Biologia Serbica, 2021, 43(1): 16-23 DOI 10.5281/zenodo.5512418

Review

The link between resistin, systemic low-grade inflammation and obstructive sleep apnea

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Accepted: 20 August 2021 / Published online: 20 September 2021

Summary. Obstructive sleep apnea is a condition manifested by airway obstruction associated with decreased or complete cessation of air flow in the upper respiratory system. This condition leads to recurrent nocturnal oxygen desaturation, fragmented sleep, and excessive daytime sleepiness. Moreover, increasing evidence suggests that obstructive sleep apnea is a risk factor for various diseases, including: cardiovascular diseases, type 2 diabetes, metabolic syndrome and non-alcoholic fatty liver disease, abdominal obesity and dyslipidemia. Chronic intermittent hypoxia is one of the main consequences of obstructive sleep apnea, and induces oxidative stress that damages endothelial cells, adipocytes and immune system cells. In addition, this condition stimulates the inflammatory response due to increased concentrations of pro-inflammatory cytokines, as well as overactivation of the sympathetic nervous system. Obstructive sleep apnea frequently occurs in obese subjects and promotes inflammation of adipose tissues. Adipose tissue has recently been recognised to be an endocrine organ, and systemic exposure to inflammation and chronic intermittent hypoxia induces structural and functional changes resulting in release of pro-inflammatory cytokines by adipocytes and vascular stromal cells. Resistin, a cysteine-rich peptide, is one such pro-inflammatory molecule whose precise role in inflammation is not well understood. Resistin is expressed mainly in bone marrow, immune cells, and macrophages, where it functions by binding to Toll-like receptor 4 and adenylyl cyclase-associated protein 1 receptors, promoting inflammation and enhancing transcription of pro-inflammatory cytokines. In humans, resistin has been reported to be associated with the development and progression of insulin resistance, type 2 diabetes, metabolic syndrome, and cardiovascular diseases by participating in pro-inflammatory-associated processes. Obstructive sleep apnea is a chronic, low-grade pro-inflammatory state; and the role of resistin in obstructive sleep apnea has been investigated in numerous studies to explain the connection between inflammation processes that may deteriorate air flow and muscular functions of the upper parts of the respiratory system. This review will discuss the relationship between resistin and obstructive sleep apnea in the context of systemic low-grade inflammation.

Keywords: inflammation, obesity, obstructive sleep apnea, resistin.

INTRODUCTION

Obstructive sleep apnea (OSA) is a major public health burden that is characterized by recurrent reduction (hypopnea) or complete cessation (apnea) of air flow due to repeated pharyngeal collapse during sleep. This highly prevalent disorder initiates pathophysiological changes in metabolic and cardiovascular functions (Dempsey et al. 2010). Although the pathophysiological mechanisms involved are poorly understood, chronic intermittent hypoxia (CIH) involving cycles of oxygen desaturation and reoxygenation, is likely to be a major contributing feature (Dempsey et al. 2010). Like ischemia–reperfusion injury, CIH provides the basis for oxidative stress, sympathetic nervous system overactivation, and systemic low-grade inflammation (Fig. 1) that may be important factors underlying OSA-associated comorbidities such as cardiovascular diseases (McNicholas et al. 2007), type 2 diabetes (Muraki et al. 2018), metabolic syndrome (Castaneda et al. 2018), non-alcoholic fatty liver disease (Mesarwi et al. 2019) and others. OSA more com-

