Endocrine Journal

Advance Publication
doi:10.1507/endocrj.EJ20-0036

REVIEW

Effects of different obesity-related adipokines on the occurrence of obstructive sleep apnea

Xiongye Xu[1] and Jixiong Xu[1), 2)]

[1)] *The First Clinical Medical College of Nanchang University, Nanchang, People's Republic of China*
[2)] *Department of Endocrinology and Metabolism, First Affiliated Hospital of Nanchang University, Nanchang, People's Republic of China*

Abstract. Obstructive sleep apnea (OSA), characterized by recurrent episodes of apnea during sleep and daytime sleepiness, seriously affects human health and may lead to systemic organ dysfunction. The pathogenesis of OSA is complex and still uncertain, but multiple surveys have shown that obesity is an important factor, and the incidence of OSA in people with obesity is as high as 30%. Adipokines are a group of proteins secreted from adipocytes, which are dysregulated in obesity and may contribute to OSA. Here, we review the most important and representative research results regarding the correlation between obesity-related adipokines including leptin, adiponectin, omentin-1, chemerin, and resistin and OSA in the past 5 years, provide an overview of these key adipokines, and analyze possible intrinsic mechanisms and influencing factors. The existing research shows that OSA is associated with an increase in the serum levels of leptin, chemerin, and resistin and a decrease in the levels of adiponectin and omentin-1; the findings presented here can be used to monitor the development of OSA and obesity, prevent future comorbidities, and identify risk factors for cardiovascular and other diseases, while different adipokines can be linked to OSA through different pathways such as insulin resistance, intermittent hypoxia, and inflammation, among others. We hope our review leads to a deeper and more comprehensive understanding of OSA based on the relevant literature, which will also provide directions for future clinical research.

Key words: Obstructive sleep apnea, Obesity, Adipokines

Introduction

Obstructive sleep apnea (OSA) is the most common type of sleep apnea, with an apnea-hypopnea index (AHI) ≥5 events/h. The overall population prevalence is between 9% and 38%, at an AHI ≥15 events/h, and the prevalence in the general adult population ranges from 6% to 17% and is as high as 49% in older people [1]. OSA is characterized by nighttime sleep snoring with apnea and daytime sleepiness, and intermittent hypoxia (IH) is the main pathophysiological characteristic. The pathophysiological mechanisms of OSA involve partial or complete obstruction of the upper airway during sleep, thereby hindering airflow into the lungs and resulting in apnea, hypopnea, or increased respiratory efforts. The disease can over time, through oxidative stress, sympathetic nerve activation, and systemic inflammation, lead to hypertension, coronary heart disease, arrhythmia, ischemic stroke, type 2 diabetes (T2DM), and insulin resistance (IR), which seriously affect human health and normal life [2, 3]. The pathogenesis of OSA is complex and still uncertain, but multiple studies have shown that obesity is an important factor. Obesity, which is defined as an abnormal or excessive accumulation of adipose tissue that can be harmful to health, is considered a chronic, multifactorial disease [4]. The incidence of OSA in people with obesity can reach 30% (the incidence in healthy individuals is 2–4%), and the incidence of OSA in patients with severe obesity is as high as 50–98% [5]. Recent studies have found that adipose tissue (especially white adipose tissue) is a very active endocrine organ that secretes a variety of biologically active signaling molecules, collectively referred to as adipocytokines or adipokines. Some of these (such as leptin, adiponectin, omentin-1, chemokines, and resistin), which are considered to be important mediators for OSA development, are secreted abnormally in patients with obesity. The purpose of this review is to provide a current overview of the relationship between OSA and obesity-related

Submitted Jan. 29, 2020; Accepted Mar. 21, 2020 as EJ20-0036
Released online in J-STAGE as advance publication Apr. 18, 2020
Correspondence to: Jixiong Xu, Department of Endocrinology and Metabolism, First Affiliated Hospital of Nanchang University, 17 Yongwaizheng Street, Nanchang, Jiangxi Province, 330006, People's Republic of China.
E-mail: xujixiong@163.com

adipokines based on the literature published in the last 5 years, and discuss therapeutic intervention targets for obesity and OSA.

Obesity and OSA

Obesity is considered to be the result of an interaction between the genetic background of an individual and the environment, affecting a large proportion of people of all ages, various social backgrounds, and both sexes; it does however affect women more than men [4]. OSA is an important complication of obesity, while the increasing prevalence of obesity has led to an increase in the prevalence of sleep and respiratory disorders in the general population. A previous study found that the incidence of OSA was 12 to 30 times higher in patients with obesity than in the general population, and the risk of OSA increased by four times for each standard deviation increment of body mass index (BMI) [6]; in addition, a four-year follow-up study showed that a modest (10%) weight gain predicted a 32% increase in AHI and six-fold odds of developing moderate-to-severe OSA [7]. Amin *et al.* found that White Europeans had a greater rate of OSA due to greater rates of obesity and central adiposity, and a logistic regression analysis in 105 South Asians and 129 White Europeans showed that the obesity index by itself can explain the OSA race differences [8]. Regarding the pathological mechanisms of OSA, it is generally believed that obesity leads to excessive accumulation of fat in the posterior wall of the maxillary, pharynx, and upper airway, thus squeezing and eventually leading to collapse of the upper airway. Some patients with obesity have increased levels of abdominal fat, elevated abdominal pressure, and decreased lung capacity due to the displacement of the diaphragm muscle towards the head; while in the supine position, the airway weight load is further increased and airway obstruction is easily generated during sleep, resulting in OSA [9, 10].

Recently, researchers have explored the association between OSA and obesity in a variety of ways, including the investigation of mechanisms involved in metabolism, inflammation, and genetics. When comparing patients with obesity to the general population, they tend to have a higher number of fat cells and suffer from dyslipidemia and IR; additionally, increasing OSA severity is associated with poorer control of diabetes, hypertension, and dyslipidemia, which are all components of metabolic syndrome [11]. Therefore, in recent years, an increasing number of clinical studies have found that bariatric surgery is an effective method to reduce the risk of OSA [12, 13]. Moreover, Gaines indicated that "visceral obesity and IR determined by genetic, constitutional, and environmental factors are the principal culprits leading to OSA, and these associations may be driven by a chronic, low-grade inflammatory state" [14]. Similarly, other studies have found that obesity and OSA are associated with alterations of inflammatory markers, including C-reactionprotein (CRP) and interleukin-6 (IL-6), and that these markers may increase the risk of cardiovascular diseases (CVDs) [12, 15]. Moreover, a positive correlation was found between the BMI and lymphocyte counts in patients with OSA with obesity [14, 16]. Furthermore, some studies reported that secretion of the hypothalamic corticotropin-releasing hormone (CRH, a type of ventilator-stimulating agent) is diminished and that the level of inflammatory cytokines, such as tumor necrosis factor (TNF-α), is upregulated in obese patients, both of which may be related to a higher risk of developing apnea; hence, controlling hypothalamic inflammation represents a new step in the treatment of OSA and obesity in the general population [17].

Obesity-Related Adipokines in OSA

In recent years, studies have found that adipose tissue is an endocrine organ that secretes a variety of adipokines, including hormones and active factors [18]. Obesity and its complications can affect the secretion of these factors, and the fluctuation of the adipokine content is closely related to insulin sensitivity and fat cell metabolism. The adipose tissue in patients with obesity can produce a variety of pro-inflammatory factors (including leptin, chemerin, and resistin) while inhibiting the secretion of anti-inflammatory adipokines (such as adiponectin and omentin-1) [19, 20]. An 8-year observational study of 959 outpatients with obesity or normal glucose tolerance found that in 133 patients with abnormal blood sugar levels and 90 patients with diabetes, APN and omentin-1 levels were lower, while leptin, chemerin, and resistin levels were higher, which indicates the predictive effect of these adipokines on the metabolic abnormality of obesity [21]. Pro-inflammatory adipokines are involved in endothelial dysfunction and have been identified as important players in CVDs [22]; changes in the levels of these factors disrupt the inflammatory response, which is also considered to be a major common pathway that causes and exacerbates OSA. Therefore, it is expected that new therapeutic targets for OSA will be developed by controlling the pathogenic effect of obesity-related adipokines. We summarize the sources and functions of adipokines mentioned in this review (Table 1) and describe their different roles in OSA below.

Table 1 Sources and Functions of Adipokines

	Sources	Receptor	Main Function
Leptin	White adipose tissue (Obesity gene encoding)	Leptin receptor, OB-R	Increase energy consumption; Inhibit fat synthesis and promote its decomposition; Inhibit the synthesis and secretion of insulin
Adiponectin	Adipocyte	Adiponectin Receptor 1 and 2; Cadherin-T	Improving insulin sensitivity; Anti-inflammatory, Anti-atherosclerotic
Omentin-1	Omental adipose tissue	Indetermination	Anti-inflammatory; regulating fat metabolism; Improving insulin sensitivity
Chemerin	Adipose tissue	Specific receptor proteins [like ChemR23 (CMKLR1), RARRES2]	Involved in immune response, inflammation, glucose metabolism
Resistin	Adipose tissue; Immune and epithelial cells	Indetermination	Inhibits insulin's ability to stimulate sugar uptake; Pro-inflammatory

Leptin

Leptin and leptin resistance

Leptin is a protein hormone secreted by white adipose tissue and encoded by the *Ob* (LEP) gene which was cloned in 1994 by Friedman and colleagues. Physiological concentration of leptin mainly results from binding to specific receptors (LepRb, a long functional isoform of the leptin receptor) and interacting with the nucleus of the hypothalamus to regulate appetite and energy expenditure. These processes are attributed to leptin suppressing the orexigenic NPY and AgRP neurons and eliciting the anorexigenic proopiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus (ARC), while in the peripheral tissue, it regulates hepatic gluconeogenesis and skeletal muscle glucose uptake, among other processes [23, 24]. While leptin levels are generally higher in patients with obesity, high levels of leptin lead to leptin resistance or hyperleptindemia. This can lead to a loss of leptin's anti-obesity properties and may induce chronic inflammation, which equates to relative leptin deficiency. Eventually, the energy metabolism and distribution of body fat will show abnormalities, resulting in centripetal fat deposition and the occurrence or aggravation of OSA [25], while significant weight loss leads to a decrease in serum leptin levels and the improvement of glycemic and lipid profiles [26]. Abnormal serum leptin levels thus increase the risk of obesity, and they could therefore be a valuable diagnostic marker of obesity and its comorbidities. The molecular mechanism underlying leptin resistance is still controversial, but elevated levels of circulating C-reactive protein, overexpression of negative regulators like suppressors of cytokine signaling 3 (SOCS3) or protein tyrosine phosphatase 1B, or decreases in histone deacetylase 5 activity may play significant roles [27]. A recent study also found that melatonin receptor 1 signaling is an important regulator of leptin signaling, and that a lack of melatonin receptor 1 signaling can also lead to leptin resistance [28]. Moreover, previous studies have suggested that leptin in the central nervous system needs to cross the blood-brain barrier (BBB) and that impaired leptin transport to the brain is an important cause of leptin resistance [29]. However, Harrison *et al.* used fluorescent BBB tracing and found that although diet-induced obesity (DIO) mice are resistant to leptin, their mediobasalhypothalami (MBH) or ventricular septal organ do not show any defects in leptin accumulation, while LepRa expression in the choroid plexus drives leptin transfer from the blood to the cerebrospinal fluid and its biodistribution in the brain. The difference between these and previous results might stem from the facts that the latter measurement was performed when the accumulation of leptin reached the maximum value of the MBH, and that the authors did not evaluate the ratio of leptin entering the brain relative to the circulation [30]. Nonetheless, these findings provide new starting points for us to explore the mechanisms underlying leptin resistance, so that future research can shift from investigations of the transport of leptin across the BBB to the search for other possible causes of leptin resistance.

