Review

Overcoming sleep disordered breathing and ensuring sufficient good sleep time for a healthy life expectancy

By Kazuo CHIN*1,†

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Abstract: Recent advances in basic and clinical medicine have resulted in major improvements in human health. Currently sleep has been considered an essential factor in maintaining and promoting a healthy life expectancy. Sleep disorders include more than 60 diseases. Sleep disordered breathings (SDB) have 17 disorders, including sleep apnea. SDB usually induces hypoxemia and hypercapnia, which would have significant effects on cells, organs, and the whole body. We have investigated SDB for nearly 35 years. We found that SDB has significant associations with humoral factors, including coagulation systems, the body’s protective factors against diseases, and metabolic and organ diseases. Currently we have been giving attention to the associations among SDB, short sleep duration, and obesity. In addition, SDB is important not only in the home but under critical care such as in the perioperative stage. In this review, I would like to describe several aspects of SDB in relation to systemic diseases and overall health based mainly on our published reports.

Keywords: sleep, sleep disordered breathing, sleep apnea, intermittent hypoxia, sleep duration, noninvasive ventilation

Introduction

It was reported in the International Classification of Sleep Disorders-3 (ICSD-3) that there are 7 groups of sleep disturbances: insomnia, sleep related breathing disorders (SRBD or Sleep disordered breathing: SDB), central disorders of hypersomnolence, circadian rhythm sleep wake disorders, parasomnias, sleep related movement disorders, and other sleep disorders.1) There are more than 60 sleep disorders under the category of “sleep disturbances”. Seventeen of those are SDB and include obstructive sleep apnea, central sleep apnea, sleep related hypoventilation disorders, etc. (Table 1 and Fig. 1). SDB usually induces hypoxemia and hypercapnia, which would have significant effects on cells, organs, and the whole body.2) In addition to SDB, we should pay attention to the tendency of short sleep duration that has arisen in recent years because short sleep duration has significant effects on general, cardiovascular, metabolic, and mental health, immune function, human performance, pain, and mortality.3) It said that the combination of systemic diseases and SDB increases the risk of mortality.4)

Abbreviations: AHI: apnea and hypopnea index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BMR: basal metabolic rate; COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; CT: computed tomography; HIF-1: hypoxia-inducible factor; ICD-3: The International Classification of Sleep Disorders; IH: intermittent hypoxia or hypoxemia; L-PGDS: lipocalin-type prostaglandin D synthase; MetS: metabolic syndrome; NASH: nonalcoholic steatohepatitis; NFκB: nuclear factor-kappa B; NIPPV: nasal mask intermittent positive pressure ventilation; NIV: noninvasive ventilation; NPPV: noninvasive positive pressure ventilation; ODI: oxygen desaturation index; OHS: obesity hypoventilation syndrome; OSA: obstructive sleep apnea; PaCO2: arterial partial pressure of carbon dioxide; PSG: polysomnography; REM: rapid eye movements; SDB: sleep disordered breathing; SFA: subcutaneous fat accumulation; SH: sustained hypoxia or hypoxemia; SpO2: percutaneous oxygen saturation; SRBD: sleep related breathing disorders; SRHD: sleep related hypoventilation disorders; TNFα: tumor necrosis factorα; VFA: visceral fat accumulation.

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Recent data showed that during a 17-year period (1993–2010), survey reports of a diagnosis of sleep apnea increased 14.6 fold, from 420,000 to 6.37 million per year (P \( \leq 0.0002 \)) in the U.S.\(^5\) In addition, more than 400,000 patients with obstructive sleep apnea (OSA) are treated by continuous positive airway pressure (CPAP) under the health insurance system in Japan, and the number of CPAP patients has increased by 40,000 per year in the past 3 years. Thus, since the prevalence of SDB, short sleep duration, or other sleep disturbances such as insomnia is high, we should promote research on the effects of not only SDB or short sleep duration itself but the effects of combinations of systemic diseases and sleep-related problems on overall human health (Fig. 2).

