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SERIES "THE GENETIC AND CARDIOVASCULAR ASPECTS OF OBSTRUCTIVE SLEEP APNOEA/HYPOPNOEA SYNDROME"
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Sleep, sleep-disordered breathing and metabolic consequences

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ABSTRACT: Sleep profoundly affects metabolic pathways. In healthy subjects, experimental sleep restriction caused insulin resistance (IR) and increased evening cortisol and sympathetic activation. Increased obesity in subjects reporting short sleep duration leads to speculation that, during recent decades, decreased sleeping time in the general population may have contributed to the increasing prevalence of obesity. Causal inference is difficult due to lack of control for confounders and inconsistent evidence of temporal sequence.

In the general population, obstructive sleep apnoea (OSA) is associated with glucose intolerance. OSA severity is also associated with the degree of IR. However, OSA at baseline does not seem to significantly predict the development of diabetes. Prevalence of the metabolic syndrome is higher in patients with OSA than in obese subjects without OSA. Treatment with continuous positive airway pressure seems to improve glucose metabolism both in diabetic and nondiabetic OSA but mainly in nonobese subjects.

The relative role of obesity and OSA in the pathogenesis of metabolic alterations is still unclear and is intensively studied in clinical and experimental models. In the intermittent hypoxia model in rodents, strong interactions are likely to occur between haemodynamic alterations, systemic inflammation and metabolic changes, modulated by genetic background. Molecular and cellular mechanisms are currently being investigated.

KEYWORDS: Diabetes, insulin resistance, intermittent hypoxia, obesity, sleep, sleep apnoea

There is compelling evidence that sleep apnoea represents a major cardiovascular risk [1–8]. Many studies have reported an independent association of obstructive sleep apnoea (OSA) with several components of the metabolic syndrome (MetS), particularly insulin resistance (IR) and abnormal lipid metabolism [9, 10]. This association may further increase cardiovascular risk [11], since the MetS is recognised to be a risk factor for cardiovascular morbidity and mortality [12, 13].

Rapidly accumulating data from both epidemiological and clinical studies [14, 15] suggest that OSA is independently associated with alterations in glucose metabolism and places patients at an increased risk of the development of type 2 diabetes. Recent reports have indicated that many patients with type 2 diabetes have OSA [15]. Even though there is emerging evidence that the relationship between type 2 diabetes and OSA is at least partially independent of adiposity [16, 17], there are several important limitations in

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the published literature that do not allow causality to be established, *i.e.* cross-sectional studies, use of snoring as a surrogate marker of OSA, and various techniques for the assessments of glucose metabolism and type 2 diabetes. Recent state-of-the art reviews have highlighted these limitations and emphasised the need for further clinical research in this direction [14, 15].

In this article, we will review the physiological effects of sleep on glucose metabolism and the possible role of sleep disruption on the pathogenesis of metabolic abnormalities, the clinical evidence linking sleep disordered breathing (SDB) and impairment of glucose metabolism, the current evidence regarding the impact of continuous positive airway pressure (CPAP) treatment on glucose and insulin control, and the major role of adipose tissue and visceral obesity. We will further discuss the possible mechanisms by which OSA may contribute to metabolic dysregulation in light of the published evidence in humans and animal models, *i.e.* increased sympathetic activity, sleep fragmentation and intermittent hypoxia. This article will also refer to a European Respiratory Society Research Seminar held in Dusseldorf (Germany) from November 30–December 1, 2007 in conjunction with two EU COST (Cooperation in the field of Scientific and Technical Research) Actions on ''Cardiovascular risk in OSAS'' (B26) and ''Adipose tissue and the metabolic syndrome'' (BM0602).

PHYSIOLOGICAL AND CLINICAL DATA

Sleep and metabolism

OSA may affect metabolism indirectly, by decreasing the amount and/or quality of sleep. Sleep loss profoundly affects metabolic pathways [18]. In healthy subjects, experimental sleep restriction caused IR, together with increased evening cortisol and sympathetic activation [19]. Sleep restriction was also shown to be associated with reduced leptin and increased ghrelin plasma concentrations and increased appetite [20]. Modest acute sleep loss, such as selective slow-wave sleep deprivation, may alter glucose tolerance in normal subjects [21]. In general population cohorts, short sleep duration was associated with altered plasma levels of leptin [22, 23] and ghrelin [22] and increased body mass index (BMI) [22, 23]. In young adults, a prospective study found a significant risk of obesity in subjects reporting short sleep duration [24], leading to speculation that decreased sleeping time over the recent decades may have contributed to the increasing prevalence of obesity in the general population. In addition, in general population cohorts, difficulties falling asleep, difficulties in sleep maintenance and reduction in sleep duration have been found to be associated with an increased incidence of diabetes in males [25, 26].

The causal relationship between sleep duration and obesity is far from being proven [27–30], as shown by recent critical reviews or meta-analyses of published data in this field [27, 31, 32]. Although cross-sectional studies from around the world show a consistent increased risk of obesity among short sleepers in children and adults [32], prospective data seem to fail to show this [33]. Causal inference is difficult due to lack of control for important confounders and inconsistent evidence of temporal sequence in prospective studies [27, 32]. Moreover, effect size and importance of sleep duration in comparison to other risk factors for obesity have been recently challenged [27, 34, 35]. However, causality is often difficult to establish in epidemiology owing to biological complexity and multiple interactions [36]. Moreover, a modest effect size, such as the average decrease in BMI by 0.35 units associated with one extra hour of sleep in the general population [32], may be unimportant on an individual basis but of major significance in public health [36]. From the available relative risk ratios and short sleep prevalence, YOUNG [36] calculated that 5–13% of the total proportion of obesity in children and 3–5% in adults could be attributable to short sleep.

The mechanisms that are possibly involved are of interest. Sleep deprivation has been found to induce a pro-inflammatory state, with increased release of interleukin (IL)-6 [37, 38] and production of IL-6 and tumour necrosis factor (TNF)-α by circulating monocytes [39]. Nuclear factor (NF)-κB activation has been identified as a molecular pathway by which sleep restriction may influence leukocyte inflammatory gene expression and the risk of inflammation-related disease [40]. The pro-inflammatory effects of sleep restriction may, at least partly, be mediated by stress activation, *i.e.* sympathetic and/or cortisol activation [41–43]. In addition, the group of KNUTSON and VAN CAUTER [44] speculated that the adverse impact of sleep deprivation on appetite regulation is likely to be driven by increased activity in neuronal populations expressing the excitatory peptides orexins, which promote both waking and feeding [44–46].

In summary, sleep loss could affect metabolism *via* several mechanisms, but it is difficult to apply the currently available data to OSA. There are no studies specifically addressing the effects of sleep fragmentation (such as in OSA) on metabolism, as recently stated [47].

Association between sleep apnoea, glucose intolerance and diabetes

Early studies indicated a possible causal association between the presence of OSA and development of type 2 diabetes. However, most studies exhibited significant limitations including small sample size, highly selected populations, inadequate adjustment for confounders and use of surrogate markers of OSA [15]. Methods have also been highly variable among studies. Table 1 summarises current definitions used in clinical studies on glucose metabolism and the MetS [48–50].