Effect of leptin on the upper airway

Leptin is a central respiratory stimulant. Yao *et al.* suggested the dorsomedial hypothalamus and nucleus tractus solitarius as the main site of the effects of leptin on ventilatory control, such as leptin relieving upper airway obstruction through the dorsomedial hypothalamus and its effect on respiratory pump muscles mediated by the nucleus tractus solitarius; however, the latter effect may be inhibited by increases in circulating leptin or even by leptin resistance [31]. Research on obese mice with leptin deficiency (ob/ob) shows that leptin can stabilize pharyngeal patency and ameliorate hypoventilation and upper airway obstruction in obesity [32, 33], and that leptin replacement therapy can improve minute ventila-

tion and tidal volumes during flow-limited breathing [34]. Besides, leptin acts on LepRb in the carotid body to stimulate breathing and the hypoxic ventilatory response, which may protect against sleep disordered breathing in obesity [35]. These findings indicate that leptin has the potential to be used in the treatment of OSA and obesity hypoventilation with relative leptin deficiency. Lately, Berger *et al.* found that intranasal leptin can reduce the number of oxygen desaturation events during rapid eye movement (REM) sleep and increase ventilation during non-REM and REM sleep in mice with diet-induced obesity. The authors thus suggested a new method of administration that bypasses leptin resistance and significantly attenuates sleep-disordered breathing independently of body weight [34]. This innovative approach demonstrates the potential of intranasal leptin for OSA treatment and provides us with new ideas, but it lacks strong evidence from clinical trial. A study in 23 obese women and three obese men showed that increased circulating leptin levels are associated with the ventilatory response enhancement of upper airway obstruction and that they can potentially reduce upper airway collapse and potential OSA severity, while OSA severity has nothing to do with circulating leptin concentrations [36]; the study has however some limitations, such as the small sample size, the lack of male subjects, the fact that the female participants had a relatively mild form of OSA, and the fact that leptin resistance was not taken into account. Moreover, a review of related research on the relationship between leptin and OSA published between 2000 and 2017 found that the results of human studies do not consistently support data from animal models, and suggests that the differences may be due to diurnal changes in leptin, obesity, and differences in age and sex [37]. Therefore, we cannot yet conclude that the effects of leptin on the upper respiratory tract that are observed in animal experiments also apply to humans. In order to better understand and clarify the relationship between leptin and OSA, improved study designs and advanced methods to evaluate functional leptin levels are necessary.

Changing leptin levels in OSA

OSA is a type of sleep disorder caused by abnormalities in the respiratory system. Previous research found that plasma leptin levels in patients with OSA gradually increased with OSA severity and that they were associated with AHI and nocturnal oxygen saturation levels [37, 38]. There are, however, studies that show that leptin levels are associated with obesity but not OSA severity [36, 39]. The existing research does not allow us to judge which conclusion is correct, but we believe that leptin levels are related to the factors outlined above, and that differences in results may be caused by differences in research methods and samples. However, Bingol *et al.* reported recently that patients with severe OSA had lower leptin levels (p = 0.023) [40], and we speculate that these discrepancies in experimental results are due to severe OSA having an inhibitory effect on leptin secretion; the underlying mechanism still has to be investigated.

The mechanism underlying the changes in leptin levels is not clear. On the one hand, hyperplasia of adipose tissue in obese patients with OSA leads to increased leptin secretion [25]; on the other hand, some researchers have suggested that this is related to IH and oxidative stress, and that IH may induce high leptin levels *via* phosphorylated signal transducer and activator of transcription 3 (STAT3), up-regulation of POMC, and the activation of the sympathetic nervous system (SNS) and the renin-angiotensin system (RAS) [24, 41]. IH can also directly stimulate the hypothalamic-pituitary-adrenal (HPA) axis with increasing leptin release and leptin resistance, which has well-known negative consequences on glucose metabolisms, including the inhibition of insulin secretion and IR [42]. Besides, leptin-mediated increases in reactive oxygen species (ROS) production and oxidative stress might be potential mechanisms that link OSA to an increased CVD risk [24]. Repeated episodes of hypoxia and chronically increased serum leptin levels in OSA and excessive supply of energy substrates to metabolic pathways in patients with obesity promote the production of ROS, which results in oxidative stress and induces serial inflammatory reactions that cause endothelial dysfunction, accompanied by up-regulation of adhesion molecules, increases in monocytes, and inactivation of nitric oxide. Eventually, these factors may induce atherosclerosis, but effective OSA surgery can reduce serum leptin levels and improve the CVD risk [43, 44]. Hypothalamic oxidative stress can damage POMC-positive neurons and inhibit leptin signaling in the hypothalamus, thereby leading to the development of systemic leptin resistance, obesity, and IR. However, the activation of NF-E2-related factor 2 (Nrf2) in the hypothalamus prevents the accumulation of oxidative damage in POMC-positive neurons and improves metabolic abnormalities [45]. In addition, the overexpression of IL-10 can restore POMC expression, while inhibiting IKKs (IκB kinases) activation and SOCS3 expression in the ARC of DIO mice, which may help improve hypothalamic inflammation and leptin resistance [46].

Association between leptin and OSA at the genetic level

Although previous studies have not found an association between leptin/leptin receptor (LEPR) gene polymorphisms and OSA, or found that such an association was only related to obesity and neck fat formation in patients [47], two meta-analyses have found that the LEPR Gln223Arg and the Pro1019Pro polymorphism in

the Chinese population are risk factors for OSA [48, 49]. Moreover, Li *et al.* identified a novel variant of the LEPR gene in obese patients with OSA and found that the variant genotype *rs3790435 CC* is associated with a lower risk of OSA [50].

In conclusion, related studies have suggested that OSA causes elevated plasma leptin levels and leptin resistance and inhibits the physiological function of leptin to regulate body fat; subsequently, elevated leptin levels can also promote fat deposition, thereby affecting normal metabolism and neurological function, which may aggravate the collapse or the occlusion of the respiratory tract during sleep and ultimately contributes to OSA or to its aggravation (Fig. 1). Controlling leptin levels in patients with OSA may contribute to their recovery, but the specific clinical effects remain to be discussed and verified.

Adiponectin

The physiological function of APN

Adiponectin (APN), also known as adipocyte complement-related protein 30 (Acrp30), is a plasma protein that interacts with the extracellular matrix [51]. Compared to leptin, it has several beneficial and protective effects. Although APN is mainly secreted by adipose tissue, previous studies have found that it is negatively correlated with obesity. APN activates AMP-activated protein kinase (AMPK), peroxisome proliferators-activated receptors (PPAR)-α-γ or other signaling pathways to regulate body weight and prompt the function of anti-inflammation and antioxidative stress through two receptors (AdipoR1, predominantly present in skeletal muscles; AdipoR2, mainly found in the liver) [22, 52]. APN reduces free fatty acid levels, promotes lipid metabolism, improves insulin function, and alleviates inflammation, atherogenic dyslipidemia, and CVDs [53]. In the clinical practice, hypoadiponectinemia has become one of the diagnostic criteria for metabolic syndrome. Moreover, APN can induce the depolarization of POMC neurons by activating phosphoinositide-3-kinase (PI3K) signaling and inhibiting NPY/AgRP neurons and then regulates the energy balance and glucose metabolism synergistically with leptin [54]. Considering that leptin resistance and hypoadiponectinemia are common in patients with obesity and T2DM, the disruption of leptin