From the end of the 1970s’, patients’ breathing, arterial saturation, and transcutaneous PCO\(_2\) (P\(\text{teCO}_2\)) during sleep could be monitored noninvasively.\(^6\) Then from the beginning of the 1980s we could also noninvasively measure breathing during sleep. When we began to monitor patients’ breathing during sleep, we were truly surprised at the irregularity of breathing with severe hypoxemia with or without hypercapnia during sleep and that their blood gases worsened greatly compared to awake levels (Figs. 1 and 3). From that time, we began to study and manage patients with SDB including OSA, central sleep apnea, and sleep-related hypoventilation disorders.\(^1\)

1. SDB including OSA in Japan at the first stage of research and as a clinical issue: small number of polysomnography (PSG) cases that could be studied in our hospital

When we began to study SDB, it was suggested that there would be few patients with OSA in Japan because obesity, which is the most important factor in OSA, is much less prevalent compared with Western countries. But it was known that East Asians could easily develop OSA because of their genetically-determined facial skeleton.\(^7,8\) From our cohort data (\( n = 322, \) all males, mean age 43.8 \( \pm 8.4 \) (SD) y, BMI 23.7 \( \pm 3.1 \) kg/m\(^2\)), the prevalence of moderate to severe OSA that should be treated has reached almost 20% among middle-aged males in the general population.\(^9\)

When we began to study SDB at the end of the 1980s, it began to be recognized that the rate of mortality was increased in untreated patients with OSA syndrome and that patients with OSA are at an increased risk of cardiovascular events.\(^10,11\) We did not have PSG technicians and could perform PSG only once weekly, while the number of PSG cases in a week was over 20 in Western universities. In that era in Japan, doctors usually prepared all the instruments for PSG during the day and night, applied several monitors to patients with SDB, and observed the patients who were being monitored all night. Therefore, the next day, the doctors were very sleepy, even if they did not have SDB. Since the number of patients with SDB for whom we could do PSG and include in our clinical studies was small under such a research environment, I was determined to find parameters that had significant associations with events of cardiovascular diseases that not been researched yet in Western countries using unique but not so complex methods.

From the end of the 1980s to the middle of the 1990s, hypertension, which is one of the most important factors in cardiovascular diseases, has been given attention by researchers in OSA.\(^12,13\) I hit

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ICSD-3: International Classification of Sleep Disorders 3rd edition
upon the idea that the blood coagulation system, which is one of the most important pathophysiological systems\textsuperscript{14),15}) and must be correlated with the occurrence of cardiovascular attacks, had not been studied in OSA. Next, it was necessary for me to determine how to identify the associations between OSA and coagulation systems from the small number of OSA cases who were diagnosed by PSG. Since I saw all of the patients with OSA (but only one patient per week) at that time, I also hit upon the following idea: patients with OSA have increased water and salt excretion during sleep, which normalizes after treatment with continuous positive airway pressure (CPAP) treatment; therefore, before CPAP treatment, hemoconcentration may occur in patients with OSA in the morning. Ischemic heart events and cerebrovascular attacks are also more likely to occur in the morning than at other times of the day.\textsuperscript{16}) Taken together, in addition to hypoxemia, which induces tissue damage and systemic inflammation, several other important and deleterious factors may concomitantly occur in the morning in patients with OSA, the occurrence of which may be reduced after CPAP treatment. To test these hypotheses, we measured several parameters in the evening or at night before sleep and in the morning upon awakening in patients with OSA before and after CPAP therapy. The concentration of plasma fibrinogen and whole blood viscosity predicted by the hematocrit and total plasma protein increased significantly more in the morning compared with afternoon values (Fig. 4). These increases in plasma fibrinogen and whole blood viscosity in the morning disappeared after CPAP treatment (Fig. 4).\textsuperscript{17)}

Interestingly, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in patients with OSA also increased significantly in the morning from values in the previous afternoon. Differences in AST and ALT levels between the morning and afternoon decreased significantly following CPAP treatment.\textsuperscript{18) In addition, AST and ALT levels in OSA patients with abnormally high levels increased significantly overnight, changes that were significantly greater than in those with normal levels.\textsuperscript{18)} Therefore, the elevation in aminotransferase levels during the night would not be due to hemoconcentration but to other factors (probably due to OSA with hypoxemia), and there were significant correlations between serum aminotransferase levels in the morning and increases from afternoon values to those the next morning.
Fig. 2. Achieving a healthy life is affected by not only systemic diseases but sleep-related disturbances such as sleep disordered breathing (SDB), short sleep duration, and other sleep disturbances. Sleep apnea and related hypoventilation are representative diseases of SDB. Insomnia, shift work, etc. induce short sleep duration. SDB might also induce short sleep duration. The other sleep disturbances include several diseases. Each factor has interactions with several variables. To prolong a healthy life expectancy, sleep medicine would be needed in addition to conventional medicine. Solid lines show tighter interactions than dashed lines.

