〈Regular Article〉

Urinary 8-oxo-2'-deoxyguanosine is associated with respiratory-related arousal index: potential implications for screening obstructive sleep apnea as a preliminary study

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ABSTRACT **Background**: Obstructive sleep apnea (OSA) harms health and quality of life. Its high prevalence necessitates mass-screening. Intermittent hypoxia caused by pharyngeal stenosis or obstruction causes sleep fragmentation and leads to impaired vascular endothelial function and atherosclerosis, increasing the risk for cardiovascular disease. In patients with severe OSA (apnea-hypopnea index AHI ≧ 30 times/h), urinary 8-oxo-2'-deoxyguanosine (8-OHdG), an oxidative stress marker, is associated with respiratory-related markers of OSA, including AHI. Treatment with continuous positive airway pressure (CPAP) decreases urinary 8-OHdG and improves endothelial function. In patients with mild to moderate OSA (AHI 5-29 times/h), sleep fragmentation can lead to daytime sleepiness and impaired concentration, compromising work efficacy and road safety. CPAP can also decrease sleep fragmentation. Here we investigated the relationship between urinary 8-OHdG and sleep-related markers of OSA to clarify its usefulness as a screening tool.

Methods: From 72 patients admitted to Kawasaki Medical School Hospital for polysomnography, the first urine sample in the morning following polysomnography was collected, and urinary 8-OHdG was measured by ELISA.

Results: Urinary 8-OHdG differed significantly between subjects with a respiratory arousal index (RAI) of < 15 times/h and those with RAI ≧ 15 (p = 0.046, 5.70 ± 2.84 vs 7.23 ± 3.52 ng/mg creatinine). The normal value of RAI is about 15 times/h in healthy adults aged in their 40s to 60s. The cut-off value was 4.03 ng/mg creatinine with respect to RAI ≧ 15 on the urinary 8-OHdG. Apart from sex (p = 0.011) and body mass index (p = 0.022), patient groups did not differ in age (p = 0.201), smoking (p = 0.857), alcohol consumption (p = 0.511), hypertension (p = 0.2), diabetes (p = 0.366), or dyslipidemia (p = 0.408).

Conclusion: Urinary 8-OHdG significantly increased in OSA patients with RAI ≧ 15 times/h. This result suggests that combined with specific symptoms such as snoring and sleepiness,

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urinary 8-OHdG may be useful as a mass-screening tool not only for respiratory-related severe cases (AHI ≧ 30 times/h), but also for abnormal sleep-related cases.

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Key words：8-OHdG, Screening, Respiratory arousal index, OSA

INTRODUCTION

Obstructive sleep apnea (OSA) harms health and quality of life[1]. Its high prevalence necessitates mass-screening. Recent data from the USA and Europe suggest that between 14% and 49% of middle-aged men have clinically significant OSA, and that prevalence rates in women are lower but still substantial[2]. Another study reported that OSA affects approximately 34% of men and 17% of women, highlighting its widespread occurrence[3]. The overall prevalence of OSA in Japan is estimated at 15%, with moderate-to-severe OSA affecting 20% of adult males and 10% of postmenopausal women[4].

Among Japanese commercial drivers, 23.9% have moderate to severe OSA, with significant associations with obesity, hypertension, and diabetes[5]. Among Japanese public transportation drivers, 9.8% were diagnosed with OSA, indicating a substantial prevalence[6]. In OSA, intermittent hypoxia caused by disrupted breathing during sleep is often accompanied by brief episodes of arousal. This is due to pharyngeal stenosis, a narrowing or occlusion of the pharynx, during sleep. Intermittent hypoxia in turn leads to impaired vascular endothelial function and atherosclerosis, increasing the risk for cardiovascular disease[7]. Arousal fragments sleep, increasing sympathetic nerve function and inflammation[8], which induce hypertension, insulin resistance, atherosclerosis, and cognitive decline[9]. Arousal can also lead to daytime sleepiness and impaired concentration[10], which affects work efficacy and road safety[11]. Fortunately, these adverse effects can be ameliorated by treatments such as continuous positive airway pressure (CPAP)[12, 13]. Despite the high prevalence of OSA in Japan, treatment rates remain insufficient. This gap suggests a need for enhanced screening, diagnosis, and treatment strategies to address the unmet needs of people with OSA.