Table 2 summarises the available epidemiological studies on the association of SDB with IR and diabetes [16, 51–62]. In general population studies [25, 63], snoring was shown to be a risk factor for the development of diabetes over 10 yrs independent of confounding factors. Importantly, two population cross-sectional studies including only lean subjects (BMI <25 kg·m^{-2}) found an independent association between frequent snoring and reduced glucose tolerance [56, 62]. Several other sleep anomalies have also been related to type 2 diabetes [25, 26, 63]. The relationship between self-reported sleep complaints and risk of diabetes may be less pronounced in females [63] than in males [25]. The Sleep Heart Health Study [16] (performed in 2,656 individuals) showed that sleep-related hypoxaemia was associated with glucose intolerance independently of age, sex, BMI and waist circumference. OSA severity was also associated with the degree of IR after

TABLE 1 Current definitions used in clinical studies

Fasting plasma glucose [48]
- Normal: <100 mg·dL^{-1} (5.6 mmol·L^{-1})
- Impaired fasting glucose: 100–125 mg·dL^{-1} (5.6–6.9 mmol·L^{-1})
- Provisional diagnosis of diabetes: $\geqslant 126$ mg·dL^{-1} (7 mmol·L^{-1})

Oral glucose tolerance test (75 g of glucose) [48]
- 2-h post-load glucose
  - Normal glucose tolerance: <140 mg·dL^{-1} (7.8 mmol·L^{-1})
  - Impaired glucose tolerance: 140–199 mg·dL^{-1} (7.8–11.1 mmol·L^{-1})
  - Provisional diagnosis of diabetes: $\geqslant 200$ mg·dL^{-1} (11.1 mmol·L^{-1})

Occult diabetes [48]
- Fasting plasma glucose $\geqslant 126$ mg·dL^{-1}
- Glucose $\geqslant 200$ mg·dL^{-1} 2-h post-oral glucose tolerance test challenge

Metabolic syndrome: Adult Treatment Panel III definition [49]
- Any three or more of the following criteria:
  1) Waist circumference >102 cm in males and >88 cm in females
  2) Serum triglycerides $\geqslant 1.7$ mmol·L^{-1}
  3) Blood pressure $\geqslant 130/85$ mmHg
  4) High-density lipoprotein cholesterol <1.0 mmol·L^{-1} in males and <1.3 mmol·L^{-1} in females
  5) Serum glucose $\geqslant 6.1$ mmol·L^{-1} ($\geqslant 5.6$ mmol·L^{-1} may be applicable)

Metabolic syndrome: World Health Organization definition [50]
- Diabetes, impaired fasting glucose, impaired glucose tolerance or insulin resistance (assessed by clamp studies) and at least two of the following criteria:
  1) Waist-to-hip ratio >0.90 in males or >0.85 in females
  2) Serum triglycerides $\geqslant 1.7$ mmol·L^{-1} or high-density lipoprotein cholesterol <0.9 mmol·L^{-1} in males and <1.0 mmol·L^{-1} in females
  3) Blood pressure $\geqslant 140/90$ mmHg
  4) Urinary albumin excretion rate >20 μg·min^{-1} or albumin-to-creatinine ratio $\geqslant 30$ mg·g^{-1}

adjustment for obesity. More recently, these data have been confirmed in the same cohort, and the association between SDB and impaired glucose metabolism was found to be similar in normal-weight and overweight subjects [61]. The Wisconsin Sleep Study (n=1,387) demonstrated a significant cross-sectional association between OSA and type 2 diabetes for all degrees of OSA, which persisted for moderate-to-severe OSA after adjustment for obesity (odds ratio 2.3) [56]. However, although the longitudinal data showed that OSA at baseline predicted the development of diabetes over 4 yrs, significance disappeared after adjusting for obesity [56]. Finally, OSA was recently found to be independently associated with decreased insulin sensitivity in a population-based sample of females investigated with full-polysomnogram (PSG) and insulin sensitivity index (ISI) calculated from the results of an oral glucose tolerance test [62].

Similar data have been obtained in samples of OSA patients (tables 3 and 4) [64–80], with a large prevalence of positive [63, 64–79] rather than negative [78–80] studies. In clinical populations, OSA patients characterised by full-PSG were significantly more likely to have impaired glucose tolerance (IGT) and diabetes than subjects free of OSA syndrome (OSAS) [71]. The relationship between SDB and impaired glucose–insulin metabolism was independent of obesity and age [71]. A number of reports found increased IR and IGT in OSAS patients, independent of body weight [68–70, 75], and a worsening of IR with increasing apnoea/hypopnoea index (AHI) [54]. However, other studies failed to demonstrate an independent effect of AHI owing to the major impact of obesity [64, 65, 80]. Excessive daytime sleepiness (EDS) may also be of importance, as underlined by the recent findings that hyperglycaemia and IR only occurred in OSA patients presenting with EDS [77].

It may be concluded, in agreement with TASALI and IP [9], that despite the abundance of cross-sectional evidence for the link between OSA and abnormal glucose control, further well-designed longitudinal and interventional studies are clearly needed to address the direction of causality.

OSA and the metabolic syndrome

According to clinical and epidemiological studies, the cluster of risk factors known as the MetS is associated with increased risk for diabetes, cardiovascular events and mortality in the general population [12]. Although the definition of the MetS is still under debate [81–83], IR is considered as the major metabolic abnormality, and is usually associated with an increased amount of visceral (dysfunctional) fat [84]. The World Health Organization definition of the MetS is based on the direct measurement of IR (table 1) [50]. Another definition (National Cholesterol Education Program–Adult Treatment Panel (ATP) III) is based on simple clinical findings (abdominal obesity, dyslipidaemia, hypertension and increased plasma glucose), and is easily applicable as it does not require tests to be performed in a specialised environment (table 1) [49]. Finally, the definition proposed by the International Diabetes Federation shares many features with the ATP III definition, but defines the cut-offs for waist circumference according to ethnicity [85], thus accounting for differences in body habitus between Caucasian and Asian populations. All these definitions should be considered as ''in progress'' and subject to

TABLE 2 Epidemiological studies on insulin resistance (IR) and metabolic syndrome (MetS) in sleep disordered breathing (SDB)