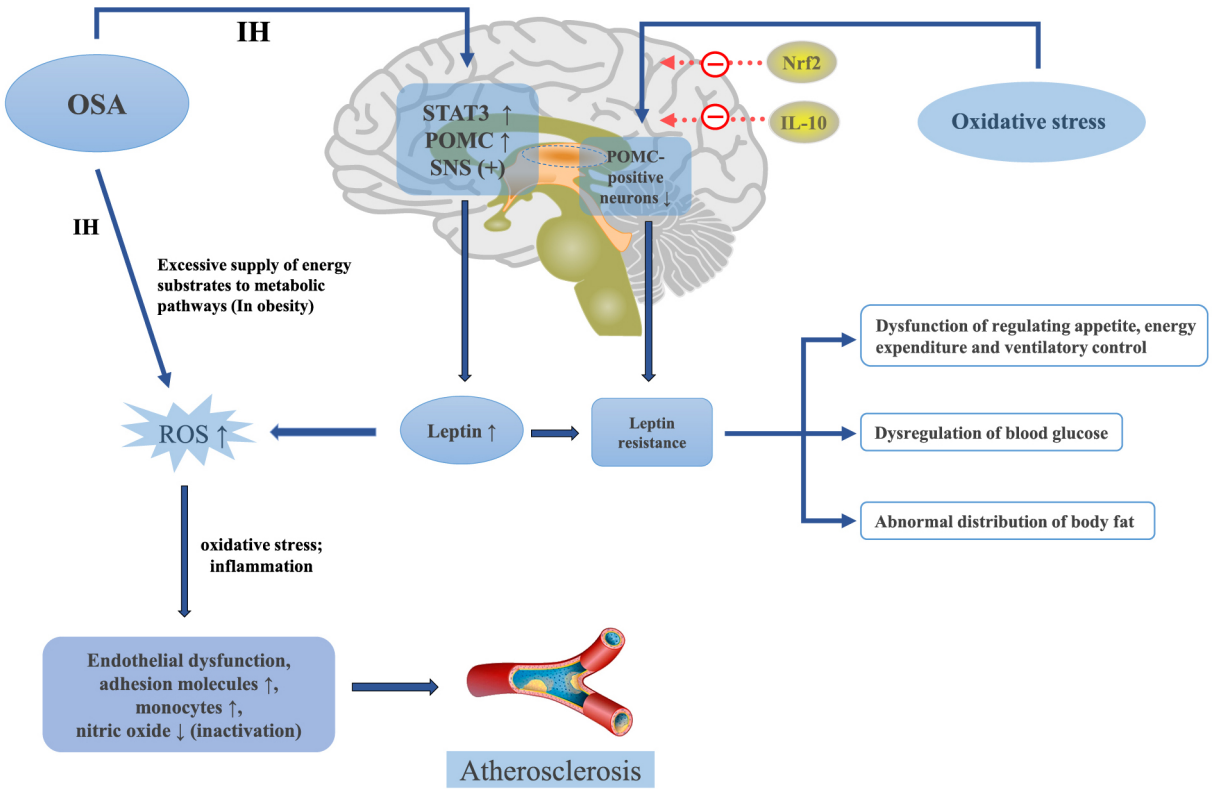

Fig. 1 OSA induces abnormal secretion of leptin then causes different dysfunctions

Leptin levels are significantly higher in patients with OSA, IH in OSA may induce high leptin levels mainly *via* phosphorylated STAT3, up-regulation of POMC, and the activation of the SNS; oxidative stress can lead to leptin resistance by damaging POMC-positive neurons and inhibiting leptin signaling in the hypothalamus, which can be inhibited by Nrf2, IL-10. Elevated leptin levels or leptin resistance may not only induce atherosclerosis by promoting the production of ROS, but promote fat deposition, inflammation, and affect normal metabolism and neurological function in OSA patients.

and adiponectin interactions may collectively affect anorexia, by promoting caloric intake and energy accumulation [55].

Association between APN and OSA

One study involving 486 patients (prevalence of obesity: 28%; prevalence of OSA: 42%) found that APN levels decreased gradually with the increasing severity of OSA in the obesity group but not in the nonobese group [56], suggesting that obesity affects APN secretion. Domagała *et al.*, however, observed low concentrations of APN also in nonobese patients with OSA and a correlation between APN concentrations and an important index of OSA severity [57]. Lu *et al.* conducted a meta-analysis, after controlling for effects of age, sex, and BMI on serum/plasma APN levels, which also revealed that serum/plasma APN levels are significantly lower in patients with OSA than in controls [58]. As mentioned earlier, OSA is characterized by recurrent episodes of apnea during sleep and daytime sleepiness, and IH is the main pathophysiological characteristic. IH induced by OSA has been shown to reduce APN levels *via* suppressing APN mRNA levels in adipose tissue and disrupting APN secretion, while other factors like IR or hypoxia-induced sympathetic activation may also result in the same effect [59]. In brief, OSA is associated with decreased plasma APN levels, which is a significant risk factor for the development and progression of OSA and its complications. In addition, continuous positive airway pressure (CPAP) is an effective and preferred method for the treatment of OSA, as it can significantly normalize the hypoxemic stimulus and improve insulin sensitivity [60]. However, CPAP seems to have no obvious effect on serum adiponectin recovery in patients with OSA [61, 62].

The role of APN in OSA comorbidities

Patients with OSA with significantly reduced plasma APN levels often have hypertension [63], which is closely associated with early cardiac impairments [64]. A lower APN/BMI index correlates with a higher risk of cardiovascular and metabolic complications of OSA [57]. IH causes human adult cardiac myocyte (HACM) dysfunction by enhancing inflammatory mechanisms [65]; however, some studies have demonstrated that APN is a feasible novel therapeutic agent for the prevention of IH-induced HACM dysfunction, which is possibly mediated by AMPK and the nuclear factor kappa-B (NF-κB) pathway [64, 66]. These results are consistent with the cardiovascular protection of APN. Furthermore, plasma APN levels in patients with OSA correlate with T2DM, and dysregulation of the expression of APN may lead to IR and impaired glucose tolerance (IGT) [67]. Moreover, chronic IH may induce oxidative stress in islet cells, damage mitochondrial oxidative phosphorylation, and reduce mitochondrial synthesis, thereby resulting in reduced mitochondrial ATP production and abnormal cytochrome C distribution. Moreover, APN can ameliorate the pancreatic islet injury induced by chronic IH through the inhibition of oxidative stress [68]. High APN levels are therefore considered to be a good predictor for OSA and T2DM [51, 56]. OSA is also considered to be associated with impaired renal function, and hypoxia activating the RAS and sympathetic excitation leading to glomerular ultrafiltration may be the potential underlying mechanisms [69]. Currently, serum APN is considered to play an important role in maintaining normal renal function, because of its anti-fibrotic and anti-inflammatory activities that inhibit albuminuria and oxidative stress through AMPK or ATP processes [70, 71]. Levels of cystatin C, which is a more sensitive marker than creatinine to detect kidney function, have been found by Chen *et al.* to be increased as a result of lower circulating APN levels in patients with OSA [71]. This finding strongly suggests APN as a regulator of renal function in OSA (Fig. 2).

APN gene polymorphisms in OSA

The relationship between APN gene polymorphisms and OSA has become a hot topic in research. Wu *et al.* found that the allele or genotype distributions of *rs12495941*, *rs182052*, and *rs16861205* showed significant differences relative to OSA severity [72]. In addition, Yang *et al.* identified four ADIPOQ variants, *rs4686803*, *rs3774262*, *rs1063537*, and *rs2082940*, associated with OSA prevalence in a Chinese han population after adjusting for confounding effects, among which *CT/TT* genotypes of *rs4686803*, *GA/AA* genotypes of *rs3774262*, and *CT/TT* genotypes of *rs1063537* were associated with an increased risk of OSA, and the *rs2082940 CC* genotype was associated with a decreased risk of OSA [73]. These findings confirm that ADIPOQ variants are involved in the etiology of OSA, and suggest that gene analysis may be helpful for the individualized genotyping of patients with OSA and can contribute to personalized diagnosis and treatment in the future. Badran *et al.* recently found that gestational IH led to vascular disease in adult male offspring of women with OSA, which was associated with low adiponectin levels and epigenetic modifications on the adiponectin gene promoter [74]. Besides, some microRNAs (miRNAs) regulated by APN have been identified as novel targets for controlling adipose tissue inflammation. Among these, the expression of *miR-335* increased significantly with the increase of leptin, resistin, TNF-α, and IL-6 concentrations in human adipocytes. A fragment approximately 600 bp upstream of the *miR-335* coding region has significant transcriptional activity. These findings suggest a new role for *miR-335* in adipose tissue inflam-

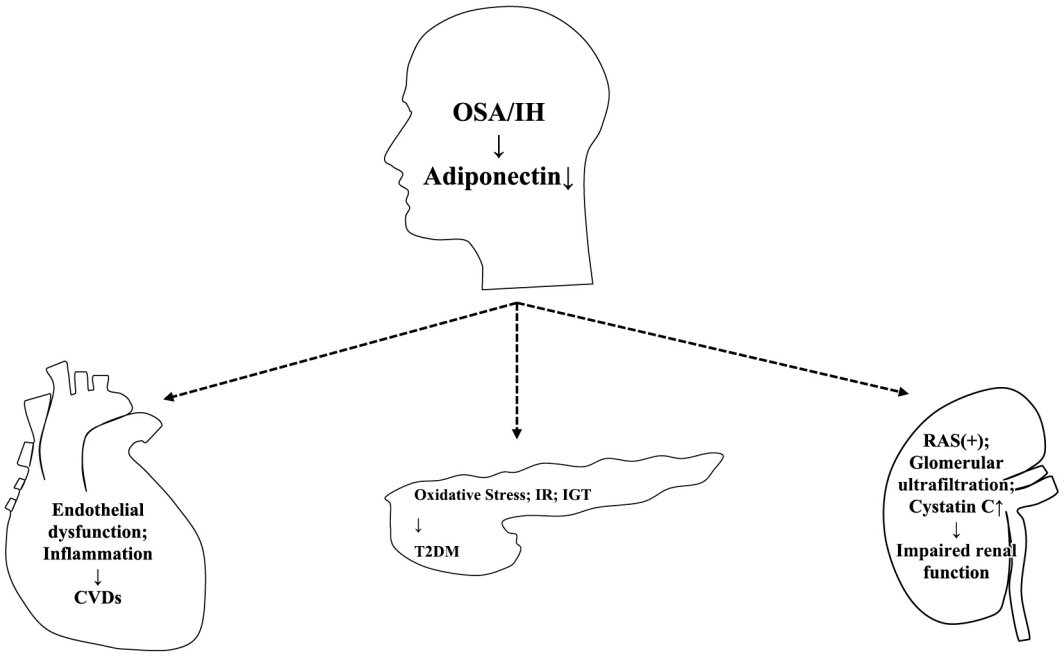

Fig. 2 APN contributes to different comorbidities in patients with OSA

The incidence of obesity-induced OSA or IH is associated with decreased plasma APN levels, which induces cardiomyocyte function, T2DM, kidney function mainly by inflammation, IR, activating RAS respectively.

mation, and that *miR-335* may be involved in obesity complications through its transcriptional regulation [75, 76]; there is however no research indicating a relationship with OSA. Current research on the correlation between OSA susceptibility loci and single nucleotide polymorphisms in the *APN* gene in han Chinese individuals is limited, and the APN relationship with OSA thus remains to be further examined and verified.

