.

The first studies aimed at finding differentially expressed metabolites at the urinary level in children with OSA, was carried out by Krishna et al. (Krishna et al. 2006, 221–27). They adopted a mass-spectrometry technique on a cohort of 22 subjects, who demonstrated an alteration in the glomerular and tubular filtration of the kidneys, compared to the healthy counterpart. High levels of proteins such as jasmine, perlecan (a heparan sulfate proteoglycan), albumin, and immunoglobulin were detected in urine. Result which suggested increased catabolic activity of some proteins in OSA patients (Krishna et al. 2006, 221–27). Also in the same period, Shah et al. identified at the silky level, three proteins of 5896, 3306 and 6068 kDa respectively differently expressed in pathological children, capable of discriminating the latter from healthy patients with 90% specificity and 93% sensitivity (Shah et al. 2006, 466–70). Three years later, Gozal et al., through a method based on the use of 2D-DIGE-MS, were able to identify 16 metabolites differently expressed in the urine of OSA patients compared to controls. In particular, the analysis of concentrations of some of these, including uromodulin, urocortin-3, orosomucoid-1, and kallikrein, were able to identify the pathogenic phenotype with a sensitivity of 95% and even a specificity of 100% (Gozal et al. 2009, 1253–61).
The contribution of Seetho et al. and Zeng et al. in the field of research into potential OSA biomarkers was extremely interesting, with the first, focusing on the research of polypeptides using the urine of obese OSA patients used as a biological matrix, and the second, looking for proteins differently expressed between OSA patients suffering from CVD and not, in saliva. The work of the two groups allowed identifying 27 potential biomarkers, fibrinogen alpha chain (FGA), tubulin alpha-4A chain (TUBA4A) and AHSG. More specifically, AHSG has been shown to be expressed at lower levels in OSA frameworks associated with changes in cardiovascular function (Seetho et al. 2014, 1104–15; Zheng and Li 2014, 7046).

Alteration in the amino acid biosynthesis were also reported in OSA through metabolomics approach. Xu et al. identified 21 differentially expressed urinary metabolites among simple snoring group and control, including aspartylserine, isoleucine-threonine (Ile-Thr), and methionine, whereas levels of 3-hydroxyanthranilic acid and 5-hydroxytryptophan decreased. Hydroxyprolyl-methionine, hypoxanthine, Ile-Thr, indole-3-acetamide, isoleucine, lactic acid, myo-inositol, pentanoic acid, threitol, threoninyl-methionine, trimethylamine N-oxide (TMAO), uridine, and valine were consistently higher or lower (Xu et al. 2016, 30958). Other groups have also reported that methylcysteine and serine decreased in OSA condition (Kawai et al. 2013; Engeli et al. 2012, 2345–51).

The metabolomics profiling of spermine biosynthesis, indoles and tryptophan metabolism, tyrosine metabolism as well as porphyrin metabolism were also altered significantly (Xu et al. 2016, 30958; Papandreou 2013, 569–72).

Conclusions

OSA is characterized by recurrent episodes of collapse of the upper airways during sleep, which are reflected in a desaturation of haemoglobin that leads to the awakening of affected subjects. The chronic IH registered in this condition, leads the body to enact molecular adaptations to the low-oxygen conditions to which it is subject (Young et al. 1993, 1230–35). Despite this, sleep fragmentation results in a dangerous condition of excessive sleepiness during the rest of the day. In addition to the long-term problems that are listed, this sleep fragmentation entails a daily danger for the individual linked to the increased risk of road or work accidents. The body responds to chronic fatigue through compensatory mechanisms that evoke inflammatory responses, hyperactivation of the sympathetic system and alteration of endothelial function, like regulation of tight junctions; these events have an important role in promoting the onset of atherosclerosis and, in the long run, of cardiovascular and cerebrovascular diseases (Nadeem et al. 2013, 1003–12).

Recent studies show also a significant correlation between OSA and metabolic and neurocognitive risk (Sjöström et al. 2002, 602–7; Drager et al. 2010, 1135–39; Gami et al. 2004, 364–67; Sin et al. 1999, 1101–6), as well as an association with cancer mortality.
In literature, proteomics and metabolomics approaches were used to detect change in physiological or pathological status of OSA patients compared to controls, in order to find out new mediators that can be used as biomarkers of the disease. Notwithstanding OSA is a 'quite new' emerging disease, there are lots of proteins and metabolites that arise during disease, in particular those involved in inflammation and oxidative stress, in line with the clinical IH that patient undertaken in OSA disease.
Lipid dismetabolism in OSA reflects alteration in phospholipids biosynthesis, steroidogenesis and fatty acids expression. This may influence the cell membrane formation, incrementing lipid uptake, atherogenesis and inflammation. In addition, alterations in amino acids, nucleic acid and some mediators that act as neurotransmitters, such as Hcy and the endocannabinoid system were seen in OSA patients, suggesting an increased risk of cardiometabolic diseases such as type 2 diabetes, dyslipidaemia, arterial hypertension, myocardial infarction and stroke, conditions normally found in OSA patients.

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