Association of Obstructive Sleep Apnea and Glucose Metabolism in Subjects With or Without Obesity

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OBJECTIVE—The purpose of this study was to investigate whether the impact of obstructive sleep apnea (OSA) on glucose metabolism was different according to the presence or absence of obesity.

RESEARCH DESIGN AND METHODS—A total of 1,344 subjects >40 years old from the Korean Genome and Epidemiology Study were included. OSA was detected by home portable sleep monitoring. Plasma glucose, HbA_{1c}, and insulin resistance were compared according to OSA and obesity status. The associations between OSA and impaired fasting glucose (IFG), impaired glucose tolerance (IGT), IFG + IGT, and diabetes were evaluated in subjects with and without obesity after adjusting for several confounding variables. The effect of visceral obesity on this association was evaluated in 820 subjects who underwent abdominal computed tomography scanning.

RESULTS—In subjects without obesity, fasting glucose, 2-h glucose after 75-g glucose loading, and HbA_{1c} were higher in those with OSA than in those without after controlling for age, sex, and BMI. In addition, the presence of OSA in nonobese subjects was associated with a higher prevalence of IFG + IGT and diabetes after adjusting for several confounding variables (odds ratio 3.15 [95% CI 1.44–6.90] and 2.24 [1.43–3.50] for IFG + IGT and diabetes, respectively). Further adjustment for visceral fat area did not modify this association. In contrast, in those with obesity, none of the abnormal glucose tolerance categories were associated with OSA.

CONCLUSIONS—The presence of OSA in nonobese individuals is significantly associated with impaired glucose metabolism, which can be responsible for future risk for diabetes and cardiovascular disease.

Diabetes Care 36:3909–3915, 2013

Many population- and clinic-based cross-sectional studies have found that obstructive sleep apnea (OSA) is associated with glucose intolerance and insulin resistance (1,2). Furthermore, the Sleep Heart Health Study demonstrated that sleep-disordered breathing was associated not only with diabetes, but also with intermediate hyperglycemia, such as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), after controlling for age, sex, BMI, and waist circumference (WC) (3). However, the effects of continuous positive airway pressure (CPAP) therapy on glucose metabolism were inconclusive (4–6). These results may be attributable to the differences in populations, variable treatment duration, differences in BMI, discrepant methodologies and cutoffs for OSA, and the presence or absence or excessive daytime sleepiness (EDS). Harsch et al. (5) found that CPAP therapy significantly improved insulin sensitivity after only 2 days of treatment. Of note, the improvement of insulin sensitivity with CPAP therapy was minimal in patients with a BMI >30 kg/m^2, but it was more prominent in less obese individuals, suggesting that the impact of OSA on glucose metabolism may be larger in those without obesity.

Although obesity is a key risk factor for OSA, a substantial proportion of individuals with OSA are not obese, especially those of Asian descent (7–9). In a few studies in nonobese subjects (BMI <25 kg/m^2), OSA was independently associated with insulin resistance, compensatory hyperinsulinemia (10), and metabolic abnormalities (7–10). However, there have been few studies on the difference in metabolic consequences of OSA on the basis of obesity status. In addition, there is a paucity of research that has adequately analyzed the influence of visceral obesity, a cardinal feature of sleep apnea and glucose metabolism.

Therefore, the purpose of the current study was to evaluate whether the association of OSA and impaired glucose regulation (IFG, IGT, IFG + IGT, and diabetes) was different in subjects with or without obesity, even after adjusting for generalized or visceral adiposity. To explain the possible mechanism of this association, insulin resistance and secretion was compared according to obesity and OSA status in a large community-based cohort study in Korea.