Sleep apnea related parameters

1. Apnea-hypopnea index: AH/1/h
2. Arousal index (/h)
3. Oxygen desaturation index (ODI) (/h): hypoxemia and reoxygenation a parameter of intermittent hypoxia (IH)
4. Minimum SpO2 (%)
5. Mean SpO2 (%)
6. %Time of SpO2<90% (%): sustained hypoxemia (SH)

Fig. 3. Trends in polysomnography (PSG) of a patient with obstructive sleep apnea. Parameters that show characteristics of sleep apnea: apnea and hypopnea index (AHI), number of episodes of apnea and hypopnea per 1 h sleep; arousal index, number of episodes of arousals per 1 h sleep; 3% or 4% oxygen desaturation index (ODI), number of episodes of a decrease in percutaneous oxygen saturation (SpO2) of at least 3% or 4% from the basal levels per 1 h sleep. ODI is one of the parameters for intermittent hypoxia; %Time of SpO2<90% was SpO2<90% per total sleep time, which is a parameter for sustained hypoxemia (SH).
That is, higher morning aminotransferase levels resulted in greater subsequent increases. Thus, OSA-related damage could easily occur in patients with liver dysfunction according to the severity of their liver dysfunction.

Recently, we found that in only males without visceral obesity, the percent sleep time with oxygen saturation <90%, in addition to body mass index (BMI), insulin resistance, and serum triglyceride values, was independently correlated with liver fat...
accumulation ($R^2 = 15.1\%$, $P < 0.001$) measured by computed tomography. In males, percent sleep time with oxygen saturation $<90\%$ was also a determining factor for AST values regardless of the visceral fat area. $^{19}$ Damage to the liver by OSA may be associated with one pathogenesis of nonalcoholic steatohepatitis (NASH), which is one of the most challenging diseases in recent hepatology.

Thus, it is now known that OSA induces oxygen desaturation, arousals, and intrathoracic pressure changes which can result in sympathetic activation, endothelial dysfunction, hypercoagulability, systemic inflammation, oxidative stress, and metabolic dysregulation ($\text{Fig. 6}$. $^{20,21}$) Patients with OSA can easily develop systemic hypertension, arrhythmias especially atrial fibrillation, heart failure, myocardial ischemia and infarction, stroke, and sudden death ($\text{Fig. 6}$. $^{21}$) Indeed, OSA has been newly recognized as a secondary cause of hypertension by the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. $^{22}$ It is said that about 50% of OSA patients are hypertensive and an estimated 30% of hypertensive patients also have OSA, often undiagnosed. $^{23}$ The prevalence of OSA that should be treated amounted to over 65% in patients with resistant hypertension. $^{24}$

OSA attacks not only organs but also protective factors associated with health. We have investigated the associations between OSA and several protective factors such as heat shock protein-72, $^{25}$ bilirubin, $^{26}$ thioredoxin, $^{27}$ and exhaled CO. $^{28}$ Interestingly, although blood heat shock protein-72 and exhaled CO levels increased in the evening or at night in OSA patients before sleep, heat shock protein-72 was shown to decrease from evening to morning ($\text{Fig. 7}$) and exhaled CO in a control group increased in the morning, but did not significantly change in the OSA group. Exhaled CO is derived from heme oxygenase-1, which is also known as heat shock protein 32. $^{26}$ The relative reduction in HO-1 and heat shock protein-72 might be a response to night-time stress by OSA. Since the levels of protective factors for health become relatively low in the morning, patients with OSA might be naïve to and have less protection from conditions that are more likely to occur in the morning, such as cerebro-cardiovascular diseases. Indeed, it has been reported that snoring, which is one of the most frequent symptoms in patients with

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**Fig. 6.** Obstructive sleep apnea (OSA) consequences and intermediate mechanisms that potentially contribute to risk of cardiovascular disease. The events associated with collapse of the upper airway lead to brain arousal, intrathoracic pressure changes, hypoxemia, and reoxygenation. Several intermediate mechanisms link OSA with the initiation and progression of cardiovascular diseases (CVD). Solid lines with arrows show tighter interactions than dashed lines. Obesity (especially visceral fat accumulation) also has a tight interaction with OSA and induces CVD through the almost same mechanism as OSA. $\text{NF-κB} =$ nuclear factor-kappa B, $\text{HIF} =$ hypoxia inducible factor, $\text{NASH} =$ nonalcoholic steatohepatitis.
OSA, was an important risk factor for stroke and adversely affects the prognosis in patients admitted to hospital with stroke.29)