Omentin-1

The physiological function of omentin-1

Omentin is a newly discovered adipokine that has three subtypes, and omentin-1 is the major subtype in human plasma. Omentin-1 shows several important effects related to its anti-inflammatory and vasculoprotective properties, to its regulation of the distribution of human fat in visceral and subcutaneous fat warehouses, and to its role in improving insulin sensitivity [77]; it may also play a part in food storage and decomposition [78], which suggests it as a biomarker for obesity-related metabolic disorders. Some studies suggest that levels of omentin-1 are inversely related to BMI, waist circumference, leptin levels, and the IR index, and that they positively correlate with adiponectin and high density lipoprotein levels; higher omentin levels have been associated with leanness or found to act as a positive factor against obesity [79, 80]. In addition, omentin-1 levels are decreased in metabolic syndrome, coronary atherosclerosis, and other inflammatory diseases, suggesting that omentin-1 may be involved in the occurrence and development of some inflammatory diseases [81, 82].

Correlation between OSA and omentin-1

With the exception of patients with OSA, those with chronic obstructive pulmonary disease, pulmonary hypertension, asthma, acute respiratory distress syndrome, or other diseases also show abnormal serum omentin-1 levels in the respiratory system, which may be used for the diagnosis of related diseases [83]. However, the association between omentin-1 and OSA is controversial: some small-sample studies in previous years have suggested increased omentin-1 levels in patients with OSA [84], potentially due to OSA stimulating compensatory mechanisms and omentin-1 increasing to counteract the acute symptoms, while recent large-sample clinical trials have shown that serum omentin-1 levels are significantly reduced in patients with OSA and decrease with OSA severity. A study in 65 patients with OSA found that omentin-1 was negatively correlated with AHI [85]. Zhang *et al.* also found that plasma omentin-1 levels were significantly lower in 30 overweight male patients with severe OSA compared to 20 controls [86]. Besides, CPAP can restore omentin-1 levels in the serum, and effective 3-month CPAP treatment can reverse low omentin-1 levels in patients with OSA [87].

Hypothetical association between omentin and OSA

Omentin-1 levels are positively correlated with high-density lipoprotein levels and APN levels in patients with OSA, which indicates that omentin-1 up-regulates APN and then affects the lipid metabolism [81, 86]. However, whether it plays the same role as APN in OSA remains to be tested. Lower serum omentin-1 levels may be an early marker of endothelial dysfunction in patients with obesity with OSA [80]. AMPK/Akt/NF-κB/(ERK, JNK, and p38) signaling is the main pathway for omentin-1 to exert anti-inflammatory and cardiovascular protective effects [88]. In addition, Liu *et al.* found that omentin-1 can prevent hyperglycemia-induced vascular endothelial dysfunction through inhibiting endoplasmic reticulum stress and oxidative stress and increasing NO production by activating the AMPK/PPARδ pathway [89]. The Akt/eNOS pathway, which may be mediated by AMPK, is possibly another mechanism [90]. At present, no study has reported on the mechanism underlying changes in serum omentin-1 levels in patients with OSA. Based on the existing relevant studies, we assume that it is related to obesity, IR, and inflammation, and that decreases in omentin will also weaken its anti-inflammatory effect and thus add to the development of OSA. In conclusion, we postulate that serum omentin-1 levels in patients with OSA can predict the presence and severity of OSA and can evaluate the therapeutic effect of noninvasive positive pressure ventilation. However, the mechanism underlying the pathophysiological association between omentin and OSA remains unclear, and further research is needed in the future.

Chemerin

The physiological function of chemerin

Chemerin is a newly discovered adipokine with the function of leukocyte chemotaxis, induced by a chemotactic signal from chemokine-like receptor 1 (CMKLR1), and can recruit inflammatory cells of chemerin receptors and alter cell adhesion molecule expression to promote the development of inflammation in injured tissues [91]. It is generally involved in immune responses, inflammation, glucose metabolism, and other processes in the body and is closely related to metabolic syndrome and OSA [92]. In obese patients, the expression of chemerin mRNA in adipose tissue is higher, but contents will decrease after weight loss, while inflammatory biomarkers like TNF, CRP, inflammation-related adipokines FABP-4, and progranulin can also promote the growth of chemerin in adipose cells, suggesting a close relationship between adipose tissue inflammation and chemerin generation [93, 94]. Similarly, the same change was also found in some studies on adolescents and children with obesity, showing a positive correlation with BMI-standard deviation scores and a negative correlation with age, indicating that it is an important factor affecting metabolic syndrome [95, 96].

The physiological/pathophysiological association between chemerin and OSA

Current clinical studies have found that increased serum chemerin levels in patients with OSA are correlated with the severity of the disease and IR, and that the BMI, AHI, and mean SaO2% are the main factors that influence chemerin levels [85, 97, 98]. In recent years, experimental evidence supports a role for chemerin in various aspects of human physiology/pathophysiology that result in OSA, including obesity, inflammation, IR, and CVDs.

Pharyngeal fat deposition

It is known that factors such as abnormal accumulation of pharyngeal adipose tissue in patients with obesity with OSA tend to cause narrowness of the pharyngeal cavity, which further promotes upper airway obstruction and collapse during sleep and aggravates the severity of symptoms in patients with obesity with OSA [9, 10]. A study on the correlation between chemerin and pharyngeal fat deposition in patients with OSA found that chemerin levels in pharyngeal fat were higher in patients with OSA than in the control group [97]. Gong *et al.* treated patients with obesity with OSA with uvulopalatopharyngoplasty, which improved the patients' condition to a certain extent. Importantly, serum chemerin levels were significantly reduced, and IR was significantly improved [99]. Chemerin has lately been shown to induce adipogenesis and angiogenesis through Meg3/miR-217/Dkk3 in 3 T3-L1 preadipocytes, which is due to chemerin reducing miR-217 expression and increasing Meg3 expression through the regulation of Dickkopf-3, which promotes the expression of fatty acid binding protein 4 and vascular endothelial growth factor and inhibits the expression of cyclin D1, c-Myc, and β-catenin proteins [100]. These results suggest that chemerin may be involved in the pharyngeal fat deposition process and its potential mechanism in patients with OSA. In addition, chemerin can also cause obesity by promoting abnormal decomposition and uneven distribution of adipose tissue [101]. Xu *et al.* found that when chemerin and the *CMKLR1* gene were knocked out in adipocytes, the expression of glucose transporter 4, leptin, adiponectin, and hormone-sensitive lipase was reduced [98], suggesting that chemerin may also promote the progression of OSA by promoting fat cell decomposition and affecting mature adipocyte metabolic functions.

Inflammation

OSA can increase the level of serum inflammatory cytokines like IL-6 and TNF-α, while TNF-α, adiponectin, and other factors in the inflammatory process pro-

mote the secretion of chemerin, thereby accelerating the decomposition of the adipose tissue, leading to abnormal accumulation of fat. CMKLR1 is most highly expressed in mature adipose tissue, and the increase of CMKLR1 in fat promotes the secretion of chemerin by autocrine signaling. Chemerin can recruit a large number of CMKLR1-expressing dendritic cells and macrophages at the site of inflammation, thus activating an inflammatory response, which increases the oxidative stress in adipose tissue and consequently results in IR. As mentioned above, this may ultimately contribute to the occurrence and development of OSA [101-103]. PPAR-γ is a ligand-activated nuclear receptor that regulates glycolipid metabolism and inhibits inflammation. Lin *et al.* recently found that exercise-induced decrements of chemerin/CMKLR1 in rats with obesity and diabetes were mediated by PPAR-γ [103], and PPAR-γ has been identified as a therapeutic target for obesity, hyperlipidemia, and diabetes [104, 105]. However, the efficacy of the PPAR-γ pathway in the treatment of OSA remains to be tested.

IR

OSA can increase the blood glucose fluctuation range and aggravate IR due to IH and sleep fragmentation; in addition, IR can also cause OSA by disrupting the body's normal metabolism [11, 14]. El-Deeb *et al.* showed that serum chemerin levels are positively correlated with hemoglobin A1c, homeostasis model assessment-IR, fasting blood glucose, IL6, and CRP by analyzing 71 patients with T2DM and 14 healthy controls [106]. Neves *et al.* found that CCX832 (CMKLR1 antagonist) treatment in *db/db* mice decreased vascular oxidative stress, IR, and glucose levels [107]. Previous studies have found that chemerin may induce the occurrence of OSA-related IR, either through NF-κB-mediated inflammation [108] or by activating the ERK1/2 pathway to reduce the stimulation of insulin and thereby reduce the uptake of glucose [109]. Therefore, chemerin may promote the production and development of OSA through IR; these findings also provide more evidence to understand the association between chemerin and OSA and obesity as well as their complications.

CVDs

Chemerin is considered an additional risk factor for CVDs in OSA. Elevated levels of serum chemerin in patients with OSA can abolish the function and inhibit the formation of the vascular endothelium, thereby promoting the occurrence and development of hypertension [110]. Further research has found that increased expression of chemerin and CMKLR1 may activate the ROCK2/P-MYPT1 pathway, which is one of the classical MLC phosphorylation-dependent pathways, thereby inducing the contraction of vascular smooth muscle cells (VSMC) [111] or the activation of the L-type Ca2+ channel through the Gi protein, causing calcium-dependent calcium influx in VSMC [112]; additionally, chemerin can stimulate aortic smooth muscle cell proliferation *via* autophagy, which leads to vascular remodeling in metabolic hypertension [113].

Taken together, chemerin is currently considered a potential indicator of OSA detection, can be used to assess disease severity, and can promote the progression of OSA through various processes including fat metabolism, inflammation, and IR. The chemerin/CMKLR1 axis may be a new target for the treatment of obesity and related diseases, including OSA.

Resistin

The physiological function of resistin

Resistin is a cysteine-rich polypeptide encoded by the RETN gene, which has been postulated to be a molecular link between obesity and T2DM. It was named after its association with IR, but their relationship in humans remains unclear. Recently, a meta-analysis showed that levels of resistin are positively correlated with IR in people with hyperresistinemia (≥14.8 ng/mL), but not in those with normal circulating resistin levels [114], which indicates that the association is related to resistin levels. Numerous studies have shown that resistin can antagonize insulin to prevent cells from taking up glucose, resulting in decreased glucose tolerance in patients with T2DM, and that it can cause obesity by promoting blood sugar elevation and stimulating fat cell proliferation [115]. It is also involved in the inflammatory response, stimulating the release of endothelin-1 and monocyte chemotactic protein-1 by vascular endothelial cells, and promoting atherosclerosis, thereby leading to endothelial dysfunction [116, 117]. While reducing weight and fat accumulation through exercise, which is an effective treatment for obesity and its complications, also has a positive effect on resistin concentrations, the relationship between the two is not clear. One study suggests a relation with exercise-induced anti-inflammatory cytokine release rather than alterations in glucose metabolism and reductions in BMI [118].