RESEARCH DESIGN AND METHODS

—All study subjects were from the ongoing, prospective, population-based Korean Genome and Epidemiology Study (KoGES) cohort. The original study was designed to establish a representative adult cohort in an urban area, the city of Ansan, and to identify the epidemiologic

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Received 13 February 2013 and accepted 27 June 2013.
DOI: 10.2337/dc13-0375
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-0375/-/DC1.

characteristics, frequency, and determinants of chronic diseases in Koreans. Initially, 5,015 participants (2,521 men and 2,494 women 40–69 years old) who participated in a comprehensive health examination and onsite interviews at Korea University Ansan Hospital formed a longitudinal cohort from June 2001 to January 2003. Follow-up assessments were conducted biennially with scheduled site visits. At each visit, subjects signed an informed consent form, which was approved by the Human Subjects Review Committee at the Korea University Ansan Hospital. The fifth biennial examination was conducted from March 2009 to February 2011 and the sixth examination from March 2011 to February 2013. Polysomnography (PSG) was included randomly in the study protocol in September 2009 in about one-half of the KoGES participants. Although PSG will be administered to the entire study population during the 4-year period, the present study includes only the subset of the sample with PSG data acquired between September 2009 and November 2011. After excluding the subjects who had missing data and extreme outliers of glucose concentrations, 1,344 subjects (706 men and 638 women) were finally recruited into the current study. Further details from the protocol and design of the KoGES are described elsewhere (11).

Anthropometric and laboratory measurements

All participants responded to an interviewer-administered questionnaire and underwent a comprehensive physical examination. Sociodemographic characteristics were age, sex, occupation, marital status, and income. Lifestyle characteristics were smoking status and alcohol consumption categorized as never, former, and current. Level of exercise was categorized as never, lightly (<3 times/week, ≥30 min/session), or regularly (≥3 times/week, ≥30 min/session) during the previous month. The presence of chronic illnesses, including diabetes, hypertension, dyslipidemia, and cardiovascular disease (CVD), was noted as were prescribed medications. Subjects with documented events or medical records of myocardial infarction, angina, heart failure, stroke, or peripheral artery disease were considered to have CVD.

Diabetes was defined by American Diabetes Association criteria, using a 75-g oral glucose tolerance test (fasting plasma glucose [FPG] ≥7.0 mmol/L or 2-h plasma glucose [2hPG] ≥11.1 mmol/L), and medical history (12). For subjects without diabetes, glucose tolerance status was assessed by American Diabetes Association criteria (12) as follows: IFG only (5.6 ≤ FPG <7.0 mmol/L and 2hPG <7.8 mmol/L), IGT only (FPG <5.6 mmol/L and 7.8 ≤ 2hPG <11.1 mmol/L), and IFG + IGT (5.6 ≤ FPG <7.0 mmol/L and 7.8 ≤ 2hPG <11.1 mmol/L). Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or medical history (13).

Height and body weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. BMI was calculated as weight in kilograms divided by height in meters squared. WC was measured at the midpoint between the lower rib margin and the iliac crest in the standing position. Obesity was defined as BMI ≥25 kg/m^2 according to the Asian-specific BMI cutoffs from the World Health Organization report (14).

Blood was drawn for biochemical analysis after an overnight fast. Plasma glucose, serum triglycerides, HDL cholesterol, and LDL cholesterol levels were measured with an autoanalyzer (ADVIA 1650; Siemens, Tarrytown, NY). Insulin was measured with an immunoradiometric assay kit (INS-IRMA Kit; BioSource, Nivelles, Belgium) using a Packard γ counter system. Insulin resistance was estimated with the homeostasis model of assessment for insulin resistance (HOMA-IR) and calculated as fasting glucose (mmol/L) × fasting insulin (μU/mL) / 22.5. HOMA β-cell function (HOMA-β) (%) was calculated as 20 × fasting insulin (μU/mL) / fasting glucose (mmol/L) − 3.5 (15).

Visceral fat measurements

For subjects who participated in the fifth biennial examination (n = 820), single-slice computed tomography (CT) scanning (Brilliance 64; Philips, Cleveland, OH) was used to quantify intra-abdominal adipose tissue. The scans were conducted at 120 kV with a slice thickness of 5 mm at the level of the L4–L5 vertebral interspace. The total area of intra-abdominal fat was delineated by manual tracing within the muscle wall, and the visceral fat area (VFA) was defined as an area with an attenuation range between −190 and −30 Hounsfield units.