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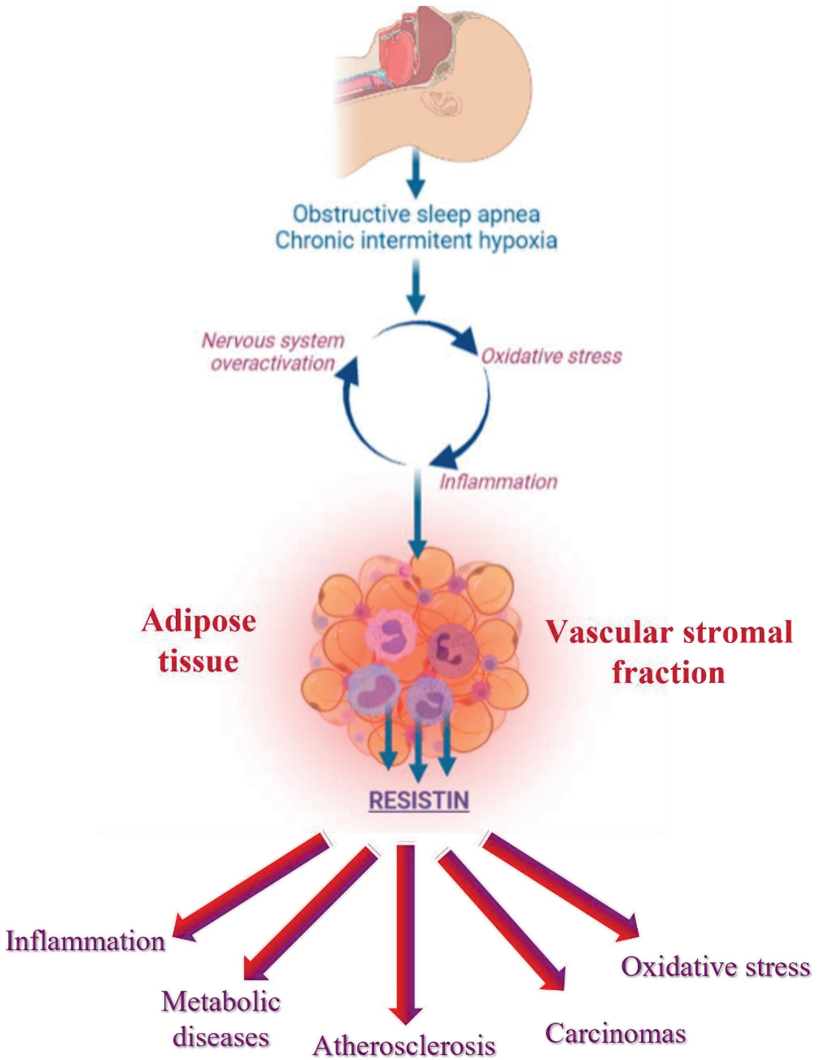

Fig. 1. Potential link between obstructive sleep apnea, resistin and other pathophysiological conditions.

monly occurs in males, the elderly and obese individuals (Dempsey et al. 2010). Continuous positive airway pressure (CPAP) applied to the nose and/or mouth, is the most used therapy for OSA, and can ameliorate pathophysiological cardio-metabolic derangements in OSA (Spicuzza et al. 2015).

One of the most important factors in the development of OSA comorbidities may be oxidative stress (Jullian-Desayes et al. 2015). Oxidative stress induces a low-grade pro-inflammatory state in the blood by increasing production of pro-inflammatory cytokines, which in turn exacerbates oxidative stress. Fragmented sleep, intrathoracic pressure variations and increased shear stress, together with increased oxidative stress, activate the sympathetic nervous system, leading to endothelial dysfunction and atherosclerosis, further exacerbating oxidative stress. This vicious circle leads to pathophysiological changes in all body organs (Jullian-Desayes et al. 2015). In turn, such unfavourable conditions lead to pathophysiological changes in adipocytes and the stromal vascular cells of adipose tissue (Fig. 1). Of these stromal vascular cells, immune cells are of specific relevance for inflammation (Ryan 2017), mainly via overactivation of the master transcription factor, nuclear factor kappa-light-chain-enhancer in activated B cells (NF-κB) in vascular tissues, as well as in circulating leukocytes (Greenberg et al. 2006)). Recently, adipose tissue has been proposed to be an endocrine organ that secretes more than 600 bioactive molecules which are significantly involved in the regulation of metabolism, immunity, and inflammation (Coelho et al. 2013).

Resistin was first discovered in mice as a secretory molecule in white adipose tissue (Steppan et al. 2001). Primarily, mouse resistin antagonises insulin action and is highly associated with obesity and diabetes (Codoñer-Franch and

Alonso-Iglesias 2015). In contrast, human resistin is mainly secreted by bone marrow, peripheral blood mononuclear cells (PBMCs) and macrophages (Steppan et al. 2001; Yang et al. 2003). The main link between human resistin and various pathological conditions is its involvement in pro-inflammatory pathways (Bokarewa et al. 2005).

The present review will discuss the pathophysiological roles of human resistin with a focus on the relationship between inflammation and obesity-related diseases such as OSA, in order to develop a better understanding of the complex link between OSA and resistin.