Urinary 8-oxo-2'-deoxyguanosine (8-OHdG) levels can directly and simply reflect oxidative stress. Various markers have been associated with oxidative stress produced by intermittent hypoxia due to apnea[14–16]. 8-OHdG is a reactive oxygen species (ROS) produced when blood flow is restored to ischemic, hypoxic tissue[17–19]. Urinary 8-OHdG is more stable than serum and plasma 8-OHdG[20, 21] and is not affected by diurnal variations[22, 23] or the body's repair mechanisms[24]. Therefore, urine can provide a simple sample for mass-screening.

The aim of this study was to investigate the relationship between urinary 8-OHdG levels and sleep-related markers of OSA to ascertain its usefulness as a tool for screening for sleep fragmentation. Urinary 8-OHdG has been associated with respiratory-related markers of OSA, such as the apnea-hypopnea index (AHI) and the 3% oxygen desaturation index (ODI), in patients with severe OSA (AHI ≧ 30 times/h)[25–27]. Treatment with CPAP decreases urinary 8-OHdG levels and improves endothelial function[12]. Patients with mild to moderate OSA (AHI 5-29 times/h) also experience sleep fragmentation. We investigated whether urinary 8-OHdG could serve as a viable marker for screening for sleep fragmentation.

MATERIALS AND METHODS

Ethics approval

The prospective study protocol was approved by the ethics committee of Kawasaki Medical School (5865-03). Written informed consent was obtained

from all patients on the day of admission for polysomnography.

Subjects

We assessed data of 72 patients (male = 48, female = 24) admitted to Kawasaki Medical School Hospital for polysomnography between May 2023 and September 2024. Total 77 patients were examined in the period, and all of them were diagnosed as OSA; however, patients with a history of psychiatric disorders or of treatments for OSA were excluded. All patients' weight and height were recorded on the day of admission, and body mass index (BMI) was calculated. We verified all patients' medical history and preferences of smoking and drinking.

Collection of blood and urine samples

Peripheral venous blood samples were collected on the day of decision for polysomnography admission. The first urine sample in the morning was collected the next day[25] and stored at -20℃ until analysis.

Measurements of 8-OHdG

Urine samples were thawed, centrifuged at 3000 × g for 10 min, and used for analysis of urinary 8-OHdG in 1 ml with an ELISA kit (Nikken SEIL Corp.; Fukuroi, Shizuoka, Japan). The optical density was measured on a multimode microplate reader (Thermo Scientific, MA, USA) at 450 nm. The urinary 8-OHdG value was standardized to urinary creatinine.

Sleep studies

Polysomnography comprised an electroencephalogram (EEG), an electrocardiogram, oxygen saturation, airflow (nasal pressure), leg and chin electromyograms, eye movements, chest and abdominal movements, and snoring[28]. Apnea is defined as a ≧ 90% drop in airflow from baseline, lasting at least 10 s, and hypopnea was defined as a ≧ 30% drop in airflow lasting ≧ 10 s, accompanied by a decrease in oxygen saturation of 3% or an arousal response. The arousal response index (ARI) is calculated as the number of cortical arousals measured by EEG per total sleep time; the respiratory arousal index (RAI) is calculated as the number of respiratory- or saturation of percutaneous oxygen (SpO_2)-related arousal responses per total sleep time.

Statistical analyses

Patient characteristics are expressed as quartiles and percentages. To assess the relationship between urinary 8-OHdG and various parameters, we used Spearman's correlation coefficient, followed by the Wilcoxon signed rank test, with an RAI cutoff value of 15 times/h, in accordance with the established normal range of < 15 times/h in healthy adults aged in their 40s to 60s[29]. The RAI < 15 and RAI ≧ 15 groups were also compared in age, sex, BMI, SpO_2 < 90% (min), minimum SpO_2 (%), smoking, alcohol consumption, hypertension, diabetes, and dyslipidemia by the Wilcoxon test and chi-square test. The area under the receiver operating characteristic (ROC) curve (AUC) was used to assess the capacity to predict the cut-off value of continuous variable for RAI ≧ 15 in the urinary 8-OHdG. The highest value with (sensitivity + sepecificity-1) was determined as the cut-off value. All statistical analyses were conducted in SPSS v. 28 software (SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics are shown in Table 1 Urinary 8-OHdG was correlated with AHI (Spearman's: $r = 0.358$, $p = 0.002$), 3% ODI ($r = 0.355$, $p = 0.002$) (Fig. 1), ARI ($r = 0.235$, $p = 0.047$), and RAI ($r = 0.288$, $p = 0.014$) (Fig. 2). At the RAI cutoff value of 15 times/h[29], it differed significantly (Wilcoxon test: $p = 0.046$) between