Overnight sleep study

Overnight sleep study was performed at home with a portable device (Embletta X100; Embla Systems, San Carlos, CA). Two trained sleep technologists visited each subject's home in the evening, applied sensors, and instructed the subject on how to start and stop the recording. Subjects were required to record the lights-off and -on times and to report them the next morning. Recording channels were one for electroencephalography (C4–A1), one for electrooculography (right upper outer canthus to left lower outer canthus), one for chin electromyography, one for modified lead II electrocardiography, one for airflow from nasal airflow pressure transducer, two for respiratory effort from chest and abdominal respiratory inductance plethysmography, one pulse oximeter, and one position sensor. Data were scored by two well-trained technicians who had ≥5 years of experience with PSG monitoring and scoring according to standard guidelines (16,17). Internal consistency for scoring the apnea-hypopnea index (AHI) was high (Cronbach α = 0.996 and 1.00 for each rater), and interrater reliability was strong (Cronbach α = 0.998). Although we did not perform a validity study to compare PSG recordings obtained in the home and laboratory settings, the Sleep Heart Health Study clearly demonstrated that the median respiratory disturbance index was similar in the unattended home and attended laboratory settings, with differences of a small magnitude in some sleep parameters (18).

Obstructive apnea was defined when airflow dropped by ≥90% of the baseline with ongoing chest and abdominal movement, and hypopnea was defined as a reduction in airflow by ≥30% associated with at least a 4% oxygen desaturation. The duration threshold for the respiratory events was 10 s. AHI was calculated, and OSA was defined as an AHI ≥5 (1,16,19).

Definition of EDS

Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS) (20), a well-validated and frequently used subjective eight-item, self-administered questionnaire. Subjects were asked to score the likelihood of falling asleep in eight different situations with different levels of stimulation. Possible ESS scores range from 0 to 24. The higher the ESS score, the greater propensity for sleepiness implied. In the current study, EDS was defined as ESS scores >10 (20).

Statistical analysis

Subject characteristics at baseline were compared among groups stratified by the

presence or absence of OSA and obesity by Student *t* test for continuous variables and χ^2 test for categorical variables. Nonnormally distributed variables, such as HbA_{1c}, HOMA-IR, HOMA-β, AHI, and triglyceride level, are presented as the median and interquartile range for each group, and the differences were tested after logarithmic transformation. Variables associated with glucose metabolism were compared by ANCOVA after adjusting for age, sex, and BMI among the groups stratified by OSA and obesity. For ANCOVA, we confirmed the homogeneity of the slope between the covariates and the dependent variables in subjects with or without OSA. The interaction term for OSA and obesity on HOMA-β was calculated to determine whether the association between OSA and HOMA-β was modified by obesity status. To exclude the potential confounding effect of medication for diabetes or dyslipidemia on glucose metabolism, the same analyses were repeated after excluding subjects who were taking these medications.

To evaluate the impact of OSA on IFG only, IGT only, IFG + IGT, and diabetes according to the presence or absence of obesity, multivariate logistic regression analyses were conducted. In the analysis, the following five models were fit for each outcome: Model 1 was adjusted for age and sex; model 2 was adjusted for age, sex, alcohol consumption, smoking status, exercise, presence of hypertension or CVD, and medication for dyslipidemia; model 3 was the same as model 2 and adjusted for BMI; model 4 was the same as model 2 and adjusted for WC; and model 5 was the same as model 2 and adjusted for VFA in subjects who underwent abdominal CT scan. To exclude the potential confounding effect of medication for diabetes or dyslipidemia on glucose metabolism, the same analyses were repeated after excluding subjects who were taking these medications. Odds ratios (ORs) for IFG only, IGT only, IFG + IGT, and diabetes were calculated according to the tertile of AHI to demonstrate the dose-response relationship. In addition, to examine the additive effect of EDS and OSA on glucose metabolism, ORs for IFG only, IGT only, IFG + IGT, and diabetes were evaluated in subjects with OSA according to the presence or absence of EDS compared with those without OSA.

For logistic regression, we calculated adjusted R^2 and Hosmer-Lemeshow statistics to assess model adequacy. These models showed no evidence of lack of fit according to the Hosmer-Lemeshow statistic. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SAS version 9.1 for Windows software (SAS Institute Inc., Cary, NC).