The interaction between resistin and OSA

Some studies have found that serum resistin levels are increased in patients with OSA, and that levels are positively correlated with the severity of the disease [119, 120]. This might be due to the fact that resistin is a pro-inflammatory protein, which is influenced by up-regulated inflammatory factors such as IL-6 and TNF-α, and that it up-regulates its own mRNA expression [121]. Uchiyama *et al.* found that IH caused by OSA can increase levels of resistin mRNA levels by down-regulating miR-452 in adipocytes [122], which provides

a new mechanism of resistin in OSA. Besides, excessive resistin significantly increases the secretion of IL-6, TNF-α, and CRP by stimulating peripheral blood mononuclear cells and inducing IR, which then leads to inflammatory reactions and may aggravate the narrowing of the upper airway and the disturbance of the respiratory muscle function of the pharynx, eventually leading to OSA [121, 123]. In non-obese rodent models of OSA, chronic IH leads to IR and IGT, which may be due to the dysregulation of leptin, adiponectin, and resistin [67, 124]. Such a conclusion would suggest that the link between OSA and the corresponding adipokines has nothing to do with obesity; however, at present there is no human data to refute or support this notion. Primary snoring (PS) is also localized to the less severe side of sleep-disordered breathing and is often underestimated, although Zicari *et al.* observed significantly higher levels of resistin in patients with PS [125], which reminds us that it is not enough to focus solely on obvious lesions.

Controversies

The exact association between resistin and OSA in some specific populations remains controversial. In patients with OSA with a BMI >40, resistin levels were found not to differ between subgroups with IGT and NGM and did not change significantly with the severity of OSA. This shows that resistin alone cannot used as an indicator of insulin resistance in patients with OSA, at least not in extremely obese patients [126], as the patients in this study were all severely obese and it is therefore not clear whether severe obesity can inhibit the secretion of resistin. In addition, Vlaeva *et al.* postulated that resistin plasma levels are not associated with obesity, insulin resistance, or oxidative stress markers in non-diabetic, non-hypertensive patients with OSA [127]. Cherneva *et al.* found no association between resistin and vascular injury in non-hypersomnolent patients with OSA [128]. Moreover, one very recent review suggests that leptin and resistin levels do not correlate with OSA, while adiponectin is influenced by OSA alone [129]. These findings are in contrast to our previous conclusions, which may be due to the lack of multi-center studies performed in a larger number of patients as well as the specific subject population, which limits the generalizability of findings to the general OSA population. In short, the existing literature does not provide clear evidence for the correlation between resistin and OSA, and additional studies are needed to verify the possible mechanisms involved in the processes described here.

Resistin is widely present in target organs of insulin. It may affect insulin signal transduction, the transcription of metabolic enzymes, or the metabolism of sugars and lipids through inflammatory reactions, thus leading to the generation and development of OSA. With the focus of research on resistin, researchers began to study the effect of human resistin gene polymorphisms; the results are, however, still controversial. Nevertheless, these studies undoubtedly provide an important theoretical basis and new strategies for the effective treatment of OSA, obesity, and other diseases.

Other potential adipokines

Adipsine can reduce peripheral tissue sensitivity to insulin, and visfatin is an insulin-mimicking adipokine. REM sleep reduction affects the increased secretion of adipsine, which may be associated with the development of IR in patients with OSA [130]. However, the evidence on the relationship between visfatin and OSA is still conflicting [86, 130], and it would be premature to conclude that visfatin can function as a biomarker for OSA. Orexin and ghrelin are two kinds of appetite hormones, with effects that are opposite to those of leptin. Assadi *et al.* found that upper airway obstruction and inadequate sleep might cause a reduction in body temperature and the persistent elevation of energy expenditure and appetite hormones, with leptin dysfunction possibly one of the reasons [131], but other studies have suggested that ghrelin is not associated with OSA [86]. C1q/TNF-Related Protein-3 (CTRP3) is a recently discovered protein that has a deep structural homology to APN and can protect the organism against the effects of APN deficiency as well as maintain energetic homeostasis of the system [132]. Furthermore, CTRP3 has anti-inflammatory activity, can inhibit the production of glucose and fat, and decreases lipotoxicity associated with abnormal fat deposition in peripheral tissues [133]. What role does it play when the serum levels of leptin and adiponectin change in patients with OSA? Can it replace adiponectin in the treatment of OSA? Further research is needed to answer these and other related questions.

Conclusion and Future Research Direction

In this review, we have discussed serum content changes and the pathophysiologic roles of adipokines in OSA (Fig. 3). As indicated by most studies included in this review, OSA is associated with an increase in the serum levels of leptin, chemerin, and resistin and a decrease in adiponectin and omentin-1 levels. These factors are considered risk factors for IR, CVDs, and other diseases, and can be used to monitor the development of OSA and obesity and prevent future comorbidities. Considering that most patients with OSA participating in the studies reviewed here are also obese, it is currently unclear whether OSA affects the secretion of these adipokines independently of obesity. Besides, we did find evidence for some adipokines being related to the occur-

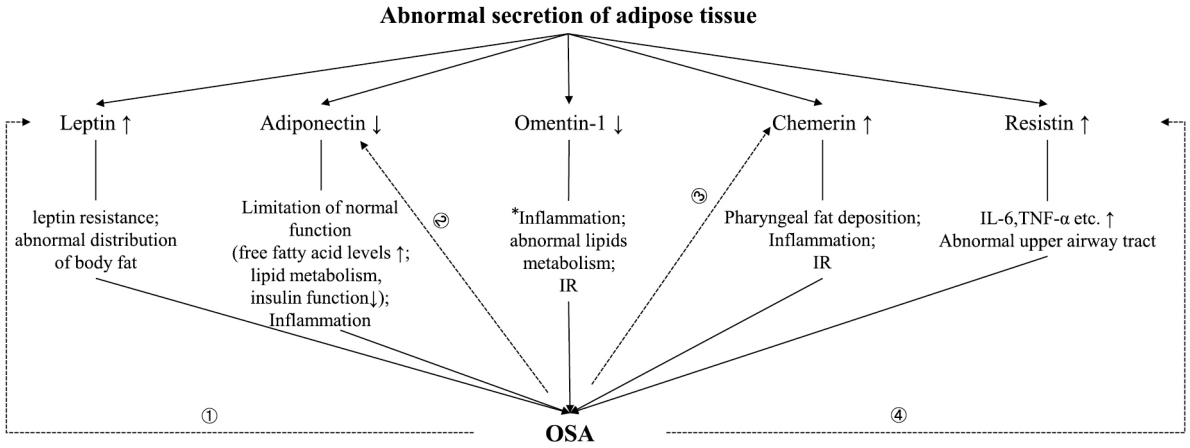

Fig. 3 The changing serum content and main pathophysiologic roles of adipokines in OSA

OSA is associated with an increase in the serum levels of leptin, chemerin, resistin and decrease of adiponectin, omentin-1, which can cause different functional abnormalities. ① IH; oxidative stress, ② IH; IR; hypoxia-induced sympathetic activation,③ Pharyngeal fat deposition; IH; sleep fragmentation, ④ MIR-452 ↓; IL-6; TNF-α; Resistin; mRNA ↑.

*Lack of related research about the exact roles and mechanisms of omentin-1 in OSA.

rence of OSA, but further studies are needed to confirm these connections. Despite the high number of studies assessing the roles of specific adipokines in OSA, the interpretation of the results is difficult because of several limitations. Firstly, most studies were cross-sectional by design, which precludes any formal conclusions about the causality of the associations between adipokines and OSA. However, these findings provide additional evidence to support potentially important connections between adipokines and OSA. Secondly, experiments often overlooked the potential impact of other diseases and different disease stages on the study results. Third, differences in study methodology, sample size, area, and population may account for the diverse findings. Differences in assay methods may be another cause of contradictory results. Finally, although researchers have made appropriate adjustments to independent variables to eliminate bias, some unmeasured and residual confounding factors may still exist.

Furthermore, however, there is still some controversy about the role of adipokines in the occurrence and development of OSA and other diseases. Claudia *et al.* suggested that high serum adiponectin may be only a neutral marker reflecting insulin sensitivity and glucose homeostasis, and may increase CVD mortality (adiponectin paradox). The authors question the anti-inflammatory, cardioprotective effects of adiponectin and its role as a promising therapeutic target [134]. There are also doubts about the relationship between circulating resistin and OSA [126-129]. As the correlations between leptin, adiponectin, and OSA have been thoroughly studied, future research should focus on the design of specific compounds that target molecules such as leptin, adiponectin, and their receptors to verify which treatment methods are effective; we still need a large number of experiments to untangle the intrinsic mechanisms underlying the connection between omentin-1 and resistin and OSA. As for chemerin, while some clinical trials that remain in the stage of theoretical conjecture have found associations with some diseases, there is a lack of convincing evidence. Regarding the interactions between them, while there is no evidence at this time that changes in some adipokines are due to the direct effects of other specific ones, we cannot rule out this possibility, and future studies may thus focus on how each adipokine is independently related to OSA.

Despite the limitations described above, we present consistent evidence on the biological role of some adipokines in OSA. However, extensive investigations are required to explore more specific effects of these adipokines in OSA. Whether adipokines can be used for the diagnosis and assessment of intervention outcomes or for the development of new therapeutic targets also requires further investigation. Finally, we expect this review to improve our understanding of the biological role of adipokines in OSA, and hope that it can provide new ideas for future clinical research and treatment.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Statement

Support was provided by grants from the National Natural Science Funds of China (Nos. 81560154, 81760168 and 81460018).