Table 1. Characteristics of subjects

	Total	RAI ≥ 15	RAI < 15
Subjects (*n*)	72	38	34
Male	48	30	18
Female	24	8	16
Age (years)	53 [43 - 66.5] M 52 [38.25 - 68] F 53.5 [51 - 64.5]	58 [49.75 - 69.25]	50 [37 - 56.5]
BMI (kg/m^2)	25.08 [22.13 - 27.06]	25.81 [23.91 - 27.38]	22.96 [20.81 - 27.09]
AHI (×/h)	26.2 [17.2 - 36.65]	35.7 [27.03 - 48.4]	16.5 [11.53 - 22]
ARI (×/h)	23.55 [15.65 - 35.28]	33.15 [26.9 - 40.85]	15.56 [12.55 - 18.98]
RAI (×/h)	13.75 [8.43 - 25.00]	23.1 [15.55 - 31.3]	8.2 [4.88 - 11]
3% ODI (×/h)	20.9 [10.9 - 34.88]	31.85 [20.35 - 45.3]	13.35 [7.8 - 21.03]
Minimum SpO_2 (%)	81.5 [76 - 86.75]	79 [71 - 84]	84 [80 - 88]
Urinary 8-OHdG (ng/mg creatinine)	6.51 ± 3.29	7.23 ± 3.52	5.70 ± 2.84
Smoking (*n*)	9 (12.5%)	5 (13.2%)	4 (11.8%)
Alcohol consumption (*n*)	21 (29.1%)	12 (31.6%)	9 (26.5%)
Hypertension (*n*)	32 (44.4%)	22 (57.9%)	10 (29.4%)
Diabetes (*n*)	9 (12.5%)	6 (15.8%)	3 (8.8%)
Dyslipidemia (*n*)	18(25.0%)	12 (31.6%)	6 (17.6%)

Data are presented as *n* (%), mean ± SD, or median [interquartile range].
BMI, body mass index; AHI, apnea-hypopnea index; ARI, arousal response index; RAI, respiratory arousal index; ODI, oxygen desaturation index; SpO_2, saturation of percutaneous oxygen; 8-OHdG: 8-hydroxy-2'-deoxyguanosine.

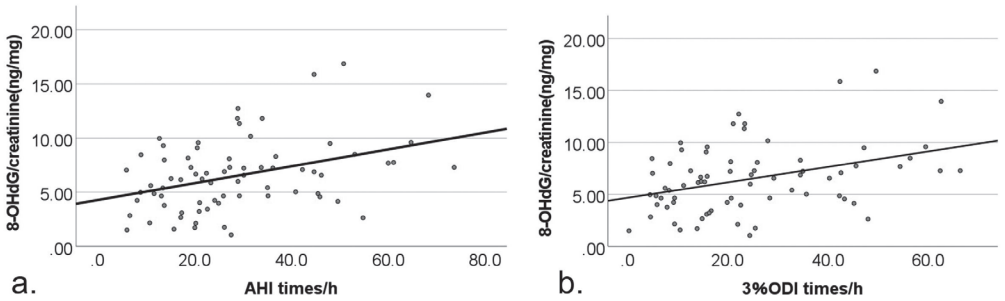

Fig. 1. Scatterplots of 8-OHdG vs AHI (left panel) and 3% ODI (right panel). Urinary 8-oxo-2'-deoxyguanosine (8-OHdG) was significantly correlated with apnea-hypopnea index (AHI; $r = 0.358$, $p = 0.002$) and 3% oxygen desaturation index (ODI; $r = 0.355$, $p = 0.002$) by Spearman's correlation coefficient.