2. Two types of hypoxemia with sleep apnea: intermittent and sustained hypoxemia

It is said that hypoxia plays critical roles in the pathobiology of heart disease, cancer, stroke, and chronic lung disease, which are responsible for 60% of deaths in the United States.2) Two broad patterns of hypoxemia (intermittent hypoxemia: IH, sustained hypoxemia: SH) have been recognized.30) Patients with OSA typically manifest short intermittent high-frequency hypoxemia (cyclical pattern of oxygen desaturation lasting 15–60 s followed by reoxygenation) that occurs for 6 to 8 h during sleep. In contrast, sustained or low frequency hypoxemia with oxygen saturation (SO₂) ranges to less than 90% and lasts from a few minutes to hours during sleep (Fig. 3).31) OSA-related high-frequency IH is characterized by cycles of hypoxemia with reoxygenation that is distinctly different than sustained low-frequency hypoxia and contributes to ischemia-reperfusion injury. Under conditions of reduced oxygen availability, hypoxia-inducible factor 1 (HIF-1) regulates the expression of genes that mediate adaptive responses. It was reported that IH results in the activation of nuclear factor-kappa B (NF-κB) with the downstream consequences of production of inflammatory genes such as tumor necrosis factor (TNF-α).32)

We have investigated the associations between IH or SH and several important parameters concerned with human health (Table 2).26),27),33)–37) The apnea and hypopnea index (AHI) was calculated as the number of episodes of apnea and hypopnea per 1 h of sleep. Oxygen desaturation index (ODI) was calculated as the number of episodes of a decrease in percutaneous oxygen saturation (SpO₂) of at least 3% or 4% from basal levels per 1 h of sleep. AHI and ODI were the parameters of IH. %Time of SpO₂ <90% was SpO₂ <90% per total sleep time, which is a parameter of sustained SH. As shown in the Table 2, some parameters had significant associations with IH, some with SH, and the others with both IH and SH. In addition, patients with not only OSA but with OSA combined with other cardiovascular risk factors such as hypertension and diabetes simultaneously had increases in platelet aggregability.37)

Recently, we also reported associations between OSA and abdominal aortic diameters,38) abdominal aortic calcification,39) or microalbuminuria.40) Although these parameters had significant relation-
Table 2. Associations between several parameters and Intermittent (ODI or AHI) or sustained (%Time of SpO2 < 90%) hypoxia

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<thead>
<tr>
<th>Parameter</th>
<th>Intermittent Hypoxia (ODI, AHI)</th>
<th>Sustained Hypoxia %Time of SpO2 &lt; 90%</th>
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<tr>
<td>sICAM-1 (Ref. 33)</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Ghrelin (Ref. 34, 35)</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Thioredoxin (Ref. 27)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Adiponectin (Ref. 27)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>I-Bilirubin/HO-1 (Ref. 26)</td>
<td>-</td>
<td>+</td>
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<tr>
<td>GLP-1 (Ref. 36)</td>
<td>+</td>
<td>-</td>
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<td>Platelet Aggregation (Ref. 37)</td>
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Table 2: Associations between several parameters and Intermittent (ODI or AHI) or sustained (%Time of SpO2 < 90%) hypoxia.

- sICAM-1: soluble intercellular cell adhesion molecules, I-Bilirubin/HO-1: indirect bilirubin which is induced by heme-oxgenase-1, GLP-1: glucagon-like peptide-1, Vascular risk (+): patients with one or more risk factors for vascular diseases such as smoking, hypertension, diabetes mellitus or, hyperlipidemia, +: the association was significant, -: the association was not significant.

shions with cardiovascular morbidity, the associations between OSA and these parameters were complex because these parameters also had significant associations between age, obesity, hypertension, or diabetes. In addition, recent data showed that in patients with OSA combined with other lifestyle-related diseases such as hypertension, COPD, metabolic syndrome (MetS), etc., those diseases became resistant to treatment or were exacerbated if OSA is not treated.4)1).2)2) It is said that IH, intrathoracic pressure changes and arousals by OSA trigger consecutive mechanisms that might result in endothelial dysfunction and arterial diseases.4)2) We also have found that endothelial dysfunction progressed when patients with MetS had severe OSA.3)4) Furthermore, IH has been associated with not only lifestyle-related diseases but wound repair.4)4)