References

1. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, *et al.* (2017) Prevalence of obstructive sleep apnea in the general population: a systematic review. *Sleep Med Rev* 34: 70–81.
2. Muraki I, Wada H, Tanigawa T (2018) Sleep apnea and type 2 diabetes. *J Diabetes Investig* 9: 991–997.
3. Geovanini GR, Wang R, Weng J, Tracy R, Jenny NS, *et al.* (2018) Elevations in neutrophils with obstructive sleep apnea: the multi-ethnic study of atherosclerosis (MESA). *Int J Cardiol* 257: 318–323.
4. Chooi YC, Ding C, Magkos F (2019) The epidemiology of obesity. *Metabolism* 92: 6–10.
5. Tuomilehto H, Seppa J, Uusitupa M (2013) Obesity and obstructive sleep apnea—clinical significance of weight loss. *Sleep Med Rev* 17: 321–329.
6. Cuccia AM, Campisi G, Cannavale R, Colella G (2007) Obesity and craniofacial variables in subjects with obstructive sleep apnea syndrome: comparisons of cephalometric values. *Head Face Med* 3: 41.
7. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J (2000) Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 284: 3015–3021.
8. Amin A, Ali A, Altaf QA, Piya MK, Barnett AH, *et al.* (2017) prevalence and associations of obstructive sleep apnea in South Asians and White Europeans with type 2 diabetes: a cross-sectional study. *J Clin Sleep Med* 13: 583–589.
9. Nicolini A, Piroddi IMG, Barbagelata E, Barbagelata E, Barlascini C (2016) Obesity and breathing related sleep disorders. In Ahimad SI, Imam SK (eds) Obesity: A Practical Guide. Springer, Cham: 131–137.
10. Isono S (2009) Obstructive sleep apnea of obese adults: pathophysiology and perioperative airway management. *Anesthesiology* 110: 908–921.
11. Soin D, Kumar PA, Chahal J, Chawla SPS, Kaur S, *et al.* (2019) Evaluation of obstructive sleep apnea in metabolic syndrome. *J Family Med Prim Care* 8: 1580–1586.
12. Jehan S, Myers AK, Zizi F, Pandi-Perumal SR, Jean-Louis G, *et al.* (2018) Obesity, obstructive sleep apnea and type 2 diabetes mellitus: epidemiology and pathophysiologic insights. *Sleep Med Disord* 2: 52–58.
13. Laratta CR, Ayas NT, Povitz M, Pendharkar SR (2017) Diagnosis and treatment of obstructive sleep apnea in adults. *CMAJ* 189: E1481–E1488.
14. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Bixler EO (2018) Obstructive sleep apnea and the metabolic syndrome: the road to clinically-meaningful phenotyping, improved prognosis, and personalized treatment. *Sleep Med Rev* 42: 211–219.
15. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Calhoun SL, He F, *et al.* (2016) Inflammation mediates the association between visceral adiposity and obstructive sleep apnea in adolescents. *Am J Physiol Endocrinol Metab* 311: E851–E858.
16. Bozkus F, Dikmen N, Samur A, Bilal N, Atilla N, *et al.* (2018) Does the neutrophil-to-lymphocyte ratio have any importance between subjects with obstructive sleep apnea syndrome with obesity and without obesity? *Tuberk Toraks* 66: 8–15.
17. Dokkedal-Silva V, Galduroz JCF, Tufik S, Andersen ML (2018) Association of obesity, sleep apnea and hypothalamic inflammation: novel possibilities of research. *Eur J Intern Med* 52: e17–e18.
18. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB (2016) Adipose tissue remodeling: its role in energy metabolism and metabolic disorders. *Front Endocrinol (Lausanne)* 7: 30.
19. Bluher M, Mantzoros CS (2015) From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. *Metabolism* 64: 131–145.
20. Singh M, Benencia F (2019) Inflammatory processes in obesity: focus on endothelial dysfunction and the role of adipokines as inflammatory mediators. *Int Rev Immunol* 38: 157–171.
21. Derosa G, Catena G, Gaudio G, D'Angelo A, Maffioli P (2020) Adipose tissue dysfunction and metabolic disorders: is it possible to predict who will develop type 2 diabetes mellitus? Role of markErs in the progreSsion of dIabeteS in obese paTIeNts (The RESISTIN trial). *Cytokine* 127: 154947.
22. Francisco V, Ruiz-Fernandez C, Pino J, Mera A, Gonzalez-Gay MA, *et al.* (2019) Adipokines: linking metabolic syndrome, the immune system, and arthritic diseases. *Biochem Pharmacol* 165: 196–206.
23. Hristov M, Landzhov B, Nikolov R, Yakimova K (2019) Central, but not systemic, thermoregulatory effects of leptin are impaired in rats with obesity: interactions with GABAB agonist and antagonist. *Amino Acids* 51: 1055–1063.
24. Berger S, Polotsky VY (2018) Leptin and leptin resistance in the pathogenesis of obstructive sleep apnea: a possible link to oxidative stress and cardiovascular complications. *Oxid Med Cell Longev* 2018: 5137947.
25. Framnes SN, Arble DM (2018) The bidirectional relationship between obstructive sleep apnea and metabolic disease. *Front Endocrinol (Lausanne)* 9: 440.
26. Rashad NM, Sayed SE, Sherif MH, Sitohy MZ (2019) Effect of a 24-week weight management program on serum leptin level in correlation to anthropometric

measures in obese female: a randomized controlled clinical trial. *Diabetes Metab Syndr* 13: 2230–2235.
27. Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC (2019) Leptin, obesity, and leptin resistance: where are we 25 years later? *Nutrients* 11: 2704.
28. Buonfiglio D, Tchio C, Furigo I, Donato J Jr, Baba K, *et al.* (2019) Removing melatonin receptor type 1 signaling leads to selective leptin resistance in the arcuate nucleus. *J Pineal Res* 67: e12580.
29. Banks WA, DiPalma CR, Farrell CL (1999) Impaired transport of leptin across the blood-brain barrier in obesity. *Peptides* 20: 1341–1345.
30. Harrison L, Schriever SC, Feuchtinger A, Kyriakou E, Baumann P, *et al.* (2019) Fluorescent blood-brain barrier tracing shows intact leptin transport in obese mice. *Int J Obes (Lond)* 43: 1305–1318.
31. Yao Q, Pho H, Kirkness J, Ladenheim EE, Bi S, *et al.* (2016) Localizing effects of leptin on upper airway and respiratory control during sleep. *Sleep* 39: 1097–1106.
32. Flak JN, Arble D, Pan W, Patterson C, Lanigan T, *et al.* (2017) A leptin-regulated circuit controls glucose mobilization during noxious stimuli. *J Clin Invest* 127: 3103–3113.
33. Pho H, Hernandez AB, Arias RS, Leitner EB, Van Kooten S, *et al.* (2016) The effect of leptin replacement on sleep-disordered breathing in the leptin-deficient ob/ob mouse. *J Appl Physiol* (1985) 120: 78–86.
34. Berger S, Pho H, Fleury-Curado T, Bevans-Fonti S, Younas H, *et al.* (2019) Intranasal leptin relieves sleep-disordered breathing in mice with diet-induced obesity. *Am J Respir Crit Care Med* 199: 773–783.
35. Caballero-Eraso C, Shin MK, Pho H, Kim LJ, Pichard LE, *et al.* (2019) Leptin acts in the carotid bodies to increase minute ventilation during wakefulness and sleep and augment the hypoxic ventilatory response. *J Physiol* 597: 151–172.
36. Shapiro SD, Chin CH, Kirkness JP, McGinley BM, Patil SP, *et al.* (2014) Leptin and the control of pharyngeal patency during sleep in severe obesity. *J Appl Physiol (1985)* 116: 1334–1341.
37. Imayama I, Prasad B (2017) Role of leptin in obstructive sleep apnea. *Ann Am Thorac Soc* 14: 1607–1621.
38. Liang W, Wu P, Zhu H, Deng Y, Zhao D, *et al.* (2018) Clinical significance of preoperative and postoperative detection of leptin in exhaled breath condensate of patients with obstructive sleep apnea-hypopnea syndrome. *New Medicine* 49: 660–664 (In Chinese).
39. Pamuk AE, Suslu AE, Yalcinkaya A, Oztas YE, Pamuk G, *et al.* (2018) The serum leptin level in non-obese patients with obstructive sleep apnea. *Auris Nasus Larynx* 45: 796–800.
40. Bingol Z, Karaayvaz EB, Telci A, Bilge AK, Okumus G, *et al.* (2019) Leptin and adiponectin levels in obstructive sleep apnea phenotypes. *Biomark Med* 13: 865–874.
41. Shobatake R, Takasawa K, Ota H, Itaya-Hironaka A, Yamauchi A, *et al.* (2018) Up-regulation of POMC and CART mRNAs by intermittent hypoxia *via* GATA transcription factors in human neuronal cells. *Int J Biochem Cell Biol* 95: 100–107.
42. Ryan S (2017) Adipose tissue inflammation by intermittent hypoxia: mechanistic link between obstructive sleep apnoea and metabolic dysfunction. *J Physiol* 595: 2423–2430.
43. Chin CH, Lin PW, Lin HC, Friedman M, Lin MC (2019) Effects of OSA surgery on leptin and metabolic profiles. *Otolaryngol Head Neck Surg* 161: 1048–1055.
44. McMurray F, Patten DA, Harper ME (2016) Reactive oxygen species and oxidative stress in obesity-recent findings and empirical approaches. *Obesity (Silver Spring, Md)* 24: 2301–2310.
45. Yagishita Y, Uruno A, Fukutomi T, Saito R, Saigusa D, *et al.* (2017) Nrf2 improves leptin and insulin resistance provoked by hypothalamic oxidative stress. *Cell Rep* 18: 2030–2044.
46. Nakata M, Yamamoto S, Okada T, Yada T (2017) AAV-mediated IL-10 gene transfer counteracts inflammation in the hypothalamic arcuate nucleus and obesity induced by high-fat diet. *Neuropeptides* 62: 87–92.
47. Chen Y, Zhang X, Liu W, Zhang C, Wang Z (2017) Relationship between Gln223Arg polymorphism of leptin receptor gene and obstructive sleep apnea hypopnea syndrome in Han population in Southwest China. *Chinese Journal of Respiratory* 16: 474–477 (In Chinese).
48. Zhu M, Bai X (2019) Association of LEPR Gln223Arg polymorphism with obstructive sleep apnea syndrome: a meta-analysis. *Crit Rev Eukaryot Gene Expr* 29: 171–176.
49. Xu B, Liu J, Li T, Liu S (2017) Gln223Arg polymorphism in the Caucasian population and Pro1019Pro polymorphism in the Chinese population are risk factors for OSAS: an updated meta-analysis of 1159 subjects. *Rev Port Pneumol (2006)* 23: 62–70.
50. Li J, Yang S, Jiao X, Yang Y, Sun H, *et al.* (2019) Targeted sequencing analysis of the leptin receptor gene identifies variants associated with obstructive sleep apnoea in Chinese Han population. *Lung* 197: 577–584.
51. Lam DC, Lam KS, Ip MS (2015) Obstructive sleep apnoea, insulin resistance and adipocytokines. *Clin Endocrinol (Oxf)* 82: 165–177.
52. Yang W, Yuan W, Peng X, Wang M, Xiao J, *et al.* (2019) PPAR gamma/Nnat/NF-kappaB axis involved in promoting effects of adiponectin on preadipocyte differentiation. *Mediators Inflamm* 2019: 5618023.
53. Ebrahimi-Mamaeghani M, Mohammadi S, Arefhosseini SR, Fallah P, Bazi Z (2015) Adiponectin as a potential biomarker of vascular disease. *Vasc Health Risk Manag* 11: 55–70.
54. Sun J, Gao Y, Yao T, Huang Y, He Z, *et al.* (2016) Adiponectin potentiates the acute effects of leptin in arcuate Pomc neurons. *Mol Metab* 5: 882–891.
55. Lee TH, Cheng KK, Hoo RL, Siu PM, Yau SY (2019) The novel perspectives of adipokines on brain health. *Int J Mol Sci* 20: 5638.
56. Zeng F, Wang X, Hu W, Wang L (2017) Association of adiponectin level and obstructive sleep apnea prevalence