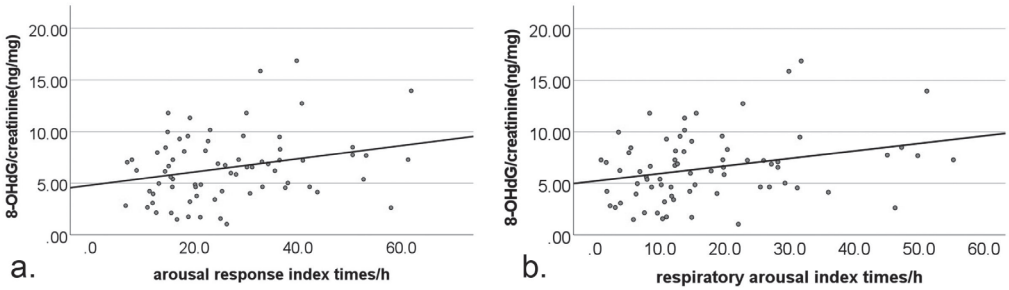

Fig. 2. Scatterplots of 8-OHdG vs ARI (left panel) and RAI (right panel). Urinary 8-oxo-2'-deoxyguanosine (8-OHdG) was correlated with arousal response index (ARI; $r = 0.235$, $p = 0.047$) and especially respiratory arousal index (RAI; $r = 0.288$, $p = 0.014$) by Spearman's correlation coefficient.

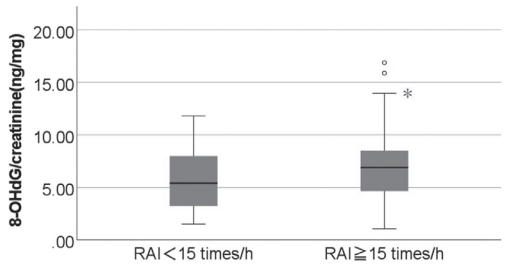

Fig. 3. Comparison of urinary 8-OHdG value by RAI. Urinary 8-oxo-2'-deoxyguanosine (8-OHdG) value differed significantly (Wilcoxon test: $p = 0.046$) between the respiratory arousal index (RAI) < 15 times/h group (mean 5.70 ± 2.84 ng/mg creatinine) and the RAI ≧ 15 times/h group (7.23 ± 3.52 ng/mg creatinine).

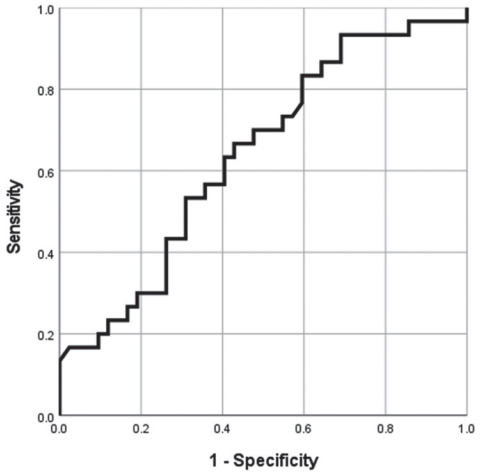

Fig. 4. Receiver operating characteristic (ROC) curve (AUC). The AUC values for RAI ≧ 15 were 0.63889 for the value of urinary 8-OHdG in the ROC curves.

groups (RAI < 15, 5.70 ± 2.84 ng/mg creatinine; RAI ≧ 15, 7.23 ± 3.52 ng/mg creatinine; Fig. 3). The cut-off value was 4.03 ng/mg creatinine with 93.3% sensitivity and 31.0% specificity with respect to RAI ≧ 15 on the urinary 8-OHdG (Fig.4). Patient backgrounds differed significantly between groups also in sex (chi-square test: $p = 0.011$) and BMI (Wilcoxon test: $p = 0.022$), but not in age (Wilcoxon test: $p = 0.201$), smoking (chi-square test: $p = 0.857$), alcohol consumption (chi-square test: $p = 0.511$), hypertension (chi-square test: $p = 0.2$), diabetes (chi-square test: $p = 0.366$), or dyslipidemia (chi-square test: $p = 0.408$).