3. Japanese health insurance system for CPAP treatment and visceral fat

CPAP treatment for OSA was introduced in 1981.2)1) From 1998, CPAP treatment for OSA has been permitted under the health insurance system in Japan. Since the principle of medical treatment is face to face in Japan and patients under home respiratory care should come to their hospital every month, we could collect data on patients under CPAP treatment for long intervals. Under such conditions, we could acquire accurate data on several metabolic dysfunctions. In the 1990s, MetS was given attention because MetS is a more important factor for cardiovascular diseases than the presence of one of its components such as obesity, hypertension, insulin resistance, and hyperlipidemia.4)6) Obesity is an important risk factor among the components of MetS and is one of the most important risk factors for OSA. Among MetS components, it was suggested that visceral fat accumulation (VFA) was the most important factor. But there had been no data on the association between VFA and OSA.

Although the weight of most OSA patients does not change significantly after CPAP treatment, the incidence of mortality from cardiovascular diseases in OSA patients can be reduced with CPAP treatment.4)7) Therefore, we hypothesized that the location of body fat deposits in OSA patients might be altered after long-term CPAP treatment. At that time, Matsuzawa et al. extensively investigated the relationship between obesity-related diseases and VFA by CT scanning.4)8) Therefore, we investigated changes in the location of body fat in OSA patients by abdominal CT.

Following more than 6 months of CPAP treatment, VFA decreased significantly in the group without body weight reduction (n = 13, P < 0.03) (Fig. 8) in addition to the body weight reduction group (n = 9, P < 0.01). In contrast, subcutaneous fat accumulation (SFA) changed significantly in the body weight reduction group only (P < 0.01). In that study, we also measured levels of plasma leptin, which is a humoral factor not only of appetite but is a respiratory stimulant. We found that plasma leptin decreased significantly following 3 to 4 days of CPAP (n = 21, P < 0.01), whereas body weight, fasting insulin, and cortisol levels did not change significantly.4)9)

To think about the relationships between OSA and mortality, we should recognize that increases in mortality in patients with OSA were shown to occur in men under the age of 70 years and with an AHI more than 30.50,5)1) Some reports, however, showed that increases in cardiovascular diseases also occurred in women.5)2,5)3) It is generally believed that there are some sex differences in the effects of OSA on morbidity and mortality but the origin of these differences is not known. We investigated 371 participants (271 men and 100 women). The relationships were analyzed between fat areas by CT and
several parameters. Multiple regression analyses revealed that in men, not only age or BMI but also minimal oxygen saturation (contribution rate \( R^2 \), 4.6%) during sleep and alveolar–arterial oxygen difference (\( R^2 \)F, 7.6%) were independently associated with VFA. Conversely, VFA was associated only with BMI in women. Thus, only in men was OSA independently associated with VFA. The lesser associations between OSA and visceral fat in women might account for the lower impact of OSA on cardiovascular disease or mortality in women.

As shown in our report of VFA during CPAP treatment, we could continuously follow patients with OSA for a long time because patients with CPAP came to our hospital every month. Although it was reported that CPAP treatment decreased blood pressure significantly, it was not known how many hours of CPAP use was sufficient to decrease blood pressure in patients undergoing long-term CPAP treatment. We investigated blood pressure and BMI before the study and at two checkpoints after usage of CPAP [620 (552–688) and 1071 (1,000–1,143) days]. We found that the use of CPAP for a daily average of 3 h would be sufficient to decrease diastolic blood pressure in hypertensive patients with adult or elderly severe OSA.