OBSTRUCTIVE SLEEP APNEA AND OBESITY AS COFOUNDERS FOR SYSTEMIC LOW-GRADE INFLAMMATION

Prolonged periods of partial or complete obstruction of the upper airways are accompanied by significantly altered oxygen and carbon dioxide exchange, hypoxia-reoxygenation events, hypercapnia and frequent arousals, which can further lead to increased production of reactive oxygen species and inflammatory responses at the systemic and tissue level (Dempsey et al. 2010; Jullian-Desayes et al. 2015). Furthermore, it could be involved in the development and progression of atherosclerosis and metabolic disorders (McNicholas et al. 2007; Castaneda et al. 2018; Muraki et al. 2018; Mesarwi et al. 2019).

Inflammation is a response of immune system cells to protect the organism during infection, injury, and various harmful conditions, which enables healing of damaged cells in order to maintain body homeostasis (Medzhitov 2010). However, chronic uncontrolled low-grade inflammation, as a result of abnormal immune reactions mediated by numerous cytokines and hormones, is implicated in OSA progression and the development of comorbidities (Imtiyaz and Simon 2010). As a consequence of CIH, an inflammatory response is stimulated due to the activation of the master transcription factor NF-κB, which enhances the expression of pro-inflammatory genes such as interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor α (TNF-α), monocyte chemotactic protein-1 (MCP-1) and other pro-inflammatory mediators (Imtiyaz and Simon 2010; Ryan 2017). Secreted by leukocytes, these pro-inflammatory factors mainly are a sign of activation of the immune system. Increased inflammation also leads to the generation and release of acute phase proteins from the liver, such as C reactive protein (CRP), which is an important inflammation serum marker whose concentrations reflect the degree of the inflammatory response (Pradhan et al. 2001). Increased serum CRP and IL-6 levels could suggest intensified vascular inflammation (Biasucci et al. 1999; Pradhan et al. 2001). Elevated levels of circulatory pro-inflammatory cytokines, CRP, fibrinogen, and adhesion molecules are evident during the progression of OSA. Although chronic low-grade inflammation may develop in all tissues, the adipose tissue and liver are of high interest due to their significant influence on metabolic homeostasis in the human body (Medzhitov 2010).

Inflammation may also be stimulated by oxidative stress. Although it is not well understood, hypoxia is associated with activation of its main transcriptional regulator, hypoxia-inducible factor 1α (HIF-1α) (Imtiyaz and Simon 2010). Under low oxygen partial pressure, HIF-1α transcription is enhanced mainly for adaptation to hypoxic conditions. Transcriptional activity of HIF-1α is enhanced by pro-inflammatory cytokines, TNF-α and IL-1β, that stabilize HIF-1α protein (Imtiyaz and Simon 2010). HIF-1α is expressed in virtually all human cells. In adipocytes, it inhibits expression of adiponectin leading to decreased adiponectin production (Jiang et al. 2013); which in turn causes glucose intolerance and insulin resistance (Halberg et al. 2009). Similarly to induced NF-κB, HIF-1α promotes the expression of pro-inflammatory cytokines (D'Ignazio et al. 2016). Additionally, HIF-1α induces polarization of adipose tissue resident anti-inflammatory (M2) and pro-inflammatory (M1) macrophages (Wang et al. 2014).

Central obesity represents a major risk factor for OSA, because it causes elevated abdominal pressure which displaces diaphragm muscle and decreases lung capacity, interfering with air flow in the upper parts of the respiratory system. Also, during expansion subcutaneous adipose tissue may be deposited in the maxillary, neck and chest regions, enabling central obesity to obstruct pharyngeal air flow and resulting in collapses, especially during sleep (Nicolini et al. 2016). Body mass index (BMI), central adiposity, and large neck circumference are significant predictors of OSA (Dempsey et al. 2010). In patients with a BMI greater than or equal to 30 kg/m^2, adipose tissue makes up more than 30% of their total body weight and is one of the most important organs that contributes to worsening inflammation (Coelho et al. 2013). Moreover, persistent inflammation in OSA is sustained by obesity (Ryan 2017). In OSA, inflammation is mainly aggravated by hypoxia, but also can occur during expansion of adipose tissue because of adipocyte hypertrophy, decreased vascularization and oxygen usage for β-oxidation of fatty acids. The inflammation state arises from a burst of cytokines release from adipocytes and immune cells (Pasarica et al. 2009).