DISCUSSION

Urinary 8-OHdG, an oxidative stress marker, may prove useful as a tool for screening sleep-related parameters as well as respiration-related parameters. Its correlation with severe OSA defined as AHI ≧ 30 times/h or 3% ODI ≧ 30 times/h has been reported[25]. Chronic intermittent hypoxia is thought to be associated with increased sympathetic nerve function and with increased 8-OHdG, indicating that urinary 8-OHdG is elevated in OSA patients[30]. We focused on respiratory arousal, a sleep characteristic that has not been studied before, and found that urinary 8-OHdG was significantly increased in patients with RAI ≧ 15 times/h, who may include patients with mild to moderate OSA, relative to patients with RAI < 15. Since respiratory arousal is associated with sleep disturbances and daytime sleepiness[1], our results suggest that urinary 8-OHdG, which can be collected safely and easily, may be useful for screening for sleep fragmentation in OSA.

In living cells, ROS such as 8-OHdG are found as a consequence of metabolic reaction in the previous reports. Under normal physiological conditions, a balance between endogenous oxidants and anti-oxidants. When an imbalance occurs, the abnormal oxidant system enters what is called oxidative stress as well. Most 8-OHdG in diabetes is generated in the mitochondria of muscle DNA, suggesting that hyperglycemia induces mitochondrial ROS, which contributes, in part, to the pathogenesis of diabetic complications[31]. Additionally, increase of 8-OHdG are found in leukocyte DNA of patients with diabetic nephropathy and retinopathy. In patients with hypertension, level of antioxidant glutathione is increased and activity of superoxide dismutase is reduced[32]. Activation of the renin-angiotensin

system has been proposed as a major stimulator of vascular NADPH oxidase activation and ROS production, 8-OHdG. Then, during vascular damage, when oxidative stress is increased, redox-sensitive growth process leads to accelerate proliferation and hypertrophy, contributing to vascular injury and remodeling. Thus, 8-OHdG are also generated in atherogenesis and advanced atherosclerosis by macrophages[33]. 8-OHdG is also correlated with oxidized LDL as well as hypercholesterolemia, hyperglyceridemia, and high levels of low-density lipoprotein[34]. It has been suggested that dyslipidemia impairs antioxidant defense functions, induces oxidative stress, and causes DNA damage[34]. Furthermore, oxidized LDL has been established as a pro-inflammatory pathogenic particle that causes endothelial dysfunction[35]. In patients with obesity, ROS products are produced in the mitochondria of fat cells[36]. Then, antioxidant defenses decreased in obese adipose tissues. ROS may act as second messengers, reflect development of insulin resistance, particularly in muscle. In cancer, oxidative damage to DNA reflected in the formation of 8-OHdG is important in mutagenesis and carcinogenesis. The level of oxidative damage that escape immediate repair and persist in DNA appear to be in the range that could contribute to mutation rate. As mentioned above, ROS including 8-OHdG have been addressed to be produced at various organs in the diseases.

Urinary 8-OHdG has been associated with various diseases[17, 18], including lifestyle-related diseases associated with OSA such as type 2 diabetes[37], hypertension[38, 39], dyslipidemia[40, 34], and obesity[41]. It also increases in life-threatening diseases such as myocardial infarction[42], bladder cancer[43], and prostate and breast cancers[44]. The urinary 8-OHdG level in healthy individuals is 3.2-4.1 ng/mg creatinine[45], in contrast, 8.8 ng/mg creatinine [range: 6.9 - 10.5] in diabetes[37], 6.6 ± 4.1 ng/mg creatinine in dyslipidemia[40], and 7.5 ng/mg creatinine [6.6 - 8.6] in hypertension[39]. Furthermore, the urinary 8-OHdG level was extremely high at 24.4 ± 3.8 ng/mg creatinine following myocardial infarction[42], 11.9 ± 1.6 ng/mg creatinine in breast cancer[44], 70.5 ± 38.2 ng/mg creatinine in bladder cancer[43], and 58.8 ± 43.4 ng/mg creatinine in prostate cancer.

Here, we considered that 8-OHdG level in patients with RAI ≧ 15 times/h, at 7.23 ± 3.52 ng/mg creatinine, acceptable because it was clearly greater than normal range and lower than those in patients with severe OSA, compared with a study in which the AHI cutoff value of was set at 30 times/h, where it was 8.5 ± 2.4 ng/mg creatinine in non-severe OSA and 9.5 ± 2.5 in severe OSA[25]. The cut-off value of 4.03 ng/mg creatinine with respect to RAI ≧ 15 on the urinary 8-OHdG closed to the upper limit value in healthy individuals (3.2 - 4.1 ng/mg creatinine)[45]. These results imply that OSA induces the same oxidative stress as lifestyle-related diseases. But, the value of urinary 8-OHdG cannot be separated patients with OSA from patients with lifestyle-related diseases, because in fact, those diseases are often merged. Therefore, we suppose that combined with specific symptoms of OSA such as snoring and sleepiness, low specificity of 31.0% may improve and the diagnose of OSA may be clarified. We believe that urinary 8-OHdG may be useful in screening for lifestyle-related diseases including OSA, and help to identify OSA in people free of lifestyle-related diseases.