4. SDB and its management in patients with hypercapnia or under critical care

As mentioned above, the management of sleep apnea improves the quality of life and may be protective against the occurrence of cardiovascular diseases and metabolic disorders. Another important SDB that should be treated is sleep related hypoventilation disorders (SRHD). The primary feature of SRHD is insufficient sleep related ventilation, resulting in abnormally elevated arterial partial pressure of carbon dioxide (\( \text{PaCO}_2 \)) during sleep. Patients with sleep apnea typically manifest short intermittent high-frequency hypoxemia (cyclical pattern of oxygen desaturation lasting 15–60 s followed by reoxygenation), while with SRHD sustained or low frequency hypoxemia with oxygen saturation (\( \text{SO}_2 \)) ranges to less than 90% and lasts from a few minutes to hours during sleep (Figs. 1 and 3). SRHD become severe especially during rapid eye movements (REM) sleep in respiratory failure patients with hypercapnia. Firstly, we prescribe oxygen for patients with hypoxemic respiratory failure. But when physical status and pulmonary function in such patients worsen, they develop hypoxemia with hypercapnia (Fig. 1).
Since we would like to manage them non-invasively without intubation, we firstly used negative pressure ventilation, which is one means of noninvasive ventilation. But we found that the negative pressure ventilation often became ineffective when the patients slept because the negative pressure ventilation induced OSA or hypopnea during sleep through the negative pressure on the upper airway induced by the ventilator. After those experiences, we began to use nasal mask intermittent positive pressure ventilation (NIPPV) so called in the later as noninvasive positive pressure ventilation (NPPV) through a nasal or face mask. But at the first stage of NPPV respiratory care, we did not have an effective mask; therefore, we made a custom fabricated mask by ourselves (Fig. 9). According to the rapid increase in the number of patients with OSA, the development of a nasal or face mask for patients with OSA was also rapid (Fig. 9). Now we have available many noninvasive masks.

In addition, we have made efforts to manage patients with SDB not only during daily life but under critical care such as in the perioperative stage. The prevalence of OSA increases according to age, and patients usually assume the supine position during the perioperative stage, a position in which OSA worsens. In addition, some surgical procedures might injure or stress respiratory muscles, especially upper abdominal surgery such as liver resection, liver transplantation, etc. We take positive action to detect SDB and have used NPPV and CPAP, which have been useful for treating SDB, in patients during the critical stage in advanced clinical practice such as in liver resection or liver or lung transplantation, cardiac surgery, intensive chemotherapy, etc. from babies to the elderly (Fig. 10). When we use noninvasive ventilation (NIV) in patients in critical condition, during the recovery and withdrawal stages we firstly remove NIV during awake periods and least prefer the removal during sleep (Fig. 10). Thus, SDB management might be useful to promote health not only in persons in stable condition but in a critical condition. Based on our experiences and reports about NPPV and CPAP, we greatly contributed to

5. OSA, obesity, sufficient duration of good sleep, and a healthy life

OSA is recognized as not only a factor in daytime hypersomnolence or other symptoms but in cardiovascular diseases and mortality. Obesity is a major risk factor for OSA and has been confirmed as a main factor in cardiovascular diseases. Therefore, the interaction between obesity and OSA should be given attention (Fig. 6). It is said that OSA affects parameters involved in energy balance regulation, including food intake, hormonal regulation of hunger/satiety, energy metabolism, and physical activity. We have investigated several humoral factors in OSA patients such as insulin, leptin, acyl, desacyl ghrelin, and incretin. OSA and CPAP treatment had significant associations with secretion of these hormones.

Including the above-mentioned studies, prior studies revealed a disruptive impact of OSA on energy metabolism including humoral factors, and there is an emerging concept that OSA itself may in turn reinforce the obese state. In fact, studies have indicated that OSA may affect energy expenditure (i.e., elevated basal/sleeping energy expenditure plausibly because of increased sympathetic activity and breathing efforts) and energy intake (i.e., increased preference for high-fat or calorie-dense food) via a complex mechanism that includes neurohormonal and behavioral changes, an imbalance of which may result in excess energy intake leading to weight gain. Given the plausible reciprocal relationship between obesity and OSA, treating OSA with CPAP in theory could act against weight gain.
However, recent studies revealed that CPAP therapy actually resulted in weight gain, although the underlying mechanism remains unclear.\textsuperscript{71–74}

Therefore, recently, we conducted a study to explore the underlying mechanism by which patients with OSA gain weight after CPAP. A comprehensive assessment of energy metabolism was performed in 63 newly diagnosed OSA study participants (51 men; 60.9±10.1 y; apnea–hypopnea index >20 /h) at baseline, at CPAP initiation, and at a 3-month follow-up.\textsuperscript{75} Measurements included PSG, body weight, body composition, basal metabolic rate (BMR), hormones (norepinephrine, cortisol, leptin, ghrelin, insulin-like growth factor-1), dietary intake, eating behavior, and physical activity. BMR significantly decreased after CPAP (1,584 kcal/d at baseline, 1,561 kcal/d at CPAP initiation, and 1,508 kcal/d at 3 months of follow-up; P < 0.001), whereas physical activity and total caloric intake did not significantly change. The weight gainers (n = 33) had higher leptin levels, lower ghrelin levels, and higher eating behavior scores than the non-weight gainers (n = 30), indicating a positive energy balance and disordered eating behavior among the weight gainers (Figs. 11, 12). Among the parameters related to energy metabolism, increased caloric intake was a particularly significant predictor of weight gain.