First author [ref.]	Sample	Age yrs	FBG mg·dL^{-1}	Insulinemia/ HOMA	BMI kg·m^{-2}	Waist-to-hip ratio	Comments
GRUNSTEIN [51]	Suspected OSA (n=864): Low risk 43% High risk 57%						Cross-sectional study. Higher FBG, SBP and DBP in obese subjects at high risk for OSAS
ELMASRY [52]	General population (n=2668 males):						Longitudinal study (10-yr follow-up). Incidence of diabetes mostly explained by obesity, but snoring seems to cause additional risk
	Snorers (14.7%)	47			25.5		
	Nonsnorers (83.5%)	45			24.2		
ELMASRY [53]	116 hypertensive males:						Cross-sectional study. Mean AHI=10. Obesity and OSA may cause diabetes; OSA could affect FBG and plasma insulin independent of obesity
	Normal FBG (n=83)	61±10	86±7	10±6	27	1	
	IGT (n=8)	55±8	102±4	12±7	30	0.99	
	Diabetes (n=25)	61±8	134±41	16±7	29	1.02	
PUNJABI [54]	150 males from the general population:			HOMA			Cross-sectional study. AHI correlated with BMI but not with waist-to-hip ratio or body fat (%). IGT and IR associated with OSA severity independent of obesity; metabolic alterations appear before OSA symptoms
	AHI <5 (n=57)	58±9	99±13	62±39	30±3	0.96	
	AHI 5–15 (n=39)	59±8	104±22	71±50	30±3	1.00	
	AHI 15–30 (n=37)	59±8	102±15	76±44	31±3	0.98	
	AHI >30 (n=17)	59±8	111±25	92±43	33±2	1.00	
AL-DELAIMY [55]	Nurses' Health Study (n=69852):						Longitudinal study (10-yr follow-up). Snoring associated with high risk for diabetes, independent of degree of obesity
	Nonsnorers 26%	50			24	0.77	
	Occasional snorers 65%	53			25	0.78	
	Habitual snorers 9%	53			28	0.81	
PUNJABI [16]	Sleep Heart Health Study: (n=2656)	68			27.4		Cross-sectional study. FBG and IGT associated with OSA; hypoxaemia during sleep rather than AHI predicted IGT
REICHMUTH [56]	General population (Wisconsin Sleep Cohort, n=1387):						Cross sectional and longitudinal study. High prevalence of diabetes in subjects with OSA, but causal relationship unclear (significance lost after adjusting for body habitus)
	Non-OSA 77%	48	30#		28		
	Mild OSA 14%	52	11#		32		
	Moderate-to-severe OSA 9%	52	17#		34		
SHIN [57]	General population (n=2719):						Trend to increased risk for IGT and IR in snorers compared with nonsnorers
	Nonsnorers 86%	51	88.3	6.5	23		
	Snorers 14%	51	88.6	6.4	24		
LAM [58]	General population (n=1612 questionnaires, n=255 PSG):						Cross-sectional study. OSA associated with several components of the MetS including IR
	Non-OSA (n=160)	42	91.3		24		
	OSA (n=95)	45	98.5		27		
JOO [59]	General population (Korean Health and Genome Study, n=6981):						Cross-sectional study. Snoring associated with increased risk for elevated HbA1c in males before age 50 yrs and in premenopausal females
	Nonsnorers (n=1224 males/n=1706 females)	53/51	87/86	5.5/5.5¶	23/23		
	Simple snoring (n=1622 males/ n=1574 females)	51/52	89/86	5.6/5.6¶	24/24		
	Habitual snoring (n=516 males/ n=339 females)	51/56	89/87	5.6/5.7¶	24/24		

TABLE 2 Continued

First author [ref.]	Sample	Age yrs	FBG mg·dL^{-1}	Insulinemia/ HOMA	BMI kg·m^{-2}	Waist-to-hip ratio	Comments
ONAT [60]	General population (n=1946):			MetS +ve similarly distributed among OSA +ve and OSA -ve males increased prevalence of MetS in OSA +ve than OSA –ve females			Cross-sectional study. MetS in males with OSA explained by abdominal obesity, IR not significant. MetS in females with OSA associated with smoking and CHD
	Males (n=944) Females (n=102)	54					
SEICEAN [61]	Sleep Heart Health Study (n=2588):		FBG/OGTT				Cross-sectional study. Magnitude of association of SDB with alterations of glucose metabolism similar in nonobese and overweight/obese subjects
	Non-overweight controls (n=643)	66	93/116		23		
	Non-overweight OSA (n=209)	75	92/119		23		
	Overweight/obese controls (n=873)	66	96/128		28		
	Overweight/obese OSA (n=1036)	68	100/136		30		
THEORELL-HAGLOW [62]	Females from Uppsala (Sweden) general population (n=7051 questionnaires, n=400 PSG):						OSA independently associated with decreased insulin sensitivity in females
	Controls (n=134)	43	5.2 mmol·L^{-1}	6.4	25	0.83	
	Mild OSA (n=131)	51	5.5 mmol·L^{-1}	7.5	26	0.85	
	Moderate (n=93)	55	5.5 mmol·L^{-1}	8.8	28	0.87	
	Severe (n=42)	58	6.1 mmol·L^{-1}	10.1	31	0.9	

Data are presented as mean ± SD, unless otherwise stated. FBG: fasting blood glucose; HOMA: homeostasis model assessment; BMI: body mass index; OSA: obstructive sleep apnoea; IGT: impaired glucose tolerance; AHI: apnoea/hypopnoea index; PSG: polysomnogram; OGTT: oral glucose tolerance test; SBP: systolic blood pressure; DBP: diastolic blood pressure; OSAS: OSA syndrome; Hb: haemoglobinCHD: coronary heart disease; +ve: positive; -ve: negative. #: diabetes (%); ¶: HbA1c (% + subjects).

change based on the evidence provided by current and future studies.

The MetS can be explained by viewing abdominal adipose tissue as an endocrine organ (see below), releasing into the circulation excess harmful free fatty acids (FFA), angiotensin II and adipokines. Increased blood FFA inhibits the uptake of glucose by muscle. Because excess FFA and angiotensin II damage the pancreas, insulin release is not sufficient to counteract hyperglyacemia, resulting in IR [86]. The most prevalent form of this group of metabolic abnormalities linked to IR is found in patients with abdominal obesity, especially with an excess of intra-abdominal or visceral adipose tissue [87]. It has been suggested that visceral obesity may represent a clinical intermediate phenotype, reflecting the relative inability of subcutaneous adipose tissue to clear and store extra energy resulting from dietary triglycerides, thus leading to fat deposition in visceral adipose depots, skeletal muscle, liver, heart, *etc*. Thus, visceral obesity may be both a marker of a dysmetabolic state and a cause of the MetS [87].

MetS is often found in OSAS patients (table 5) [10, 58, 65, 74, 75, 88–92]. However, the relative role played by OSA and obesity in the pathogenesis of MetS remains uncertain. Prevalence of the MetS is higher in patients with OSAS than in the European general population (15–20%) or in obese subjects without OSAS [81]. In subjects with SDB, prevalence rates ranged from 19% in Korean snorers [57] to 87% in OSA patients from the UK [10]. The risk of developing the MetS increased with severity of SDB in Western as well as Eastern populations [17, 58, 69, 73, 88–91, 93]. The studies published to date agree on the estimate of a five-fold (or higher) risk of MetS in OSAS patients compared with controls.

Most studies found a significant association between MetS and AHI, while the association with intermittent hypoxaemia was weak or absent. This result is at variance with the data obtained in animal models, which suggest a role of intermittent hypoxaemia in metabolic alterations (see below). In OSAS patients, apnoea or desaturation indexes showed stronger correlation with the amount of visceral fat than with

TABLE 3 Clinical studies on insulin resistance (IR) in obstructive sleep apnoea (OSA): positive studies