in obese subjects. *Medicine (Baltimore)* 96: e7784.
57. Domagala-Kulawik J, Osinska I, Piechuta A, Bielicki P, Skirecki T (2015) T, B, and NKT cells in systemic inflammation in obstructive sleep apnoea. *Mediators Inflamm* 2015: 161579.
58. Lu M, Fang F, Wang Z, Wei P, Hu C, *et al.* (2019) Association between serum/plasma levels of adiponectin and obstructive sleep apnea hypopnea syndrome: a meta-analysis. *Lipids Health Dis* 18: 30.
59. Al Mutairi S, Mojiminiyi OA, Al Alawi A, Al Rammah T, Abdella N (2014) Study of leptin and adiponectin as disease markers in subjects with obstructive sleep apnea. *Dis Markers* 2014: 706314.
60. Radovanovic D, Rizzi M, Airoldi A, Mantero M, Di Marco F, *et al.* (2019) Effect of continuous positive airway pressure on respiratory drive in patients with obstructive sleep apnea. *Sleep Med* 64: 3–11.
61. Lui MMS, Mak JCW, Chong PWC, Lam DCL, Ip MSM (2019) Circulating adipocyte fatty acid-binding protein is reduced by continuous positive airway pressure treatment for obstructive sleep apnea-a randomized controlled study. *Sleep Breath* doi: 10.1007/s11325-019-01893-5. [Epub ahead of print]
62. Chen LD, Liu JN, Lin L, Wu Z, Li H, *et al.* (2015) Effect of continuous positive airway pressure on adiponectin in patients with obstructive sleep apnea: a meta-analysis. *PLoS One* 10: e0136837.
63. Abdel-Fadeil MR, Abedelhaffez AS, Makhlouf HA, Al Qirshi GA (2017) Obstructive sleep apnea: influence of hypertension on adiponectin, inflammatory markers and dyslipidemia. *Pathophysiology* 24: 305–315.
64. Li J, Gao X, Han J, Kang L, Luo W (2019) Correlation between serum adiponectin, inflammatory factors and early cardiac dysfunction in patients with obstructive sleep apnea. *The Journal of Practical Medicine* 35: 1445–1449 (In Chinese).
65. Archontogeorgis K, Voulgaris A, Nena E, Strempela M, Karailidou P, *et al.* (2018) Cardiovascular risk assessment in a cohort of newly diagnosed patients with obstructive sleep apnea syndrome. *Cardiol Res Pract* 2018: 6572785.
66. Zhang X, Rui L, Lv B, Chen F, Cai L (2019) Adiponectin relieves human adult cardiac myocytes injury induced by intermittent hypoxia. *Med Sci Monit* 25: 786–793.
67. Lee CP, Kushida CA, Abisheganaden JA (2019) Epidemiological and pathophysiological evidence supporting links between obstructive sleep apnoea and type 2 diabetes mellitus. *Singapore Med J* 60: 54–56.
68. Ding WX, Zhang Q, Ge LY, Dong YB, Ding N, *et al.* (2019) [Adiponectin ameliorated pancreatic islet mitochondrial injury induced by chronic intermittent hypoxia]. *Zhonghua Yi Xue Za Zhi* 99: 1380–1384 (In Chinese).
69. Adams RJ, Appleton SL, Vakulin A, Hanly PJ, McDonald SP, *et al.* (2017) Chronic kidney disease and sleep apnea association of kidney disease with obstructive sleep apnea in a population study of men. *Sleep* 40: pii. zsw015.
70. Kim HY, Bae EH, Ma SK, Chae DW, Choi KH, *et al.* (2016) Association of serum adiponectin level with albuminuria in chronic kidney disease patients. *Clin Exp Nephrol* 20: 443–449.
71. Chen DD, Huang JF, Huang SP, Chen XF (2019) Association of serum adiponectin level with cystatin C in male patients with obstructive sleep apnea syndrome. *Sleep Breath* doi: 10.1007/s11325-019-01927-y. [Epub ahead of print]
72. Wu W, Li Z, Tang T, Gu L, Du J, *et al.* (2016) Single nucleotide polymorphisms in adiponectin gene are not directly associated with increased risk of obstructive sleep apnea syndrome in a Chinese Han population. *ORL J Otorhinolaryngol Relat Spec* 78: 308–319.
73. Yang Y, Yang S, Jiao X, Li J, Wu H, *et al.* (2019) Targeted sequencing analysis of the adiponectin gene identifies variants associated with obstructive sleep apnoea in Chinese Han population. *Medicine (Baltimore)* 98: e15219.
74. Badran M, Yassin BA, Lin DTS, Kobor MS, Ayas N, *et al.* (2019) Gestational intermittent hypoxia induces endothelial dysfunction, reduces perivascular adiponectin and causes epigenetic changes in adult male offspring. *J Physiol* 597: 5349–5364.
75. Zhu L, Chen L, Shi CM, Xu GF, Xu LL, *et al.* (2014) MiR-335, an adipogenesis-related microRNA, is involved in adipose tissue inflammation. *Cell Biochem Biophys* 68: 283–290.
76. Skrypnik K, Suliburska J, Skrypnik D, Pilarski L, Regula J, *et al.* (2017) The genetic basis of obesity complications. *Acta Sci Pol Technol Aliment* 16: 83–91.
77. Lis I, Pilarski L, Bogdanski P (2015) [Omentin—a newly-discovered adipocytokine in insulin resistance pathogenesis]. *Pol Merkur Lekarski* 39: 56–60 (In Polish).
78. Elsaid NH, Sadik NA, Ahmed NR, Fayez SE, Mohammed NAE (2018) Serum omentin-1 levels in type 2 diabetic obese women in relation to glycemic control, insulin resistance and metabolic parameters. *J Clin Transl Endocrinol* 13: 14–19.
79. Lesna J, Ticha A, Hyspler R, Musil F, Blaha V, *et al.* (2015) Omentin-1 plasma levels and cholesterol metabolism in obese patients with diabetes mellitus type 1: impact of weight reduction. *Nutr Diabetes* 5: e183.
80. Cimen AR, Cerit ET, Iyidir OT, Karakus R, Uyar BB, *et al.* (2017) Serum omentin-1 levels and endothelial dysfunction in obesity. *Acta Endocrinol (Buchar)* 13: 138–143.
81. Herder C, Ouwens DM, Carstensen M, Kowall B, Huth C, *et al.* (2015) Adiponectin may mediate the association between omentin, circulating lipids and insulin sensitivity: results from the KORA F4 study. *Eur J Endocrinol* 172: 423–432.
82. Du Y, Ji Q, Cai L, Huang F, Lai Y, *et al.* (2016) Association between omentin-1 expression in human epicardial adipose tissue and coronary atherosclerosis. *Cardiovasc Diabetol* 15: 90.
83. Zhou Y, Zhang B, Hao C, Huang X, Li X, *et al.* (2017) Omentin-A novel adipokine in respiratory diseases. *Int J Mol Sci* 19: 73.
84. Kurt OK, Tosun M, Alcelik A, Yilmaz B, Talay F (2014)