From this study, our conclusion was that, although a reduction in BMR after CPAP predisposes to a positive energy balance, dietary intake and eating behavior had greater impacts on weight change. We previously reported that long-term (more than 6 months) of CPAP treatment induced a decrease in VFA without body weight reduction.\textsuperscript{49} Our recent report seemed to be discordant with the previous one.\textsuperscript{49,75} Indeed, recent data showed no VFA changes following CPAP treatment.\textsuperscript{76–80} But the data were based on CPAP treatment of a relatively short duration (within 3 mo).\textsuperscript{77–80} Decreases in VFA were reported with longer durations of

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CPAP treatment.81) Another report showed a disproportional increase in lean body mass compared to fat mass following 7.8 months of CPAP treatment.82) This study also showed that body composition might change following long-term CPAP treatment. In addition, routine weight-loss recommendations were given to all the participants in the previous study,49) while no specific instructions were given in the recent study.75) Thus, with or without recommendations of weight-loss CPAP treatment might have an effect on the lifestyles of patients.

These findings highlight the importance of lifestyle modifications combined with CPAP. The recent results75) indicated that the appetite-related humoral factors were the result of body weight change, not the origin of body weight change. But we also reported that CPAP treatment changed appetite-related hormone levels in those receiving weight-loss instructions.34),35),49) Thus, the higher brain center, which controls eating behavior, is a key factor for regulating body weight following CPAP treatment. That such eating behavior has been predetermined or influenced by OSA and may be changed by CPAP treatment should be investigated in a future study. The relationship between OSA and cognitive impairment, including eating behavior, will be an important field to study for the extension of a healthy life because the prevalence of SDB is high and increases according to age.83)

6. Nagahama Cohort Study

At first, when we submitted reports about OSA patients in Japan to international journals, the reviewers in Western countries said that our patients did not have OSA but had other diseases because our patients’ BMI was too low. But now it is well known that the craniofacial structure from genetic and ethnic origins in East Asians make it easy to have OSA.7),8)

Table 3 shows the prevalence of moderate OSA in persons with type 2 diabetes in U.S., Hong Kong, and Japan.84)–86) The prevalence of moderate OSA was over 30% in each country, but the differences in BMIs between Japan or Hong Kong and U.S. patients were 6–7 kg/m². The prevalence of OSA among hypertensive patients in Western countries...
was almost 30% while it was 26% among hypertensive patients in our cohort in Japan. In addition, the prevalence of OSA patients with obesity hypoventilation syndrome (OHS), so-called Pickwickian syndrome, in which the prognosis was worse than in OSA patients without hypoventilation, was almost the same in Japan and in Western countries. But the mean BMI in Japanese OHS patients was 37.4 kg/m², while it was 44.5 kg/m² in the Western countries. Therefore, to understand the relationships between sleep-related problems and several morbidities in Japan, it is important to study such relationships in a large cohort in Japan. We have reported on Japanese with several diseases and OSA in a small cohort (n < 300). Now Kyoto University is doing a large genetic cohort study: the Nagahama Cohort Study (n > 10,000). The Nagahama City, which has 120,000 peoples, is located middle in Japan near the Biwa Lake. Using an accelerometer (Actigraphy®) and pulse oximetry as in previous studies, we have measured SDB with intermittent hypoxemia, objective and subjective sleep duration, and many health-related parameters along with the genetic data.

Recently, short sleep duration was reported to be related to obesity, cardiovascular diseases, stroke, and all-cause mortality similar to the characteristics of OSA, indicating the importance of investigations of sleep duration. However, most previous studies have been based on self-reported sleep duration, which may not accurately reflect objectively determined sleep duration. Indeed, subjective and objective sleep durations were reported to correlate only moderately, and the role of objective sleep duration is attracting rising attention. We had reported that sleep apnea had a significant association with patients’ serum triglyceride levels, that objective sleep duration correlated with HDL-cholesterol levels, and that objective sleep duration decreased according to the severity of their OSA (Fig. 13). But the number of participants in our previous report was small (n = 300).