First author [ref.]	Sample	Age yrs	FBG mg·dL^{-1}	Insulinaemia/ HOMA	BMI kg·m^{-2}	Blood pressure	Weight	Waist-to-hip ratio	Comments
KATSUMATA [66]	OSAS patients: (males, n=42; females, n=6)								Previously unknown diabetes in 38%; IGT in 35% of patients
TIIHONEN [67]	Obese subjects (n=18)	51			34.7				ODI and age predicted IR
STROHL [68]	386 males with suspected OSA	47	94 (diabetics excluded)	14	30	Mean 89±11			BP, insulinaemia and FBG significantly correlated with BMI and AHI
STOOHS [64]	Voluntary subjects (n=50)	44			27				IR and AHI significantly associated, but no correction for confounders
	Non-OSA (n=15)								
	OSA (35)								
VGONTZAS [69]	Males:								OSA is a risk factor for hyperinsulinemia possibly mediated by sympathetic activation. Plasma leptin increased with body fat
	OSA (n=14)	47	106±4	26±4	47±3	144/89			
	Obese non-OSA (n=11)	40	85±4	14±3	36±2	133/86			
	Controls (n=12)	45							
IP [70]	270 patients								IR independent of obesity indexes and correlated with SDB
	No OSA (n=85)	42	95±25	7±4/2±1	25±3	123/70	83	0.86	
	Mild OSA (n=59)	46	95±13	9±13/2±3	27±4	127/75	90	0.90	
	Moderate OSAS (n=48)	47	97±12	9±7/2±2	28±5	127/79	95	0.93	
	Severe OSAS (n=78)	46	100±12	16±34/4±8	30±5	131/79	99	0.93	
MESLIER [71]	491 males:								FBG, post-prandial blood glucose and IR increase with AHI
	No OSA (n=90)	50	93±2	11±1	27	29 HT			
	Mild OSA (n=140)	55	97±2	14±1	28	45 HT			
	Moderate OSA (n=79)	55	97±2	13±1	29				
	Severe OSAS (n=182)	58	102±20	17±1	31				
TASSONE [72]	57 patients:								More severe IR in OSA compared with non-OSA obese subjects after correcting for age, BMI and waist-to-hip ratio
	Obese OSA (n=30)	53	150#	1.0# mmol·L^{-1}	39			0.99	
	Obese controls (n=27)	48	135#	0.6# mmol·L^{-1}	39			0.94	
MAKINO [73]	OSA patients (n=213)								OSA associated with IR after correcting for visceral fat
	Mild (n=30)	55	7¶	7±2/2±1	25	37+			
	Moderate (n=98)	57	11¶	8±2/2±1	26	50+			
	Severe (n=85)	55	15¶	10±4/3±1	28	60+			
PELED [74]	98 males:								OSA significant variable for the severity of the MetS; AHI affects IR and MetS scores more than S_{a,O_2}
	Snorers (n=9)	48	88±10	24±12	26	1 HT			
	Mild OSA (n=9)	48	89±14	27±16	25	3 HT			
	Moderate OSAS (n=27)	56	102±42	42±17	29	11 HT			
	Severe OSAS (n=53)	56	109±43	50±39	31	30 HT			
MCARDLE [75]	Case–control study								IR found only in OSA. MetS: OSA +ve (n=5), Controls (n=1, nonsignificant)
	Non-OSA (n=21)	46	4.5 mmol·L^{-1}	5.0/1.0	28	120/73	97	0.96	
	OSA (n=21)	46	4.7 mmol·L^{-1}	8.0/1.7	28	122/71	98	0.96	

TABLE 3 Continued

First author [ref.]	Sample	Age yrs	FBG mg·dL^{-1}	Insulinaemia/ HOMA	BMI kg·m^{-2}	Blood pressure	Weight	Waist-to-hip ratio	Comments
KAPSIMALIS [76]	Males with suspected OSA (n=67):								Waist-to-hip ratio was the most significant determinant of HOMA-IR. OSA severity: NS§
	Non-OSA (n=15)	47	4.9 mmol·L^{-1}	14.3/3.2	29		103	0.95	
	Mild-to-moderate OSA (n=26)	51	5.0 mmol·L^{-1}	14.7/3.3	29		107	0.97	
	Severe OSA (n=26)	55	5.3 mmol·L^{-1}	15.2/3.6	31		114	0.97	
BARCELO [77]	OSA patients (n=44):								EDS in OSA associated with IR independent of obesity
	With EDS (n=22)	49	115	15.2/4.3	32	139/92			
	Without EDS (n=22)	50	103	8.6/2.3	31	147/93			
	Controls (n=23)	48	99	7.8/1.9	25	128/78			

Data are presented as mean±SE (VGONTZAS [69]), mean±SD (IP [70] and PELED [74]) or mean±SEM (MESLIER [71] and MAKINO [73]), unless otherwise stated. FBG: fasting blood glucose; HOMA: homeostasis model assessment; BMI: body mass index; OSAS: OSA syndrome; EDS: excessive daytime sleepiness; HT: hypertensive; IGT: impaired glucose tolerance; ODI: oxygen desaturation index; AHI: apnoea/hypopnoea index; SDB: sleep-disordered breathing; MetS: metabolic syndrome; Sa_{O_2}: arterial oxygen saturation: +ve: positive. #: post-oral glucose tolerance test; ¶: diabetes (%); +: HT %.

global obesity indexes, such as BMI [69], leading some authors to propose that OSAS should be considered as a component of the MetS [94]. However, the pathogenic mechanisms possibly leading from metabolic alterations to OSAS are still unclear. This is also illustrated by the fact that not all OSAS patients are obese, and not all obese subjects develop OSAS. Further studies with careful assessment of the amount and distribution of body fat are needed to better understand the pathophysiology of adipose tissue and its interaction with OSAS, taking into account the current progress in basic and clinical research on obesity.

Effects of OSA treatment

The effects of CPAP treatment on glucose metabolism have been evaluated in both nondiabetic and diabetic patients, as summarised in table 6 [78, 93, 95–109], and may provide some clues as to the relative role of OSA and obesity in the pathogenesis of metabolic alterations. Until 2003, there were very few clear results owing to methodological issues and various confounders [92]. In 2004, HARSCH *et al.* [99] reported that CPAP treatment for 2 days rapidly improved the ISI in nondiabetic patients and that the positive effects of CPAP persisted after 3 months of treatment. Conversely, ISI improved only slightly and after prolonged treatment in obese patients (BMI >30 kg·m^{-2}), suggesting that in the latter group insulin sensitivity is primarily determined by obesity and, to a lesser extent, by sleep apnoea [99]. In nondiabetic patients, increased blood glucose was found after 1 night of CPAP treatment, with a tendency to higher fasting insulin and resistance to insulin (*i.e.* homeostasis model assessment (HOMA)-IR) after CPAP [101]. Such an increase in blood glucose might be related to CPAP-associated increase in growth hormone [95, 97], leading to an increase in plasmatic FFA owing to growth hormone lipolytic effects and thus to reduced glucose utilisation by skeletal muscles.

CPAP treatment does not greatly affect the metabolic status of obese OSA patients. A randomised, placebo-controlled, blinded crossover trial comparing cardiovascular and metabolic outcomes after 6 weeks of therapeutic or sham CPAP reported no change in glucose, lipids, IR or the proportion of patients with MetS in obese males, while positive effects of treatment on blood pressure and EDS were clearly present in the therapeutic CPAP group [105]. Whether EDS is also a critical determinant of the response to CPAP treatment, as recently reported [77], needs further evaluation in randomised control trials of large samples.