LIMITATIONS

Our study had three limitations. First, there was no control group; however, the 8-OHdG value in our subjects was clearly greater than the normal range[33]. Second, the number of patients was small. Third, we were not able to eliminate confounding factors, including the severity of medical history and the degree of smoking and drinking. Further study will be needed to increase the number of subjects

in order to improve statistical reliability and to set a clear cutoff value of urinary 8-OHdG as a marker of OSA.

CONCLUSION

Urinary 8-OHdG significantly increased in OSA patients with RAI ≧ 15 times/h. The cut-off value was 4.03 ng/mg creatinine. The result shows that combined with specific symptoms of OSA such as snoring and sleepiness, urinary 8-OHdG may be useful as a tool for the mass-screening not only for severe respiratory-related cases (AHI ≧ 30 times/h) but also for abnormal sleep-related cases.

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REFERENCES

1）Pinilla L, Santamaria-Martos F, Benítez ID *et al.*: Association of Obstructive Sleep Apnea with the Aging Process. Ann Am Thorac Soc. 2021; 18: 1540-1547.
2）Garvey JF, Pengo MF, Drakatos P, Kent BD: Epidemiological aspects of obstructive sleep apnea. J Thoracic Dis. 2015; 7: 920-929.
3）Redline S: Screening for Obstructive Sleep Apnea: Implications for the Sleep Health of the Population. JAMA. 2017; 317: 368-370.
4）Khare S, Lin X, Yin C, Pettine M, Adam A, Shinde S: Empowering OSA Care: Patient Profiles and Treatment Patterns in Japan. Sleep. 2024; 47: A217.
5）Ueyama M, Kokuto H, Sugihara H, Oikawa S, Suzuki F, Goto H, Kudoh S: Investigation of Obstructive Sleep Apnea Using Portable Monitors and Health Check Data in Japanese Drivers. J Atherosclero Thromb. 2018; 25: 1118-1127.
6）Sasai-Sakuma T, Kikuchi K, Inoue Y: Cross-Sectional Study of Obstructive Sleep Apnea Syndrome in Japanese Public Transportation Drivers: Its Prevalence and Association With Pathological Objective Daytime Sleepiness. J Occup Environ Med. 2016; 58: 455-458.
7）Lavie L: Oxidative stress inflammation and endothelial dysfunction in obstructive sleep apnea. Front Biosci (Elite edition). 2012; 4: 1391-1403.
8）Arnardottir ES, Mackiewicz M, Gislason T, Teff KL, Pack AI: Molecular signatures of obstructive sleep apnea in adults: a review and perspective. Sleep. 2009; 32: 447-470.
9）Prabhakar NR, Peng YJ, Nanduri J: Hypoxia-inducible factors and obstructive sleep apnea. J Clin Invest. 2020; 130: 5042-5051.
10）Carskadon MA, Dement WC: Nocturnal determinants of daytime sleepiness. Sleep. 1982; 5 Suppl 2: S73-81.
11）Morsy NE, Farrag NS, Zaki NFW, Badawy AY, Abdelhafez SA, El-Gilany AH, El Shafey MM, Pandi-Perumal SR, Spence DW, BaHammam AS: Obstructive sleep apnea: personal, societal, public health, and legal implications. Rev Environ Health. 2019; 34: 153-169.
12）Jurado-Gámez B, Fernandez-Marin MC, Gómez-Chaparro JL, Muñoz-Cabrera L, Lopez-Barea J, Perez-Jimenez F, Lopez-Miranda J: Relationship of oxidative stress and endothelial dysfunction in sleep apnoea. Eur Resp J. 2011; 37: 873-879.
13）Mulgrew AT, Ryan CF, Fleetham JA, Cheema R, Fox N, Koehoorn M, Fitzgerald JM, Marra C, Ayas NT: The impact of obstructive sleep apnea and daytime sleepiness on work limitation. Sleep Med. 2007; 9: 42-53.
14）Wysocka E, Cofta S, Cymerys M, Gozdzik J, Torlinski L, Batura-Gabryel H: The impact of the sleep apnea syndrome on oxidant-antioxidant balance in the blood of overweight and obese patients. J Physiol Pharmacol. 2008; 59 Suppl 6: 761-769.
15）Mancuso M, Bonanni E, LoGerfo A, Orsucci D, Maestri M, Chico L, DiCoscio E, Fabbrini M, Siciliano G, Murri L: Oxidative stress biomarkers in patients with untreated obstructive sleep apnea syndrome. Sleep Med. 2012; 13: 632-636.
16）Tanır Basaranoglu S, Karadag-Oncel E, Aykac K, Ozsurekci Y, Aycan AE, Cengiz AB, Kara A, Ceyhan M: Presepsin: A new marker of catheter related blood stream infections in pediatric patients: Reply to Rivera-Moran Javier *et al.* J Infect Chemother. 2018; 24: 687.
17）Kasai H, Okada Y, Nishimura S, Rao MS, Reddy JK: Formation of 8-hydroxydeoxyguanosine in liver DNA of rats following long-term exposure to a peroxisome proliferator. Cancer Res. 1989; 49: 2603-2605.
18）Kasai H: Analysis of a form of oxidative DNA damage, 8-hydroxy-2′ -deoxyguanosine, as a marker of cellular oxidative stress during carcinogenesis. Mutat Res. 1997; 387: 147-163.