RESULTS—Table 1 shows the characteristics of the participants stratified by the presence or absence of OSA and obesity. About 36.6% of nonobese and 58.2% of obese subjects had OSA. However, the severity of OSA was mostly mild and moderate (27, 8.8, and 0.8% of nonobese and 38.4, 14.6, and 5.2% obese subjects had mild, moderate, and severe OSA, respectively). Among 396 subjects with diabetes, 351 had a history of diabetes of whom 142 were treated with oral hypoglycemic agents ($n = 140$) or insulin ($n = 4$). Subjects with OSA were older and had a higher 2hPG, HbA_{1c}, BMI, WC, VFA,

Table 1—*Characteristics of subjects according to the presence or absence of obesity and OSA*

		BMI <25 kg/m^2			BMI ≥25 kg/m^2		
	Total subjects	AHI <5	AHI ≥5	*P* value	AHI <5	AHI ≥5	*P* value
N	1,344	462 (63.4)	267 (26.6)	—	257 (41.8)	358 (58.2)	—
Men	706 (52.5)	210 (45.5)	160 (60.0)	<0.001	123 (47.9)	213 (59.5)	0.004
Age (years)	57.7 ± 7.4	55.6 ± 6.0	60.7 ± 7.9	<0.0001	56.3 ± 7.2	59.0 ± 7.7	<0.0001
FPG (mmol/L)	5.5 ± 1.0	5.2 ± 0.8	5.6 ± 1.0	<0.0001	5.6 ± 1.0	5.8 ± 1.1	0.059
2hPG (mmol/L)	8.0 ± 2.6	7.2 ± 2.3	8.1 ± 2.6	<0.0001	8.4 ± 2.6	9.0 ± 2.8	0.012
HbA_{1c} (%)	5.6 (5.4–5.9)	5.5 (5.3–5.8)	5.7 (5.4–6.0)	<0.0001	5.6 (5.4–6.0)	5.8 (5.5–6.2)	0.025
SBP (mmHg)	116.1 ± 14.7	112.8 ± 14.9	117.4 ± 15.4	<0.0001	116.6 ± 13.9	119.0 ± 13.6	0.034
BMI (kg/m^2)	24.8 ± 2.8	22.6 ± 1.5	23.0 ± 1.5	<0.001	26.9 ± 1.7	27.5 ± 2.1	<0.0001
WC (cm)	81.2 ± 8.1	75.4 ± 5.9	78.6 ± 6.0	<0.0001	85.1 ± 6.1	88.0 ± 6.3	<0.0001
VFA† (cm^2)	83.5 ± 39.3	60.3 ± 28.6	76.8 ± 32.3	<0.0001	92.9 ± 34.0	109.6 ± 40.9	<0.0001
HOMA-IR	1.9 (1.4–2.6)	1.6 (1.3–2.0)	1.8 (1.4–2.3)	<0.0001	2.2 (1.7–2.9)	2.4 (1.8–3.2)	<0.0001
HOMA-β	90.0 (68.9–121.0)	88.7 (67.5–115.6)	82.9 (60.6–109.5)	0.029	93.4 (72.0–131.1)	97.1 (73.8–127.5)	0.331
AHI	4.4 (1.6–10.3)	1.5 (0.5–2.7)	10.3 (7.0–15.4)	<0.0001	2.2 (1.2–3.6)	11.2 (7.5–17.5)	<0.0001
TG (mmol/L)	1.4 (1.0–2.0)	1.2 (0.9–1.7)	1.3 (1.0–2.0)	<0.0001	1.6 (1.1–2.1)	1.6 (1.1–2.3)	0.633
HDL-C (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.3	0.002	1.2 ± 0.3	1.2 ± 0.3	0.955
LDL-C (mmol/L)	3.1 ± 0.8	3.1 ± 0.9	3.1 ± 0.9	0.248	3.3 ± 0.8	3.1 ± 0.8	0.001
IFG only	79 (5.9)	28 (6.1)	11 (4.1)	0.262	20 (7.8)	20 (5.6)	0.276
IGT only	252 (18.8)	80 (17.3)	43 (16.1)	0.674	55 (21.4)	74 (20.7)	0.826
IFG + IGT	93 (6.9)	15 (3.3)	22 (8.2)	0.003	20 (7.8)	36 (10.1)	0.334
DM	396 (29.5)	74 (16.0)	98 (36.7)	<0.0001	76 (29.6)	148 (41.3)	0.003
CVD	90 (6.7)	19 (4.1)	23 (8.6)	0.012	13 (5.1)	35 (9.8)	0.032
DM medications	142 (10.6)	23 (5.0)	34 (12.7)	<0.001	28 (10.9)	57 (15.9)	0.075
Lipid medications	100 (7.4)	17 (3.7)	27 (10.1)	<0.001	12 (4.7)	44 (12.3)	0.001
HTN medications	380 (28.3)	70 (15.2)	80 (30.0)	<0.0001	67 (26.1)	163 (45.5)	<0.0001