The limited duration of randomised controlled studies in OSA patients could, at least partly, account for the nonsignificant effects of CPAP treatment on glucose metabolism found in most studies. An observational study in a highly selected sample of OSAS patients found improved insulin sensitivity in patients with good compliance to CPAP after 2.9 yrs of treatment [108]. Similarly, the Swedish Obesity Study reported a three-fold incidence of diabetes and hypertriglyceridaemia in patients with witnessed apnoeas compared to subjects with no OSA at 2 yrs follow-up [110]. Two studies reported that visceral fat decreased after CPAP treatment [103, 111] while a more recent study [93] found no change in IR or visceral fat after CPAP for 3 months. Therefore, large longitudinal studies

TABLE 4 Clinical studies on insulin resistance (IR) in obstructive sleep apnoea (OSA): negative studies

First author [ref.]	Sample	Age yrs	FBG mg·dL^{-1}	Insulinaemia/HOMA	BMI kg·m^{-2}	Blood pressure	Weight	Waist-to-hip ratio	Comments
DAVIES [78]	66 males:	47							Case–control study, similar IR in all groups
	Snorers (n=18)				31				
	OSA (n=15)				28				
	Controls (n=33)								
BARCELO [79]	65 males:								Stronger association of IR and MetS with obesity than with OSA
	Nonobese OSA (n=24)	50	105±11	9±3/2±1	26	128/79			
	Obese OSA (n=23)	47	113±24	14±5/4±2	35	136/88			
	Controls (n=18)	47	100±8	8±3/2±1	25	128/79			
GRUBER [65]	79 males:								OSAS independently associated with the MetS but not with IR. Waist circumference predicted MetS
	No OSA (n=41)	47	91±2	14±2/3±0	31	134/82	102		
	OSA (n=38)	51	106±5	21±3/6±1	36	147/83	114		
SHARMA [80]	Obese OSA (n=40)	42	122±44	11±8/62±47	30	139/88		1.0	Obesity major determinant of metabolic abnormalities
	Obese non-OSA (n=40)	43	113±32	9±6/48±34	29	135/87		0.9	
	Nonobese controls (n=40)	42	97±18	4±2/19±10	21	127/81		0.8	

Data are presented as mean±SD (BARCELO [79] and SHARMA [80]) or mean±SEM (GRUBER [65]). unless otherwise stated. FBG: fasting blood glucose; HOMA: homeostasis model assessment; BMI: body mass index; MetS: metabolic syndrome; OSAS: obstructive sleep apnoea syndrome.

focusing on different aspects of this complex topic are needed to assess the potential long-term effect of OSA treatment.

In type 2 diabetic patients with OSAS, several studies have assessed the impact of CPAP treatment on glycaemic control. Recent observational studies using continuous glucose monitoring techniques have reported positive effects of CPAP on glycaemic control, already present during the first night of treatment, as variability of glycaemic values decreased compared with baseline conditions [107]. DAWSON [109] found decreased glucose levels and variability without significant changes in haemoglobin (Hb)A1c levels. Conversely, BABU *et al.* [102] reported the results of 72-h continuous monitoring of interstitial glucose and measurements of HbA1c levels in 25 patients before and after 3 months of CPAP. Post-prandial glucose values were significantly reduced 1 h after treatment, and HbA1c level decreased in patients with abnormally high baseline HbA1c (>7%). Furthermore, in subjects who used CPAP for >4 h·day^{-1}, the reduction in HbA1c level was significantly correlated with CPAP use [102]. A retrospective study also confirmed a slight reduction in HbA1c in diabetic patients with OSA treated with CPAP [100]. However, obesity was likely to be a major confounding factor, since a randomised controlled trial comparing therapeutic (n=20) or placebo CPAP (n=22) for 3 months found no difference in terms of glycaemic control or IR in these patients [105]. In summary, a huge impact of obesity is also present in type 2 diabetic patients, which may offset the impact of CPAP [112, 113].

The effects of CPAP treatment on the MetS are controversial, as recently summarised in two reviews [9, 114]. A recent observational study in patients with severe OSAS reported decreased blood pressure and plasma cholesterol and improved HOMA index after 8 weeks of CPAP treatment in patients with good compliance to therapy; the estimated effect of CPAP over 10 yrs was a decrease in cardiovascular risk from 18.8% to 13.9% [106]. However, a randomised controlled study in patients with moderate-to-severe OSAS showed that IR or other MetS variables were unaffected after 6 weeks of effective CPAP [104]. Moreover, some studies suggested positive effects on plasma lipids after CPAP in patients showing a good compliance to treatment [106, 115, 116], while other studies found no effect of OSA treatment on plasma cholesterol or triglycerides [93, 104].

Other markers of glucose metabolism have been assessed in OSA patients, such as insulin growth factor (IGF)-1 and adiponectin. A high IGF-1 concentration is predictive of decreased risk of type 2 diabetes and impaired glucose tolerance [117, 118], whereas low IGF-1 concentrations were found to be associated with increased risk of cardiovascular disease [119]. The complex interactions between IGF-1, its binding proteins and insulin sensitivity promote IGF-1 as an important regulator of glucose homeostasis. While fasting insulin and blood glucose are subject to short-term changes, IGF-1 is a more stable variable subject to long-term regulation. In a population-based cohort, IGF-1 significantly increased after CPAP treatment [117]. However, in OSA patients' improvement in IGF-1 after CPAP was reported to occur only in patients presenting with EDS [76]. Adiponectin is known to counteract the effects of IR [120], and the effects of OSA treatment on adiponectin have been assessed with controversial results.

TABLE 5 Metabolic syndrome (MetS) in obstructive sleep apnoea syndrome (OSAS) patients

First author [ref.]	Sample	Waist cm	SBP mmHg	DBP mmHg	FBG mg·dL^{-1}	HDL mmol·dL^{-1}	TG mmol·dL^{-1}	MetS	Comments
Coughlin [10]	Suspected OSA:								OSAS associated with multiple
	Obese non-OSA (n=43)	103	131	86	82	1.3	1.6	35	cardiovascular risk factors. MetS: OR 9.1
	Obese OSA (n=61)	117	142	91	84	1.1	2.0	87	(95% CI 2.6–31.2)
Lam [58]	255 subjects from general population:								MetS prevalence 56% in mild OSA 54% in moderate OSA, 70% in severe OSA.
	Non-OSA (n=160)	(23)	(55)	(9)	(10)	(45)	(25)	21	Most frequent MetS components: waist
	OSA (n=95)	(69)	(33)	(23)	(23)	(63)	(46)	58	circumference, DBP, increased FBG. MetS: OR 5.3 (95% CI: 3.03–9.26)
Gruber [65]	79 subjects:								MetS: OR 5.9 (95% CI 2.0–17.6). IR
	Non-OSA (n=38)	102	134	82	102	1.3	1.7	24	not associated with OSAS
	OSA (n=41)	114	147	83	106	1.2	2.3	74	independent of obesity
Peled [74]	98 patients:								Increasing prevalence of the MetS with
	Snorers (n=9)	(67)	(13)		88	(0)	(22)	0	OSA severity; AHI affects IR and MetS
	Mild OSA (9)	(57)	(43)		89	(22)	(63)	11	score more than Sa,O_2
	Moderate OSA (n=27)	(82)	(41)		102	(39)	(48)	21	
	Severe OSA (n=53)	(91)	(58)		109	(47)	(68)	30	
Sasanabe [88]	907 subjects:								MetS associated with OSA severity.
	Controls (n=89)	(56)	(41)		(12)	49 mg·dL^{-1}	151 mg·dL^{-1}	22	In severe OSA MetS: OR 5.1
	OSA (n=819)	(84)	(50)		(12)	48 mg·dL^{-1}	189 mg·dL^{-1}	50	(95% CI 2.7–9.7) in males and OR 14 (95% CI 2.9–66.8) in females
Shiina [89]	Suspected OSA:								OSA associated with high risk for MetS
	Non-OSA (n=90)		128	80	91	1.39	1.77	16	
	OSA (n=94)		138	87	100	1.24	2.28	43	
Kono [90]	Case–control study	VFA/SFA							AHI predictive of number of MetS
	Non-OSA (n=52)	0.76	125 (15)	77	93 (10)	55 mg·dL^{-1}	117 mg·dL^{-1} (25)	4	components, BMI or Sa,O_2
	OSA (n=42)	0.89	131 (45)	77	111 (33)	50 mg·dL^{-1}	126 mg·dL^{-1} (48)	19	(nonsignificant)
McArdle [75]	Case–control study								IR found only in OSA, no additional
	Non-OSA (n=21)	97	120	73	4.5	1.2	1.0	1	cardiovascular risk factors
	OSA (n=21)	98	122	71	4.7	1.2	1.1	5	
Tkacova [91]	Cross-sectional								MetS associated with OSA severity.
	AHI <5 (n=28)	98	132	82	4.8	1.1	1.6	46	In severe OSA, MetS: 1.8 in
	AHI 5–30 (n=39)	104	138	85	5.0	1.1	1.6	51	mild-to-moderate OSA; 8.36 in
	AHI >30 (n=31)	119	144	88	5.8	1.1	2.1	77	severe OSA