Additionally, CIH and chronic sleep fragmentation induce inflammation and dysfunction in the complex structure of adipose tissue, consisting of preadipocytes, adipocytes, vascular endothelial and stromal cells, and infiltrating leukocytes (Ryan 2017). In the context of inflammation, quan-

titative and qualitative changes to all parts of adipose tissue occur (Ryan 2017; Ying et al. 2020). Abundant adipose tissue release cytokines, which affect vascular function, insulin levels and immune regulation (Wysocka et al. 2009). Furthermore, CIH stimulates the activation and migration of monocytes into adipose tissue (Dempsey et al. 2010). Macrophages are the most important immune cells involved in obesity-associated inflammation in both mice and humans (Ying et al. 2020). In the adipose tissue of lean, healthy individuals, anti-inflammatory regulatory T-cells and M2 macrophages are present, stimulating synthesis of anti-inflammatory cytokines (IL-10 and adiponectin) and decreasing production of pro-inflammatory cytokines. As obesity progresses, adipose tissue expands and cytotoxic T-cells increasingly infiltrate the tissue (Cildir et al. 2013). Also, infiltrating macrophages as well as macrophages that are resident in adipose tissue polarize from an M2 to an M1 subtype (Wang et al. 2014), producing pro-inflammatory cytokines such as TNF-α and IL-6. Ongoing inflammation in adipose tissue activates different signalling pathways that participate in metabolic dysfunction and impairment of insulin effects (Cildir et al. 2013; Wang et al. 2014).

Taken together, these research results suggest that adipose tissue structure and function are probably influenced by the synergistic effects of OSA and adiposity.

RESISTIN – GENES, ROLES AND TARGETS

Resistin is a small secretory protein that is classified into the family of Resistin-Like Molecules (RELMs). Proteins in the RELMs family are encoded by different genes in rodents and humans. Although they have different expression patterns and biological roles, they are mostly involved in the activation of inflammatory processes (Pine et al. 2018).

The RELM gene (RETN) family consists of four genes, RETN, RETNla, RETNlb and RETNlg, which encode the following proteins: resistin, RELM-α, RELM-β and RELM-γ, respectively. RELMs were first identified in mice (Steppan et al. 2001). In humans, the RETN gene family contains only two members: the RETN encoding protein resistin and the RETNlb encoding protein RELM-β (Yang et al. 2003).

Resistin genes in humans and rodents contain different promoter and 3' intron regions, which may cause variability in regulation mechanisms, activities and tissue distribution (Steppan et al. 2001; Yang et al. 2003). Furthermore, RETN and RETNlb genes in the human genome have different expression and transcriptional regulation (Yang et al. 2003). The RETN gene is localised to human chromosome 19 (Yang et al. 2003) and is predominantly expressed by bone marrow, immune cells, macrophages, monocytes and neutrophils (Nohira et al. 2004). Regardless of its wide distribution in the human body (Lin et al. 2020), its serum levels are probably determined by the pro-inflammatory environment at its main sites of production (Lehrke et al. 2004). It is not expressed by human adipocytes, probably due to the lack of a nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) binding site, which is believed to control the expression of RETN in mouse adipocytes (Tomaru et al. 2009). Yet, immune cells within adipose tissue secrete resistin (Nohira et al. 2004) which could affect all adipose tissue cells by interfering with their physiological processes (Curat et al. 2006).

The human RETN promoter has a putative binding site for adipocyte determination and differentiation-dependent factor 1 (ADD1)/sterol regulatory element binding protein 1c (SREBP1c), mitogen-activated protein kinase (MAPK) and NF-κB, as well as stimulatory proteins (Sp) 1 and 3, which have been proposed to play a role in stimulating RETN expression (Pine et al. 2018). One of the most studied single nucleotide polymorphisms localised at the 5' flanking region of the RETN gene is -420C>G. The presence of homozygous GG alleles increases Sp 1 and/or 3 binding to the promoter, accompanied by increased resistin levels in serum (Chung et al. 2005). Human RETN expression is stimulated by different inflammatory stimuli, IL-1β, IL-6, TNF-α, lipopolysaccharide (LPS), and resistin itself, particularly in PBMCs and macrophages (Kaser et al. 2003).