Data are *N* (%), mean ± SD, or median (interquartile range). Statistical significance was estimated after logarithmic transformation. DM, diabetes; HDL-C, HDL cholesterol; HTN, hypertension; LDL-C, LDL cholesterol; SBP, systolic blood pressure; TG, triglycerides. †VFA was measured in 820 subjects.

and HOMA-IR than those without OSA, regardless of obesity. In the nonobese group, subjects with OSA had higher FPG and triglyceride levels and lower HOMA-β and HDL cholesterol levels than those without OSA. The proportion of IFG + IGT and diabetes was higher according to OSA status in nonobese subjects, whereas only the prevalence of diabetes was higher in obese subjects with OSA.

Table 2 presents the age-, sex-, and BMI-adjusted values for glucose metabolism according to OSA and obesity status. In the nonobese group, FPG, 2hPG, and HbA_{1c} levels were significantly higher, and HOMA-IR was modestly higher in those with OSA than in those without OSA. However, in the obese group, only insulin and HOMA-IR levels were associated with OSA. Although not statistically significant, HOMA-β was lower in nonobese subjects with OSA than in those without OSA but higher in obese subjects with OSA than in those without OSA. Therefore, a significant interaction between OSA and obesity was observed for HOMA-β ($P = 0.025$). After excluding subjects who were taking medication for diabetes or dyslipidemia, in the nonobese group, FPG and 2hPG were still higher in those with OSA than in those without. On the contrary, in the obese group, although glucose concentrations were not different, insulin, HOMA-IR, HOMA-β were higher in those with OSA than in those without (Supplementary Table 1).

Multivariate logistic regression analyses were conducted to investigate the effects of OSA on glucose metabolism according to obesity status (Table 3). In subjects without obesity, the presence of OSA showed higher ORs for IFG + IGT and diabetes, even after adjusting for several confounding variables, including BMI or WC. OSA was significantly associated with diabetes even after adjusting for VFA in nonobese subjects. In an analysis to show the dose-response relationship, nonobese subjects with the highest AHI tertile had the highest ORs for IFG + IGT or diabetes (Supplementary Table 2). In contrast, in those with obesity, none of the abnormal glucose categories was associated with OSA. These findings were consistent even after excluding subjects who were taking medication for diabetes or dyslipidemia (Supplementary Table 3).

Supplementary Table 4 shows the joint effect of OSA and EDS on glucose tolerance categories. In the nonobese group, compared with subjects without OSA, nonsleepy subjects with OSA had higher ORs for diabetes, but sleepy subjects with OSA had the highest ORs for diabetes (hazard ratio 5.78 [95% CI 2.05–16.3]). However, this finding was not evident in obese subjects.

CONCLUSIONS—In this large community-based cohort study, we demonstrated the differential association between OSA and impaired glucose metabolism according to the presence of obesity. Of note, OSA was significantly associated with abnormal glucose metabolism in nonobese subjects, even after adjusting for several confounding variables, including generalized or visceral adiposity. To our knowledge, this study is the first to show that the impact of OSA on glucose metabolism is more evident in the nonobese than in the obese population. We also clearly demonstrated that in the nonobese group, FPG, 2hPG, and HbA_{1c} were significantly higher and that HOMA-IR was modestly higher in subjects with OSA than in those without. The only previous study to analyze the effect of OSA according to obesity status was the Sleep Heart Health Study, where the association between OSA and abnormal glucose metabolism was not different between the nonoverweight and overweight/obese groups (3). The possible mechanism of this discrepancy is not clear. We can hypothesize that OSA may have a lesser impact on glucose metabolism in obese than in nonobese individuals because of preexisting derangements in those who are obese. In accordance with this theory, the improvement of insulin sensitivity in patients with OSA receiving CPAP therapy was minimal in those with a BMI of >30 kg/m^2, whereas it was more prominent in those with less obesity (5). In addition, Reinke et al. (21) demonstrated that the acute intermittent hypoxia caused insulin resistance and increased secretion of leptin and tumor necrosis factor-α in lean mice. However, obesity was associated with striking increases in leptin and tumor necrosis factor-α levels, which overwhelmed the effects of hypoxia. On the contrary, Drager et al. (22) showed that the effect of chronic intermittent hypoxia on glucose intolerance, inflammation, and oxidative stress was prominent in obese mice but not in lean mice. The causes of these contradictory findings are not clear; however, the metabolic and proinflammatory responses to acute and chronic intermittent hypoxia may be different.