From the large volume of data in the Nagahama cohort, we have already reported the associations between lifestyle-related diseases and subjective sleep duration. And non-restorative sleep was proved to be a phenomenon representing various clinical and lifestyle features. In another study, not in the Nagahama cohort, we found a biomarker (urine Lipocalin-type prostaglandin D synthase: L-PGDS), which might be a moderately useful marker to identify patients with severe obstructive OSA, which has significant associations with cardiovascular disease. In the near future, from information on objective sleep duration, genetic data analyses, including omics analysis, and conventional lifestyle-related parameters using several questionnaires, we would like to investigate biomarkers that could detect all sleep disturbances without complex tests (Fig. 14). Such sleep disturbances would threaten achievement of a healthy life.
Fig. 13. Weekly mean sleep duration in OSA and/or MetS study participants. a) The relationship between the severity of OSA and the weekly mean sleep duration in bed, as measured by an actigraph. Only severe OSA was associated with a significantly shortened sleep duration. b) BMI- and age-matched study participants with MetS (n = 68) and without MetS (n = 68). c) MetS with severe OSA (n = 11) and MetS without severe OSA (n = 57). OSA, obstructive sleep apnea; MetS, metabolic syndrome. (Chin, K., Oga, T., Takahashi, K., Takegani, M., Nakayama-Ashida, Y., Wakamura, T., Sumi, K., Nakamura, T., Horita, S., Oka, Y., Minami, I., Fukuhara, S. and Kadotani, H. Associations between obstructive sleep apnea, metabolic syndrome, and sleep duration, as measured with an actigraph, in an urban male working population in Japan. Sleep. 2010; 33(1); 89–95 by permission of Oxford University Press.)

Fig. 14. Interrelationships among sleep disordered breathing (sleep apnea), sleep duration, and obesity. It is suggested that sleep apnea, obesity, and/or sleep duration have significant associations with several diseases and interrelationships. In the Nagahama Cohort, we are measuring not only conventional blood parameters, acquiring physiological data, and administering several questionnaires but are acquiring detailed clinical histories as well as integrated omics data. By combining these and sleep related data, we would like to find new parameters (biomarkers) that will promote preemptive medicine and extend healthy life expectancy. Normal or severe sleep disordered breathing (sleep apnea) with hypoxemia determined by a pulse oximeter is shown. One week objective sleep duration and sleep fragmentation in participants was measured by an accelerometer (Actigraphy®). A case of good or bad sleep hygiene is shown. Blue or green belt showed sleeping time. ODI: oxygen desaturation index, lines with double arrows show the interrelationships.
Conclusion

During more than 30 years, we have investigated SDB and other sleep disturbances from the viewpoints of pulmonologists. Now, we are convinced that the study of sleep is a multidisciplinary area, but that respiratory, basic, and clinical investigations are very important to make progress in uncovering the mystery of sleep. After all, I hope that we will find means to good sleep that will extend a healthy and good life.

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Profile

Kazuo (Hwaboo) Chin (Jin) was born in 1955 and brought up in Osaka. He was a second-generation Korean born in Japan. He graduated from Kyoto University in 1981. He trained in the pulmonology and clinical physiology at the Department of Clinical Pulmonary Physiology (the late Prof. Sagawa), Chest Disease Research Institute, Kyoto University, which was unified into the Graduate School of Medicine, Kyoto University at 1998. He started research on sleep disordered breathing including sleep apnea and noninvasive ventilation at Kyoto University which led to a Ph.D. in 1990. His mentor is Dr. Motoharu Ohi. Chin was among the first to report associations between visceral fat accumulation, coagulation system or liver dysfunction and obstructive sleep apnea following the continuous positive airway pressure (CPAP) treatment. He became professor of the donated Department of Respiratory Care and Sleep Control Medicine, Graduate School of Medicine, Kyoto University at 2008. Using his knowledge about sleep apnea, sleep related breathing disorders and noninvasive ventilation, he has managed high quality respiratory care from infants to elderly patients at Kyoto University Hospital which is the most famous hospital for organ transplantation and advanced medicine in Japan. For his accomplishment, he received the Young Investigator Award from the Japanese Respiratory Society and two other awards. He is an associate editor of “Sleep and Biological Rhythms”, which is the official English Journal of the Japanese Sleep Society, and “Respiratory Investigation”, which is the official English Journal of the Japanese Respiratory Society. He believes that the combined development of the conventional medicine during waking time and sleep medicine including sleep disordered breathings is one of key factors to promote healthy life extension.