Human resistin protein is a cysteine-rich secretory peptide consisting of 108 amino acids encoded by the RETN gene (Steppan et al. 2001). At its C-terminus, resistin contains 10 to 11 cysteine residues that promote assembly of the globular domain, and enable resistin to bind to its receptors. The C-terminus is linked to the N-terminal tail by a flexible neck domain (Yang et al. 2003). In the blood, resistin circulates predominantly as a trimer or hexamer, with the trimeric form having more prominent functional relevance (Patel et al. 2004).

Resistin performs its numerous biological functions via autocrine, endocrine, and paracrine mechanisms, which affect the vast majority of cells in the body (Pine et al. 2018). The effects of human resistin are mediated mainly by binding to its receptors, Toll-like receptor 4 (TLR4), a transmembrane protein, and adenylyl cyclase-associated protein 1 (CAP1), an intracellular protein (Pine et al. 2018). In addition, some other receptors, such as tyrosine kinase-like orphan receptor 1 (ROR1) for human resistin was also identified. However, its expression was determined only in some human cancers, where it acts as a survival factor for tumour cells (Hojjat-Farsangi et al. 2014). Although decorin was previously described as a mouse receptor for resistin, it probably does not participate in resistin signalling in human cells (Daquinag et al. 2011). TLR-4, the first discovered resistin receptor, is mainly expressed by macrophages (Marongiu et al. 2019) and has been well characterised as a mediator of

innate and adaptive immune responses stimulated by LPS (Marongiu et al. 2019). Resistin exerts complex and contradictory effects by binding to this receptor. On the one hand, it competes with LPS for TLR-4 binding and inhibits its ability to generate endotoxic shock in animal models (Jang et al. 2017). However, it also promotes inflammation, inducing NF-κB and MAPK which mediate the transcription of pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β), adhesion molecules and growth factors [MCP-1, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion protein 1 (VCAM-1) and vascular endothelial growth factor (VEGF)] (Sudan et al. 2020).

By binding to another receptor, CAP1, resistin induces synthesis of cyclic adenosine monophosphate (cAMP), protein kinase A (PKA) activity and synthesis of pro-inflammatory cytokines through an NF-κB signalling pathway (Lee et al. 2014). Furthermore, oxidative stress pathways are also induced by this interaction. Although CAP1 receptor does not contain a transmembrane domain, it associates with the plasma membrane via interaction with adenylyl cyclase, and two different mechanisms have proposed to explain its function. Some researchers have proposed that TLR-4 binds resistin and intracellularly presents it to CAP1 (Pine et al. 2018), while others have maintained that when synthesized within the cell and/or internalised by a still unknown mechanism, resistin binds to CAP1 intracellularly and activates transmembrane enzyme adenylyl cyclase to produce cAMP, which via PKA induces the expression of genes dependent on NF-κB transcription factor (Lee et al. 2014).

RESISTIN IN INFLAMMATION AND CARDIO-METABOLIC DISEASES

Studies have yielded conflicting results concerning the role of resistin in the development and progression of cardio-metabolic diseases. As described above, resistin could be a potential factor in obesity-mediated inflammation, insulin resistance and type 2 diabetes (Acquarone et al. 2019). Human resistin does play a role in inflammatory processes, but unlike mouse resistin, it does not contribute directly to insulin resistance, but rather via different signalling pathways (Su et al. 2019). It is speculated that human resistin interferes with glucose uptake by GLUT4 within insulin-dependent cells, as well as mouse cardiomyocytes (Graveleau et al. 2005). Although not secreted by adipocytes, a positive correlation was found between resistin levels and adipose tissue mass, determined by BMI (Su et al. 2019). In fact, resistin does appear to be related to metabolic syndrome, a cluster of metabolic disorders including obesity, dyslipidemia, hypertension and glucose intolerance or diabetes, probably because all of these components are interconnected by systemic low-grade inflammation (Acquarone et al. 2019). High resistin levels were also positively associated with atherosclerosis, hypertension, myocardial infarction and ischemia and eventually coronary artery disease (Jamaluddin et al. 2013). It participates in the formation of atherosclerotic plaque by stimulating lipid accumulation in macrophages and if hyperresistinemia persists it could cause plaque destabilization and disruption. These processes are further sustained by resistin, which stimulates monocytes to exacerbate vascular inflammation (Pine et al. 2018). It affects the ability of endothelial cells to increase synthesis of MCP-1, ICAM-1 and VCAM-1 as well as pro-inflammatory cytokines IL-1, IL-6, IL-12 and TNF-α (Acquarone et al. 2019). Enhanced resistin levels could induce hypercholesterolemia by stimulating gene expression of proprotein convertase subtilisin/kexin type 9 (PCSK9), which binds and directs hepatic low-density lipoprotein (LDL)-receptor to degradation (Melone et al. 2012). The other proposed mechanism is based on the structural similarity between cysteine domains in the C-terminus of resistin and PCSK9, which suggest that resistin could be a ligand for the LDL receptor (Hampton et al. 2007).