Table 2—*Variables associated with glucose metabolism according to obesity and OSA status after adjusting for age, sex, and BMI*

	Total			BMI <25 kg/m^2			BMI ≥25 kg/m^2		
	AHI <5	AHI ≥5	*P* value	AHI <5	AHI ≥5	*P* value	AHI <5	AHI ≥5	*P* value
FPG (mmol/L)	5.44 ± 0.04	5.56 ± 0.04	0.029	5.28 ± 0.04	5.46 ± 0.06	0.017	5.64 ± 0.07	5.71 ± 0.06	0.485
2hPG (mmol/L)	7.85 ± 0.10	8.28 ± 0.11	0.006	7.34 ± 0.11	7.84 ± 0.16	0.014	8.51 ± 0.18	8.85 ± 0.16	0.157
HbA_{1c}* (%)	5.69 (5.64–5.74)	5.79 (5.74–5.84)	0.008	5.60 (5.55–5.65)	5.73 (5.66–5.8)	0.003	5.81 (5.72–5.90)	5.87 (5.79–5.95)	0.304
F-insulin* (mmol/L)	7.91 (7.68–8.14)	8.47 (8.20–8.74)	0.003	7.07 (6.83–7.33)	7.35 (7.00–7.71)	0.227	9.02 (8.59–9.46)	9.88 (9.48–10.30)	0.006
2h-insulin* (mmol/L)	37.94 (35.85–40.15)	44.02 (41.27–46.95)	0.001	33.10 (30.96–35.39)	35.92 (32.69–39.47)	0.178	44.77 (40.57–49.40)	55.26 (50.66–60.28)	0.002
HOMA-IR*	1.88 (1.82–1.95)	2.06 (1.99–2.14)	0.001	1.64 (1.57–1.71)	1.76 (1.66–1.85)	0.055	2.23 (2.10–2.36)	2.46 (2.35–2.59)	0.009
HOMA-β*	89.10 (85.98–92.35)	89.88 (86.46–93.45)	0.756	86.09 (82.39–89.95)	82.44 (77.71–87.46)	0.265	92.02 (86.73–97.64)	97.67 (92.85–102.75)	0.142

Data are adjusted mean ± SE or geometric mean (95% CI). 2h-insulin, 2-h insulin after 75-g glucose loading; F-insulin, fasting insulin. *Statistical significance was estimated after logarithmic transformation.

Table 3—*Association between OSA and abnormal glucose metabolism according to obesity status*