The data in parenthesis are percentage of subjects, unless otherwise stated. SBP: systolic blood pressure; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL; high-density lipoprotein; TG: triglycerides; OSA: obstructive sleep apnoea; AHI: apnoea/hypopnoea index; VFA: visceral fat accumulation; SFA: sub-cutaneous fat accumulation; OR: odds ratio; CI: confidence interval; IR: insulin resistance Sa,O_2: arterial oxygen saturation; BMI: body mass index.

TABLE 6 Clinical studies on glycaemic control and insulin resistance (IR) in obstructive sleep apnoea syndrome (OSAS) patients before and after continuous positive airway pressure (CPAP) treatment

First author [ref.]	Sample	Mean age yrs	Measurement	Mean BMI kg·m^{-2}	Comments
SAINI [95]	OSAS (n=8)	43	FBG and insulinaemia	33	No change after 1 night of continuous CPAP
DAVIES [78]	Males (n=66):	47	Insulinaemia		No change after CPAP for 4 months
	No OSA (n=33)			31	
	Snorers (n=18)			28	
	OSA (n=15)			31	
BROOKS [96]	Male patients with OSA:		Hyperinsulinaemic		IR improved after CPAP for 4 months
	Mild (n=9)	51	euglycaemic clamp	42	
	Moderate (n=13)	52		42	
	Severe (n=9)	46		41	
COOPER [97]	OSA patients (n=6)	52	FBG, HbA1c	38	No change after 2 nights of continuous CPAP
SAARELAINEN [98]	OSA patients (n=7)	34–60	Insulin suppression test	34	IR unchanged after CPAP for 3 months
HARSCH [99]	OSA patients (n=40)	54	Hyperinsulinaemic euglycaemic clamp	33	IR improved after 2 days of CPAP in nonobese patients, and after 3 months in obese patients
HASSABALLA [100]	Diabetic OSA patients (n=38)	53	HbA1c	42	Decreased after >4 months of CPAP
CZUPRYNIAK [101]	Nondiabetic OSA patients (n=9)	53	Continuous glucose monitoring system, FBG, OGTT	35	Worsened glucose metabolism after CPAP for 1 night
BABU [102]	Diabetic OSA patients (n=24):		Continuous glucose monitoring for 72 h, HbA1c		IR improved after CPAP for 3 months, especially if good compliance and baseline values out of control
	CPAP <4 h (n=12)	52		45	
	CPAP >4 h (n=12)	49		41	
TRENELL [103]	OSA patients (n=29):		FBG, fasting insulin, HOMA		Unchanged IR after CPAP for 12 weeks
	Regular CPAP (n=19)	49		36	
	Irregular CPAP (n=10)	51		32	
COUGHLIN [104]	Newly diagnosed OSA (n=34)	49	FBG, HOMA index	37	No change after CPAP for 6 weeks (RCT)
WEST [105]	Diabetic OSA patients (n=42):		HOMA index, HbA1c		No change after CPAP for 3 months (RCT)
	Placebo (n=22)	55		37	
	CPAP (n=20)	58		37	
DORKOVA [106]	Severe OSA patients with MetS (n=32)	54	HOMA	35	IR improved after CPAP for 8 weeks in patients using CPAP for >4 h·night^{-1}
PALLAYOVA [107]	Diabetic OSA patients (n=14)	54	Continuous glucose monitoring, FBG, HbA1c	37	Decreased nocturnal glucose variability during CPAP application
SCHAHIN [108]	9 OSA patients out of 31 previously studied	59	Hyperinsulinaemic euglycaemic clamp	31	IR improved after CPAP for 2.9 yrs, but highly selected sample
VGONTZAS [93]	OSA patients (n=16)	48	FBG, insulinaemia	37	No change after CPAP for 3 months
	Obese controls (n=15)	45	HOMA	35	
	Nonobese controls (n=13)	41		27	
DAWSON [109]	Diabetic OSA patients (n=20)	60	Continuous glucose monitoring system, HbA1c	40	Decreased nocturnal glucose variability during CPAP application, unchanged HbA1c

BMI: body mass index; OSA: obstructive sleep apnoea; MetS: metabolic syndrome; FBG: fasting blood glucose; Hb: haemoglobin; OGTT: oral glucose tolerance test; HOMA: homeostasis model assessment; RCT: randomised controlled trial.

Some studies found increased adiponectin after 1 night [121] or 2 weeks [122] of CPAP treatment, while other studies found no change in adiponectin levels after OSA treatment for 1 night [123] or 1–3 months [93, 124, 125].

It is possible that OSA treatment may positively affect only some MetS components, rather than affecting all of them [110, 115]. The available results need further confirmation. There is a strong need for controlled prospective studies, to evaluate

whether some patient subgroups might especially benefit from the effects of CPAP treatment on metabolic variables [14].

OSA and glucose metabolism in paediatrics

Children and adolescents represent a very important clinical population since epidemic obesity in paediatrics is a major health concern [125, 126] and is associated with high MetS prevalence [127], although the real relevance of the MetS in adolescents is currently under discussion [128]. In addition, children classically represent a good clinical model for examining the relationship between SDB and glucose metabolism with limited coexistent comorbidity, even though differences between adult and paediatric OSA may have become smaller due to the current high prevalence of obesity at a young age [129]. The causal role of SDB in paediatric metabolic abnormalities is currently unclear, as indicated in a recent review [130].

In the general population, SDB in children seems to be associated with MetS [131]. In the Cleveland Cohort [131], after adjusting for age, race, sex and preterm status, children with SDB had a 6.49 increased odds of MetS compared with children without SDB [131]. Approximately 25% of the sample was overweight and 19% had MetS. In clinical samples of obese children, SDB was found to correlate with fasting insulin levels independent of BMI [132, 133]. This has been challenged among children with suspected SDB, in whom IR and dyslipidaemia seem to be determined primarily by the degree of body adiposity rather than by the severity of SDB [134, 135]. In nonobese children, severity of SDB was not a significant predictor of fasting insulin or HOMA index values [136].