19) McCord JM: The evolution of free radicals and oxidative stress. Am J Med. 2000; 108: 652-659.
20) Matsumoto Y, Ogawa Y, Yoshida R, Shimamori A, Kasai H, Ohta H: The stability of the oxidative stress marker, urinary 8-hydroxy-2'- deoxyguanosine (8-OHdG), when stored at room temperature. J Occup Health. 2008; 50: 366-372.
21) Li YS, Kawasaki Y, Watanabe S, Ootsuyama Y, Kasai H, Kawai K: Diurnal and day-to-day variation of urinary oxidative stress marker 8-hydroxy-2'-deoxyguanosine. J Clin Biochem Nutr. 2021; 68: 18-22.
22) Shigenaga MK, Gimeno CJ, Ames BN: Urinary 8-hydroxy-2'-deoxyguanosine as a biological marker of in vivo oxidative DNA damage. PNAS. 1989; 86: 9697-9701.
23) Poulsen HE, Loft S, Prieme H, Vistisen K, Lykkesfeldt J, Nyyssonen K, Salonen JT: Oxidative DNA damage in vivo: relationship to age, plasma antioxidants, drug metabolism, glutathione-S-transferase activity and urinary creatinine excretion. Free Radic Res. 1998; 29: 565-571.
24) Lunec J, Holloway KA, Cooke MS, Faux S, Griffiths HR, Evans MD: Urinary 8-oxo-2'-deoxyguanosine: redox regulation of DNA repair in vivo? Free Radic Biol Med. 2002; 33: 875-885.
25) Yamauchi M, Nakano H, Maekawa J, Okamoto Y, Ohnishi Y, Suzuki T, Kimura H: Oxidative stress in obstructive sleep apnea. Chest. 2005; 127: 1674-1679.
26) Jordan W, Cohrs S, Degner D, Meier A, Rodenbeck A, Mayer G, Pilz J, Rüther E, Kornhuber J, Bleich S: Evaluation of oxidative stress measurements in obstructive sleep apnea syndrome. J Neural transm (Vienna, Austria : 1996). 2006; 113: 239-254.
27) Volná J, Kemlink D, Kalousová M, Vávrová J, Majerová V, Mestek O, Svarcová J, Sonka K, Zima T: Biochemical oxidative stress-related markers in patients with obstructive sleep apnea. Medical science monitor : Int Med J Exper Clin Res. 2011; 17: Cr491-497.
28) Iber C A-IS, Chesson AL, Jr., Quan SF for the American Academy of Sleep Medicine.: The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. 1st ed. Westchester, IL. Am Acad Sleep Med; 2007. 2007.
29) Bonnet MH, Arand DL: EEG arousal norms by age. J Clin Sleep Med. 2007; 3: 271-274.
30) Takahashi K, Ueda S, Kobayashi T *et al.*: Chronic intermittent hypoxia-mediated renal sympathetic nerve activation in hypertension and cardiovascular disease. Sci Rep. 2018; 8: 17926.
31) Nishikawa T, Sasahara T, Kiritoshi S, *et al.*: Evaluation of urinary 8-hydroxydeoxy-guanosine as a novel biomarker of macrovascular complications in type 2 diabetes. Diabetes Care 2003; 26: 1507-1512.
32) Xu S, Touyz RM: Reactive oxygen species and vascular remodelling in hypertension: still alive. Can J Cardiol 2006; 22: 947-951.
33) Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Clin Chim Acta 2004; 339: 1-9.
34) Babakr A, Mukhtar M, Althubiti M, Al-Amodi H, Almaimani R, Nour Eldin MM, Elzubeir Abdalla M, Nasif W: Investigation of Hyperlipidemia Associated with Increased Levels of Oxidized Low-Density Lipoproteins and 8-Hydroxy-2'-Deoxyguanosine. Diabetes Metab Syndr Obes. 2023; 16: 447-455.
35) Mertens A, Holvoet P. Oxidized LDL and HDL: antagonists in atherothrombosis. FASEB J. 2001; 15 (12): 2073-2084.
36) Le Lay S, Simard G, Martinez MC, Andriantsitohaina R: Oxidative stress and metabolic pathologies: from an adipocentric point of view. Oxid Med Cell Longev 2014; 2014: 908539.
37) Kotani K, Yamada T: Association between urinary 8-OHdG and pulse wave velocity in hypertensive patients with type 2 diabetes mellitus. Singapore Med J. 2014; 55: 202-208.
38) Di Minno A, Turnu L, Porro B, Squellerio I, Cavalca V, Tremoli E, Di Minno MN: 8-Hydroxy-2-Deoxyguanosine Levels and Cardiovascular Disease: A Systematic Review and Meta-Analysis of the Literature. Antioxid Redox Signal. 2016; 24: 548-555.
39) Hazukova R, Rezacova M, Pleskot M, Zadak Z, Cermakova E, Taborsky M: DNA damage and arterial hypertension. A systematic review and meta-analysis. Biom Pap Med Fac Univ Palacky Olomouc Czech Repub. 2024; 168: 15-24.
40) Yagi S, Akaike M, Aihara K *et al.*: Effect of low-dose (1 mg/day) pitavastatin on left ventricular diastolic function and albuminuria in patients with hyperlipidemia. Am j Cardiol. 2011; 107: 1644-1649.
41) Hu C, Yang Y, Li J *et al.*: Maternal Diet-Induced