Increased resistin levels were observed in inflammatory diseases including sepsis, rheumatoid arthritis, and inflammatory bowel disease (Pine et al. 2018). Association of resistin is limited not only to cardio-metabolic diseases, but also to various malignancies in which systemic low-grade inflammation could be involved (Sudan et al. 2020). Elevated resistin levels initiate synthesis of inflammatory cytokines through activation of p38 MAPK – NF-κB pathways in which pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α are produced. In the context of the onset and progression of cancer, these cytokines participate by activating cell proliferation and differentiation, as well as angiogenesis and metastasis (Sudan et al. 2020).

RESISTIN – NEGLECTED FACTOR OF INFLAMMATORY RESPONSE IN OBSTRUCTIVE SLEEP APNEA OR NOT?

The exact mechanisms by which obesity and CIH predispose human organisms to systemic low-grade inflammation and insulin resistance are highly complex and have not yet been fully elucidated. Although both OSA and obesity may provoke resistin secretion, mainly via macrophages and activated leukocytes, it is still debatable whether resistin can be considered to be an important player in their connection and progression.

A study by Yamamoto and colleagues (2008) indicates a positive association between OSA severity and serum resistin levels, independently of BMI, metabolic syndrome, and leptin levels. In this study, the authors assumed that

the pathophysiological state of OSA may induce resistin production as a part of systemic low-grade inflammation. CIH activates circulating monocytes to accelerate infiltration into the vascular wall of all susceptible tissues (Snodgrass et al. 2016). Resident and newly formed macrophages produce pro-inflammatory cytokines (TNF-α and IL-6) that could induce resistin expression (Cildir et al. 2013). In addition, higher levels of resistin could increase secretion of IL-6, TNF-α from PBMCs and CRP levels from the liver via a positive feed-back mechanism, sustaining inflammatory reactions that could deteriorate air flow and muscular function in the upper parts of respiratory system (Xu et al. 2020). After CPAP therapy, resistin levels were found to decrease to the level of non-OSA patients (Yamamoto et al. 2008). Another research group demonstrated that CIH increased resistin messenger RNA levels in adipocytes through a post-transcriptional mechanism involving small non-coding RNA (microRNA) and not by stimulating resistin gene promoter activity (Uchiyama et al. 2019).

Harsch and colleagues (2004) reported that resistin levels positively correlated with IL-6, CRP and leptin levels, but no significant associations were found between resistin and the severity of OSA in patients, regardless CPAP therapy was applied or not. Also, no significant difference was evident in resistin levels between OSA patients and controls (Ursavas et al. 2010). Furthermore, there were no significant correlation between resistin levels and data obtained by polysomnography. It was proposed that comorbidities and pathophysiological processes that frequent accompany OSA can influence resistin levels and in addition to OSA itself (Ursavas et al. 2010).

CONCLUSIONS

To date published scientific data indicate that resistin may potentially play a pathophysiological role in inflammatory reactions that could be regulated differently in human tissues depending upon specific pathophysiological changes. Specifically, data that suggest a link between OSA and resistin are scarce and controversial, due to the complex interaction between CIH, obesity and resistin, and, more importantly, the poorly understood role of resistin in inflammatory pathways.

Further investigation is clearly needed concerning resistin expression at the transcriptional and post-transcriptional level, in order to provide better understanding of the complex relationship between resistin, systemic low-grade inflammation, obesity and OSA.

ACKNOWLEDGMENTS

The work was financially supported by the Ministry of Education, Science and Technological Development of Republic of Serbia (№ 451-03-9/2021-14/200161).

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