Serum omentin levels in patients with obstructive sleep apnea. *Sleep Breath* 18: 391–395.
85. Tang Y, Zhou X, Zhou Y, Li W (2019) Correlation between visceral adipose tissue vaspin, chemerin and omentin expression and insulin resistance in patients with OSA. *World Latest Medicine Information* 19: 10–11+14 (In Chinese).
86. Zhang DM, Pang XL, Huang R, Gong FY, Zhong X, *et al.* (2018) Adiponectin, omentin, ghrelin, and visfatin levels in obese patients with severe obstructive sleep apnea. *Biomed Res Int* 2018: 3410135.
87. Uygur F, Tanriverdi H, Can M, Erboy F, Altinsoy B, *et al.* (2016) Association between continuous positive airway pressure and circulating omentin levels in patients with obstructive sleep apnoea. *Sleep Breath* 20: 939–945.
88. Watanabe T, Watanabe-Kominato K, Takahashi Y, Kojima M, Watanabe R (2017) Adipose tissue-derived omentin-1 function and regulation. *Compr Physiol* 7: 765–781.
89. Liu F, Fang S, Liu X, Li J, Wang X, *et al.* (2020) Omentin-1 protects against high glucose-induced endothelial dysfunction *via* the AMPK/PPARdelta signaling pathway. *Biochem Pharmacol* 174: 113830.
90. Qi D, Tang X, He J, Wang D, Zhao Y, *et al.* (2016) Omentin protects against LPS-induced ARDS through suppressing pulmonary inflammation and promoting endothelial barrier *via* an Akt/eNOS-dependent mechanism. *Cell Death Dis* 7: e2360.
91. Kaur J, Mattu HS, Chatha K, Randeva HS (2018) Chemerin in human cardiovascular disease. *Vascul Pharmacol* 110: 1–6.
92. Watts SW (2015) Trash talk by fat: chemerin as a reactive oxygen species provocateur in the vasculature. *Hypertension* 66: 466–468.
93. Catalan V, Gomez-Ambrosi J, Rodriguez A, Ramirez B, Rotellar F, *et al.* (2013) Increased levels of chemerin and its receptor, chemokine-like receptor-1, in obesity are related to inflammation: tumor necrosis factor-alpha stimulates mRNA levels of chemerin in visceral adipocytes from obese patients. *Surg Obes Relat Dis* 9: 306–314.
94. Eichelmann F, Weikert C, di Giuseppe R, Biemann R, Isermann B, *et al.* (2017) Methodological utility of chemerin as a novel biomarker of immunity and metabolism. *Endocr Connect* 6: 340–347.
95. Ba HJ, Xu LL, Qin YZ, Chen HS (2019) Serum chemerin levels correlate with determinants of metabolic syndrome in obese children and adolescents. *Clin Med Insights Pediatr* 13: 1179556519853780.
96. Niklowitz P, Rothermel J, Lass N, Barth A, Reinehr T (2018) Link between chemerin, central obesity, and parameters of the metabolic syndrome: findings from a longitudinal study in obese children participating in a lifestyle intervention. *Int J Obes* 42: 1743–1752.
97. Wu H, Cao S, Shi B, Bai Z, Li Y (2018) Chemerin in obstructive sleep apnea-hypopnea patients' pharyngeal fat deposition. *Journal of Kunming Medical University* 39: 77–80 (In Chinese).
98. Xu T, Lin Y, Sun S, Zhang Q (2017) Changes in four plasma adipokines before and after sleep in OSAS patients. *Clin Respir J* 11: 968–974.
99. Gong Z, Wei YW, Gao J (2017) The changes of adipocytokines after surgery in OSAHS patients with insulin resistance. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 31: 674–677 (In Chinese).
100. Huang X, Fu C, Liu W, Liang Y, Li P, *et al.* (2019) Chemerin-induced angiogenesis and adipogenesis in 3T3-L1 preadipocytes is mediated by lncRNA Meg3 through regulating Dickkopf-3 by sponging miR-217. *Toxicol Appl Pharmacol* 385: 114815.
101. Shi B, Wu H, Bai Z (2017) Research progress of correlation between chemerin and obstructive sleep apnea hypopnea syndrome. *Hainan Medical Journal* 28: 951–954 (In Chinese).
102. Perumalsamy S, Aqilah Mohd Zin NA, Widodo RT, Wan Ahmad WA, Vethakkan SRDB, *et al.* (2017) Chemokine like receptor-1 (CMKLR-1) receptor: a potential therapeutic target in management of chemerin induced type 2 diabetes mellitus and cancer. *Curr Pharm Des* 23: 3689–3698.
103. Lin X, Yang Y, Qu J, Wang X (2019) Aerobic exercise decreases chemerin/CMKLR1 in the serum and peripheral metabolic organs of obesity and diabetes rats by increasing PPARgamma. *Nutr Metab (Lond)* 16: 17.
104. Wang S, Dougherty EJ, Danner RL (2016) PPARgamma signaling and emerging opportunities for improved therapeutics. *Pharmacol Res* 111: 76–85.
105. Ruffino JS, Davies NA, Morris K, Ludgate M, Zhang L, *et al.* (2016) Moderate-intensity exercise alters markers of alternative activation in circulating monocytes in females: a putative role for PPARgamma. *Eur J Appl Physiol* 116: 1671–1682.
106. El-Deeb TS, Bakkar SM, Eltoony L, Zakhary MM, Kamel AA, *et al.* (2018) The adipokine chemerin and fetuin-A serum levels in type 2 diabetes mellitus: relation to obesity and inflammatory markers. *Egypt J Immunol* 25: 191–202.
107. Neves KB, Nguyen Dinh Cat A, Alves-Lopes R, Harvey KY, Costa RMD, *et al.* (2018) Chemerin receptor blockade improves vascular function in diabetic obese mice *via* redox-sensitive and Akt-dependent pathways. *Am J Physiol Heart Circ Physiol* 315: H1851–H1860.
108. Huang Z, Xie X (2015) Chemerin induces insulin resistance in C2C12 cells through nuclear factor-kappaB pathway-mediated inflammatory reaction. *Chinese Journal of Cellular & Molecular Immunology* 31: 725–729 (In Chinese).
109. Zhang R, Liu S, Guo B, Chang L, Li Y (2014) Chemerin induces insulin resistance in rat cardiomyocytes in part through the ERK1/2 signaling pathway. *Pharmacology* 94: 259–264.
110. Kennedy AJ, Yang P, Read C, Kuc RE, Yang L, *et al.* (2016) Chemerin elicits potent constrictor actions *via* chemokine-like receptor 1 (CMKLR1), not G-protein-coupled receptor 1 (GPR1), in human and rat vasculature. *J Am Heart Assoc* 5: e004421.
111. Weng C, Shen Z, Li X, Jiang W, Peng L, *et al.* (2017)

Effects of chemerin/CMKLR1 in obesity-induced hypertension and potential mechanism. *Am J Transl Res* 9: 3096–3104.
112. Ferland DJ, Darios ES, Neubig RR, Sjogren B, Truong N, *et al.* (2017) Chemerin-induced arterial contraction is Gi- and calcium-dependent. *Vascul Pharmacol* 88: 30–41.
113. Wen J, Wang J, Guo L, Cai W, Wu Y, *et al.* (2019) Chemerin stimulates aortic smooth muscle cell proliferation and migration *via* activation of autophagy in VSMCs of metabolic hypertension rats. *Am J Transl Res* 11: 1327–1342.
114. Su KZ, Li YR, Zhang D, Yuan JH, Zhang CS, *et al.* (2019) Relation of circulating resistin to insulin resistance in type 2 diabetes and obesity: a systematic review and meta-analysis. *Front Physiol* 10: 1399.
115. Song R, Wang X, Mao Y, Li H, Li Z, *et al.* (2013) Resistin disrupts glycogen synthesis under high insulin and high glucose levels by down-regulating the hepatic levels of GSK3beta. *Gene* 529: 50–56.
116. Liu X, Zheng X, Su X, Tian W, Hu Y, *et al.* (2018) Plasma resistin levels in patients with acute aortic dissection: a propensity score-matched observational case-control study. *Med Sci Monit* 24: 6431–6437.
117. Ramirez JL, Khetani SA, Zahner GJ, Spaulding KA, Schaller MS, *et al.* (2019) Serum resistin is associated with impaired endothelial function and a higher rate of adverse cardiac events in patients with peripheral artery disease. *J Vasc Surg* 69: 497–506.
118. Cobbold C (2019) Type 2 diabetes mellitus risk and exercise: is resistin involved? *J Sports Med Phys Fitness* 59: 290–297.
119. Pan H, Cai W, Zhang X, Yang J, Jin F, *et al.* (2018) Association between resistin levels and vascular endothelia function in patients with obstructive sleep apnea syndrome. *International Journal of Respiration* 38: 522–525 (In Chinese).
120. Yamamoto Y, Fujiuchi S, Hiramatsu M, Nishigaki Y, Takeda A, *et al.* (2008) Resistin is closely related to systemic inflammation in obstructive sleep apnea. *Respiration* 76: 377–385.
121. Ouchi N, Parker JL, Lugus JJ, Walsh K (2011) Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 11: 85–97.
122. Uchiyama T, Itaya-Hironaka A, Yamauchi A, Makino M, Sakuramoto-Tsuchida S, *et al.* (2019) Intermittent hypoxia up-regulates CCL2, RETN, and TNFalpha mRNAs in adipocytes *via* down-regulation of miR-452. *Int J Mol Sci* 20: 1960.
123. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y (2017) Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci* 13: 851–863.
124. Fu C, Jiang L, Zhu F, Liu Z, Li W, *et al.* (2015) Chronic intermittent hypoxia leads to insulin resistance and impaired glucose tolerance through dysregulation of adipokines in non-obese rats. *Sleep Breath* 19: 1467–1473.
125. Zicari AM, Cutrera R, Occasi F, Carbone MP, Cesoni Marcelli A, *et al.* (2014) Serum resistin levels in children with primary snoring. *Int J Immunopathol Pharmacol* 27: 449–454.
126. Cherneva RV, Georgiev OB, Petrova DS, Mondeshki TL, Ruseva SR, *et al.* (2013) Resistin—the link between adipose tissue dysfunction and insulin resistance in patients with obstructive sleep apnea. *J Diabetes Metab Disord* 12: 5.
127. Cherneva RV, Georgiev OB, Petrov DS, Valev DG, Petrova JI (2014) Resistin and oxidative stress as markers of atherosclerosis in obstructive sleep apnea. *Curr Respir Med Rev* 10: 131–137.
128. Cherneva RV, Cherneva ZV, Georgiev OB, Petrova DS, Petrova JI (2017) 8-isoprostanes and resistin as markers of vascular damage in non-hypersomnolent obstructive sleep apnoea patients. *Clin Physiol Funct Imaging* 37: 695–702.
129. Mashaqi S, Badr MS (2019) The impact of obstructive sleep apnea and positive airway pressure therapy on metabolic peptides regulating appetite, food intake, energy homeostasis, and systemic inflammation: a literature review. *J Clin Sleep Med* 15: 1037–1050.
130. Martynowicz H, Kornafel-Flak O, Urbanik D, Laczmanski L, Sobieszczanska M, *et al.* (2019) Coexistence of obstructive sleep apnea and telomerase activity, concentration of selected adipose tissue hormones and vascular endothelial function in patients with arterial hypertension. *Respir Med* 153: 20–25.
131. Assadi MH, Segev Y, Tarasiuk A (2019) Irreversible metabolic abnormalities following chronic upper airway loading. *Sleep* 42: zsz176.
132. Li Y, Wright GL, Peterson JM (2017) C1q/TNF-Related Protein 3 (CTRP3) Function and regulation. *Compr Physiol* 7: 863–878.
133. Komosinska-Vassev K, Olczyk P, Kuznik-Trocha K, Jura-Poltorak A, Derkacz A, *et al.* (2019) Circulating C1q/TNF-related protein 3, omentin-1 and NGAL in obese patients with type 2 diabetes during insulin therapy. *J Clin Med* 8: 805.
134. Menzaghi C, Trischitta V (2018) Erratum. The adiponectin paradox for all-cause and cardiovascular mortality. *Diabetes* 2018; 67: 12–22. *Diabetes* 67: 2710.