	Total	BMI <25 kg/m^2	BMI ≥25 kg/m^2
IFG only (*N* = 79/603)			
Model 1	1.14 (0.69–1.88)	0.92 (0.43–1.97)	0.97 (0.47–1.97)
Model 2	1.03 (0.62–1.73)	0.79 (0.35–1.74)	0.94 (0.46–1.95)
Model 3	0.90 (0.53–1.54)	0.79 (0.35–1.78)	0.95 (0.46–1.99)
Model 4	0.87 (0.51–1.49)	0.70 (0.31–1.58)	0.94 (0.45–1.95)
Model 5	0.90 (0.48–1.70)	0.81 (0.31–2.14)	0.83 (0.34–2.04)
IGT only (*N* = 252/776)			
Model 1	1.49 (1.07–2.07)	1.23 (0.77–1.98)	1.28 (0.78–2.10)
Model 2	1.46 (1.05–2.03)	1.21 (0.75–1.96)	1.26 (0.77–2.08)
Model 3	1.15 (0.81–1.63)	1.09 (0.67–1.78)	1.18 (0.71–1.97)
Model 4	1.15 (0.81–1.63)	1.04 (0.63–1.70)	1.19 (0.72–1.98)
Model 5	1.37 (0.88–2.15)	1.09 (0.58–2.07)	1.55 (0.80–3.02)
IFG and IGT (*N* = 93/617)			
Model 1	3.06 (1.91–4.91)	3.13 (1.50–6.52)	1.94 (1.02–3.69)
Model 2	2.66 (1.63–4.33)	3.26 (1.51–7.03)	1.55 (0.79–3.06)
Model 3	2.04 (1.23–3.40)	2.95 (1.35–6.44)	1.48 (0.74–2.94)
Model 4	2.15 (1.30–3.57)	3.15 (1.44–6.90)	1.47 (0.74–2.93)
Model 5	2.15 (1.15–4.02)	2.41 (0.98–5.94)	1.76 (0.70–4.44)
DM (*N* = 396/920)			
Model 1	2.50 (1.88–3.34)	2.48 (1.64–3.76)	1.74 (1.13–2.67)
Model 2	2.27 (1.67–3.07)	2.47 (1.59–3.84)	1.53 (0.97–2.40)
Model 3	1.85 (1.35–2.54)	2.42 (1.55–3.77)	1.36 (0.86–2.17)
Model 4	1.83 (1.34–2.51)	2.24 (1.43–3.50)	1.40 (0.88–2.23)
Model 5	1.60 (1.07–2.39)	2.24 (1.27–3.96)	0.99 (0.54–1.81)

Data are OR (95% CI). Reference group, normal glucose tolerance. Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, alcohol consumption, smoking, exercise, presence of hypertension or CVD, and medication for dyslipidemia. Model 3 adjusted for age, sex, alcohol consumption, smoking, exercise, presence of hypertension or CVD, medication for dyslipidemia, and BMI. Model 4 adjusted for age, sex, alcohol consumption, smoking, exercise, presence of hypertension or CVD, medication for dyslipidemia, and WC. Model 5 adjusted for age, sex, alcohol consumption, smoking, exercise, presence of hypertension or CVD, medication for dyslipidemia, and VFA (*N* = 820, for subjects who underwent abdominal CT scan). DM, diabetes.

An alternative hypothesis may be a presence or absence of EDS in subjects with OSA. EDS is reportedly associated with hyperglycemia and insulin resistance in subjects with OSA (23,24). Intermittent hypoxemia has been shown to result in disturbed sleep architecture or to damage neuronal structures that promote wakefulness in animal models (25). Indeed, higher degrees of hypoxemia predict both sleepiness and insulin resistance (1,26). According to these studies, we can expect that the effect of hypoxemia on glucose metabolism may be more evident in patients with OSA and EDS. In the current study, we demonstrated that the joint effect of OSA and EDS on the OR for diabetes was highly significant only in nonobese subjects. Therefore, the differential impact of EDS on glucose metabolism according to obesity status may be responsible for the discrepant effect of OSA in subjects with or without obesity in the current study.

The association between HOMA-IR and OSA was similar in subjects with and without obesity, as seen in previous research (1,3,27). However, few studies have evaluated insulin secretion according to OSA status. Recently, in healthy young men without diabetes and obesity (most of them Caucasian), subjects with OSA had increased insulin resistance and compensatory hyperinsulinemia (10). In the current study, however, HOMA-β was lower in nonobese subjects with OSA than in those without OSA but was higher in obese subjects. This finding was more evident in obese subjects after excluding those taking medication for diabetes or dyslipidemia and suggests that inadequate insulin secretion against the increased insulin resistance may be responsible for the abnormal glucose metabolism in nonobese individuals, which is characteristic for diabetes in Asians (28,29). On the contrary, increased insulin secretion in response to insulin resistance in obese individuals with OSA may explain why glucose metabolism is less impaired by OSA. However, the hyperinsulinemic-euglycemic clamp technique should be used to further explore the mechanisms of the impairment of glucose metabolism by OSA.