As for adipokine levels in children with SDB, obesity appeared as the primary determinant although SDB and associated hypoxaemia may contribute to elevated leptin levels [137]. In a recent study conducted in obese and nonobese children, GOZAL *et al.* [138] showed that SDB was associated with altered lipid homeostasis and systemic inflammation. In the presence of obesity, SDB also affected glucose metabolism through reduction in insulin sensitivity, independent of obesity [138]. Therefore, in obese children there could be an interaction between increased adiposity and SDB to promote and amplify IR.

Few data have been obtained in children on the effects of treatment for OSA on metabolic abnormalities. A small study reported a slight improvement in plasma high-density lipoprotein cholesterol after adenotonsillectomy, but no major changes in insulin level [135]. Leptin and sympathetic markers were found to be increased at baseline in children with SDB compared to simple snorers, and decreased after CPAP treatment for 3 months [139]. However, IR was unaffected by treatment [139]. Also, no change was shown in insulin level or HOMA index compared to baseline measurements in a sample of Greek children after adenotonsillectomy [140].

In summary, the field of SDB and its metabolic consequences together with its interaction with obesity is rapidly developing, but uncertainties remain significant as highlighted by recent reviews and editorials [141–143].

MECHANISMS AND EXPERIMENTAL DATA

Role of adipose tissue and visceral obesity

White adipose tissue is considered to be a key endocrine and secretory organ that releases a large number of adipokines with a major link to inflammation and immunity. The paradigm shift in adipose tissue biology was initiated in 1994 by the discovery of leptin [144]. Subsequently, a growing number of proteins, peptides and other factors released from white adipocytes, collectively termed adipocytokines, have been described [145]. Most of these adipocytokines are linked to inflammation and their production is increased in obesity. To date, only adiponectin is known to exert anti-inflammatory and anti-diabetic activity, and is reduced in obesity and type2 diabetes [146, 147].

Human obesity is characterised by increased rather than low leptin production. In OSAS patients, several studies reported increased leptin levels compared to weight-matched controls [69, 148–152], which correlated with OSA severity [148, 150, 151] and decreased after CPAP [111, 148, 153, 154]. Similar results were recently reported in paediatric OSA [139]. Therefore, OSA may exert an independent effect on leptin levels, causing leptin resistance, possibly through hypoxia, which acts by increasing leptin gene transcription [155].

Adipose tissue inflammation is thought to play a key role in the development of MetS, type 2 diabetes and cardiovascular disease [156]. In 2004, TRAYHURN and WOOD [157] suggested that adipose tissue inflammation may represent a specific response to relative hypoxia in clusters of adipocytes that become distant from the vasculature as cell size increases. It has since been demonstrated that hypoxia occurs in adipose tissue of obese mouse models and triggers expression of inflammatory adipokines [158].

Hypoxia-induced factor (HIF)-1 plays a key role in the response to hypoxia in most tissues. Transcription factors such as NF-κB and CREB are downstream targets of HIF-1. The number of hypoxia-sensitive genes is continuously growing, and to date >70 genes have been described as targets of HIF-1. These genes include proteins involved in angiogenesis, cell proliferation, apoptosis and energy metabolism [159]. Hypoxia may increase expression and secretion of a variety of inflammation-related adipocytokines such as IL-6, macrophage migration inhibitory factor and vascular endothelial growth factor. Therefore, hypoxia is likely to affect adipocyte function and promote adipose tissue inflammation. This may play a critical role in obesity-related disorders and may trigger the development of peripheral resistance to insulin and thus promote the development of type 2 diabetes and the MetS. The relationship between HIF-1 and inflammation has been discussed in detail in another article of this series [160].

Analysis of secretory products from primary human adipocytes revealed that these cells release classical adipocytokines such as TNF-α, IL-6, leptin, and adiponectin, as well as newly discovered adipocytokines *i.e.* tissue inhibitor of metalloproteinases-1 and monocyte chemotactic protein (MCP)-1 [161]. MCP-1 was first described as a secretory product of monocytes and endothelial cells with a prominent role in arteriosclerosis but it is also associated with the obese state. MCP-1 exhibits IR-inducing capability in adipocytes and myocytes [162].

Increased expression and secretion of adipokines in obesity may be a marker of low-grade chronic inflammation in adipose tissue. Protein kinase C and IκB kinase (IKK) are two kinases known to

be involved in the inflammatory processes underlying IR. IKK influences insulin sensitivity, especially in skeletal muscle, by inhibiting insulin signalling by insulin receptor substrate-1 phopshorylation on serine residues and by activating NF-κB. In turn, NF-κB regulates production of pro-inflammatory cytokines such as TNF-α and IL-6 [163], and generates both hepatic and systemic inflammation as well as IR [164].

In summary, the adipose tissue in obesity shows abnormal function and evidence of hypoxia and inflammation. This might be worsened by the occurrence of apnoeas during sleep, with further hypoxia and inflammation. The relative role of obesity and OSA in the pathogenesis of metabolic alterations is still unclear and is being intensively studied both in clinical and experimental models.

OSA, oxidative stress, inflammation and adipose tissue

OSA cardiovascular and metabolic consequences are now viewed as a component of a systemic disease resulting from oxidative stress [165], and systemic and vascular inflammation [166–172]. Inflammation appears to be mostly confined to the vascular compartment, while systemic inflammation is often absent or mild. This may account for the variable level of C-reactive protein, which is often found not to be elevated in OSA patients without comorbidities [173, 174].

Obesity associated with OSA appears to be the strongest determinant of systemic inflammation [175]. Adipose tissue inflammation may play a critical role in OSA-associated morbidity [176], with peri-vascular adipose tissue especially contributing to the release of cytokines, TNF-α, pro-atherogenic chemokines, and pro-angiogenic peptides [177, 178] (fig. 1). Whether these factors contribute directly to alterations in the function and structure of the vascular wall and the development of atherosclerosis and cardiovascular complications in OSA remains to be studied.

Intermittent hypoxia

Intermittent hypoxia (IH) is considered the peculiar pathophysiological aspect of OSA and has been extensively studied in lean and obese rodent models. Recent reviews have