Obesity Compromises Oxidative Stress Status and Angiogenesis in the Porcine Placenta by Upregulating Nox2 Expression. Oxid Med Cell Longev. 2019; 2019: 2481592.

42) Nagayoshi Y, Kawano H, Hokamaki J, Miyamoto S, Kojima S, Shimomura H, Tsujita K, Sakamoto T, Yoshimura M, Ogawa H: Urinary 8-hydroxy-2' -deoxyguanosine levels increase after reperfusion in acute myocardial infarction and may predict subsequent cardiac events. Am J Cardiol. 2005; 95: 514-517.

43) Chiou CC, Chang PY, Chan EC, Wu TL, Tsao KC, Wu JT: Urinary 8-hydroxydeoxyguanosine and its analogs as DNA marker of oxidative stress: development of an ELISA and measurement in both bladder and prostate cancers. Int J Clin Chem. 2003; 334: 87-94.

44) Lee KH, Shu XO, Gao YT, Ji BT, Yang G, Blair A, Rothman N, Zheng W, Chow WH, Kang D: Breast cancer and urinary biomarkers of polycyclic aromatic hydrocarbon and oxidative stress in the Shanghai Women's Health Study. Cancer Epidemiol Biomarker Prev. 2010; 19: 877-883.

45) Hara M, Nishida Y, Shimanoe C, *et al.*: Intensity-specific effect of physical activity on urinary levels of 8-hydroxydeoxyguanosine in middle-aged Japanese. Cancer Sci. 2016; 107: 1653-1659.