Another possible explanation for this finding may be ethnic differences in body composition. Asians generally have more visceral fat in the same BMI range compared with Caucasians. Therefore, the prevalence of metabolically obese normal weight (MONW) individuals who have not only a normal BMI, but also a cluster of obesity-related risk factors for diabetes and CVD is reportedly higher in Asians (30,31). Higher levels of inflammatory adipokines and atherogenic LDL profiles in MONW individuals (32,33) may mediate the increase in CVD and mortality in this population (34). The finding that a worse cardiometabolic profile was more prominent in nonobese subjects with OSA in the current study supports the notion that these individuals may have similar characteristics as those with MONW.

Although the relationship between OSA and abnormal glucose metabolism has been demonstrated in several previous studies (1,2,35), a few have evaluated the association between OSA and distinct prediabetic groups (IFG and/or IGT), where sleep-disordered breathing was associated with occult diabetes, IFG only, IFG + IGT (3), or glucose intolerance (1,35) in population and clinic-based studies. Subjects with IFG had a greater impairment of early phase insulin secretion and increased endogenous glucose output, whereas IGT was associated with peripheral insulin resistance (36). In the current study, however, OSA was associated with neither IFG only nor IGT only. Because more severe metabolic abnormalities are present in individuals with IFG + IGT, diabetes develops more rapidly and unfavorable cardiovascular risk factors and mortality are increased compared with individuals with IFG only or IGT only (36–38). From this point of view, the significant association between OSA and IFG + IGT in the current study suggests that subjects with OSA are at a greater risk for developing diabetes and CVD and have a higher risk of mortality.

Compared with previous studies, which had several methodological limitations in terms of the study population (39,40) or lacked rigorous control for numerous confounders, especially obesity, the

current study used a large community-based sample and differentiated the effect of OSA according to the presence of obesity in addition to adjustment for generalized or visceral obesity. Another strength of the current study was the evaluation of OSA status during sleep at home, which provides a more realistic estimation of OSA severity than hospital-based studies because of the maintenance of regular daily habits of sleep, physical activity, and diet in the general population.

The major limitation of the current study was its cross-sectional design, which makes it difficult to determine whether there is a causal relationship between OSA and impaired glucose metabolism. Secondly, because we did not have a sufficient number of subjects with severe OSA (AHI ≥30), it is unclear whether the present findings would be consistent in those with severe OSA. However, the positive association between the AHI tertile and glucose tolerance categories in the nonobese group supports a dose-response relationship. In addition, the small numerical, but significant differences of some metabolic variables between those with and without OSA would be more evident if we had more subjects with severe OSA. However, the analysis of the association between AHI tertile and glucose tolerance categories showed that subjects with the third AHI tertile had the highest OR for IFG + IGT and diabetes in the nonobese group, which supports a dose-response relationship (data not shown). Finally, because BMI and body fat distribution in this population are different from other ethnicities, the present findings may not be generalizable to non-Asian populations.

In summary, the current study provides original evidence that the presence of mild to moderate OSA in nonobese individuals confers a higher risk for impaired glucose metabolism, even after adjusting for important risk factors. OSA can be responsible for the future risk for diabetes and CVD in nonobese individuals, whereas the prognostic implication of OSA in obese individuals is unclear. Whether this finding is universal across different populations with diverse ethnicity and obesity status should be studied in the future.

Acknowledgments—This research was supported by funding from the Korea Centers for Disease Control and Prevention (2009-E71002-00, 2010-E71001-00, 2011-E71004-00).

No potential conflicts of interest relevant to this article were reported.

N.H.K. conceived, designed, and supervised the study and wrote the first draft of the manuscript. N.H.K., N.H.C., C.-H.Y., S.K.L., D.W.Y., H.J.C., J.H.A., J.A.S., S.G.K., K.M.C., S.H.B., D.S.C., and C.S. contributed to subsequent versions of the manuscript and took responsibility for the decision to submit for publication. N.H.C. designed and supervised the study and obtained funding. C.-H.Y. helped with the analysis, supervised the study, and reviewed the manuscript critically. S.K.L. and D.W.Y. collected the data and coordinated the study. H.J.C. analyzed the data. J.H.A., J.A.S., and S.G.K. supervised the data collection and assisted with the data interpretation. K.M.C., S.H.B., and D.S.C. contributed to the study design and reviewed the manuscript critically. C.S. designed and supervised the study and reviewed the manuscript critically. C.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at ENDO 2012: The Endocrine Society 94th Annual Meeting, Houston, Texas, 23–26 June 2012.

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