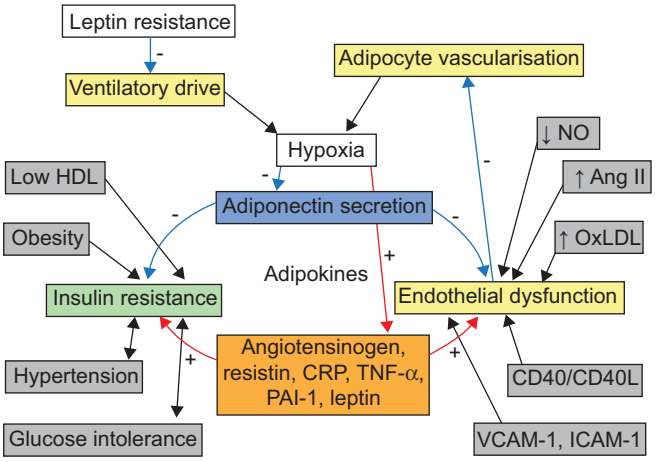

FIGURE 1. Effects of hypoxia on adipokines and their interactions with insulin metabolism and endothelial function. The main factors involved are leptin, angiotensinogen (Ang), resistin, C-reactive protein (CRP), tumour necrosis factor (TNF)-α and plasminogen activator inhibitor (PAI)-1. Leptin promotes (red arrows) insulin resistance and endothelial dysfunction, whereas adiponectin is protective (blue arrows). Obesity, a state of leptin resistance and endothelial dysfunction, also exhibits hypoxia, which is known to activate (red arrow) promoting adipokines and inhibit (blue arrows) adiponectin production. In OSA, obesity and night-time hypoxia might act synergistically in producing inflammation at the systemic and vascular level, and in promoting metabolic and cardiovascular dysfunction. HDL: high-density lipoprotein; OxLDL: oxidised low-density lipoprotein; CD40L: CD40 ligand; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: intercellular adhesion molecule-1; +: activation/promotion; -: inhibition/protection. Modified from [178].

summarised experimental and clinical data linking IH to cardiovascular and metabolic alterations [178]. Metabolic and atherosclerotic changes have been shown in mice exposed to chronic IH [179–183].

In the chronic IH model (35 days) in mice, both systemic and localised inflammation of small and large arteries occurred, with evidence of peri-adventitial localisation of T-cells infiltration highly suggestive of a critical role of the peri-adventitial fat in the IH-related vascular inflammation (C. Arnaud,

TABLE 7 Summary data on metabolic variables in studies on the effects of intermittent hypoxia (IH) in lean and obese mice

IH exposure	Fasting blood glucose	Fasting insulin	Insulin sensitivity-fasting (HOMA index)	Glucose tolerance or euglycaemic hyperinsulinaemic clamp#	Plasma TG/TC/PL	Liver content TG/TC/PL
Lean mice						
Acute	↑[185]	=[185]	↓[185]	↓[185]		
Short term	↓[189]	=[189]	↑[189]	↑[189]	↑/↑/↑[179]	↑/=/=[179]
Long term	↑[189]	↓[188]	↓[189]		↑/↑[192]	↓/↓/↓[192]
Ob/Ob mice						
Short term	=[189]	↑↑↑[189]	↓↓↓[189]	↓↓↓[189]	=/=/=[179]	=/=/=[179]
Long term	=[189]	↑↑[189]	↓↓[189]	↓↓[189]	=/=/=[189]	↑/=/↑[189]
High-fat fed mice						
Long term	↓[191]	↓[191]	=[191]		=/=/NA[191]	=/↑/NA[191]

The arrows indicate the direction of change (increase or decrease) of each parameter in mice exposed to IH. Numbers indicate reference. HOMA: homeostasis model assessment; TG: triglyceride; TC: total cholesterol; PL: phospholipids; Ob: genetically obese; NA: not available. ↑: increase; ↓: decrease; =: no change. #: glucose load by intraperitoneal glucose tolerance test or euglycaemic hyperinsulinaemic clamp.

University of Grenoble, Grenoble, France; personal communication). Indeed, this does not rule out haemodynamic factors as, in another study in mice [180], platelet endothelial cell adhesion molecule-1, a marker of the endothelial cell, was decreased at both the heart and aorta level with a specific gradient, without loss of endothelial cells, possibly indicating a role for shear forces applied to the heart and aorta. Thus, vascular remodelling may result from either haemodynamic or inflammatory changes, or both. From these studies and others already published [166, 179, 183–185], strong interactions are likely to occur in response to chronic IH between haemodynamic alterations, systemic inflammation and metabolic changes, and modulated by genetic background [178, 182]. Inflammation may largely contribute to glucose homeostasis dysregulation.

Indeed, from a metabolic perspective, several pieces of evidence support a role for IH in the metabolic alterations seen in OSA. Exposure of lean mice (C57BL/6J) to IH for 5 days increased serum cholesterol and phospholipids levels, up-regulated triglycerides and phospholipid biosynthesis, and inhibited cholesterol uptake in the liver [179]. These effects may be mediated through HIF-1 activation for triglycerides and the post-transcriptional regulation of lipid biosynthesis (sterol regulatory element binding protein-1) but not for serum cholesterol levels [186].

IH may result in acute IR in otherwise lean, healthy animals, and the response is associated with decreased glucose utilisation of oxidative muscle fibres, independent of autonomic nervous system activation [185]. The magnitude of metabolic alterations may also depend on the severity of IH [184]. However, in contrast to the persistent effects of chronic IH on sympathetic activity and blood pressure, the effects of IH on glucose homeostasis appear to be limited to the periods of hypoxic exposure [187]. Moreover, combining IH exposure and glucose infusion amplified the alteration of blood glucose diurnal rhythm and led to high rates of apoptosis in β-cells [187]. The overall effects of IH on glucose homeostasis are summarised in table 7 [179, 185, 188–192], and appear highly complex, in part, because IH causes loss of weight in lean animals, which counteracts IR. However, these data support the findings in humans suggesting a synergistic effect of increased adiposity and SDB in promoting metabolic dysfunction. Finally, it should be reminded that sleep fragmentation and intermittent hypoxia may also interact in modulating glucose homeostasis in animal models as well as in OSA, but the effects of sleep fragmentation are extremely difficult to study, even in animal models [182].

A recent area of investigation is the potential role of IH as a ''second hit'' stimulus for the transition from hepatic steatosis to nonalcoholic steatohepatitis (NASH) [190–192]. Recent studies in mice exposed to chronic IH would support this possibility, since animals fed a regular diet developed mild liver injury, while animals fed a high-fat diet showed evidence of inflammation and fibrosis of the liver [191]. In both groups, there was evidence of hepatic oxidative stress. NASH is likely to be associated with hepatic IR and this may further contribute to glucose homeostasis dysregulation. This topic is still largely unexplored in the clinical context, since few studies to date have examined hepatic function in OSA patients. The available data suggest that at least some patients, both adults and children, may show evidence of hepatic dysfunction correlated with the severity of nocturnal IH [193, 194].

CONCLUSIONS

Alterations in sleep quantity or quality may affect glucose metabolism. However, although cross-sectional studies from around the world show a consistent increased risk of obesity among short sleepers in children and adults, large prospective studies are needed. In addition, in SDB, despite the abundance of cross-sectional evidence for the link between OSA and abnormal glucose control, further well-designed longitudinal and interventional studies are clearly needed to address the direction of causality. The available evidence also suggests that CPAP has little or no effect on the metabolic status of obese subjects, presumably owing to the major impact of visceral obesity. However, recent data obtained in diabetic OSA patients by using the technique of continuous monitoring suggest that CPAP treatment may improve glycaemic control. Thus, the synergistic negative effects of obesity and SDB represent a major research challenge, as shown by the complex picture emerging from studies in animal models. The interaction between hypoxia and metabolism possibly involves stress activation, oxygen radical production, and multiple cellular pathways (NF-κB, HIF and apoptosis) and cell types (inflammatory cells, vascular endothelium, adipocytes). There is a potential role for adipose tissue inflammation both regarding vascular remodelling and metabolic dysfunction. Clinical and translational research is urgently needed in this field.

STATEMENT OF INTEREST

None declared.

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