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Obstructive sleep apnea: Is it a biomarker of metabolic health in obesity

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ABSTRACT

Context: The prevalence of obstructive sleep apnea (OSA) increases with obesity, and OSA has been linked to increased cardiovascular risk via hypoxemia and sleep disruption.
Objective and Main Outcome Measure(s): We hypothesized that if OSA contributes to cardio-metabolic risk, then 1) obese individuals with OSA will have more cardio-metabolic disease, and 2) patients with OSA who are non-adherent to CPAP treatment will have a greater incidence of cardio-metabolic abnormalities.
Design, setting and patients: We prospectively recruited obese patients (n = 83; BMI 49 ± 9 kg/m^2). All patients had polysomnography and were stratified by 1) the absence/presence of OSA, and 2) metabolic health. Detailed CPAP reports were analyzed for compliance and OSA severity in 38 subjects.
Results: OSA by polysomnography was present in 69% of patients. While 79% of patients with OSA and 54% without OSA were categorized as MAO ($\chi 2 = 5.47$, $p < 0.02$), when adjusted for age, gender and BMI this difference was not significant ($p = 0.36$). Insulin levels were higher in the OSA group, but when adjusted there was no significant difference ($p = 0.350$). In patients on CPAP therapy, there was a negative associative trend between OSA control (apnea-hypopnea index) and beta-cell function (HOMA-β) ($r = -0.406$, $p = 0.076$), but no association between CPAP compliance and AHI with age, BMI, glucose, insulin, adiponectin, or insulin resistance.
Conclusions: OSA is not independently associated with overall cardio-metabolic health and insulin resistance in obese patients, even when accounting for treatment compliance. The strongest predictors of the obese metabolic healthy phenotype in OSA patients are age, gender and BMI.

1. Introduction

Obesity is associated with numerous metabolic complications including Type 2 diabetes mellitus (T2DM), hypertension (HTN), dyslipidemia, non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH), cardiovascular disease (CVD) and several forms of cancer (Flegal et al., 2012). However, the presence of these obesity-related metabolic abnormalities varies among obese individuals (Bonora et al., 1998; Ferrannini et al., 1997). The phenotype of a metabolically healthy obese (MHO) individual was initially described in 1980 and includes a subset of obese patients (as defined by body mass index [BMI]) who do not manifest the typical metabolic abnormalities associated with obesity (Karelis et al., 2004). Although results are conflicting, highly dependent on the studied patient population, and differ based on the diagnostic criteria for metabolic health used (Phillips, 2013), these individuals tend to have a preserved level of insulin sensitivity, absence of HTN, and a more favorable lipid, inflammatory, and immunologic profile compared to metabolically abnormal obese (MAO) patients (Karelis et al., 2004; Aguilar-Salinas et al., 2008; Lynch et al., 2009; Stefan et al., 2008). This seeming paradox underscores that excess body weight is not the sole determinant of obesity-related complications and allows for novel pathogenic

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investigation.

The postulated mechanism(s) underlying the differential risk in these obese individuals is not well known and the physiologic and molecular basis for 'healthy' obesity remains relatively undiscovered. In addition, a recent meta-analysis demonstrated that although MHO patients have a comparable metabolic profile to normal weight individuals, their risk of adverse, long-term CV and mortality outcomes remains higher, calling into question the clinical importance of the healthy obese categorization (Kramer et al., 2013). Despite these knowledge gaps, a number of studies have recently attempted to elucidate the processes that lead to the MHO profile, including characterization of lifestyle factors and physical activity level, adipocyte size, amount and location of ectopic fat, inflammatory mediators, immune cells, and differences in gene expression (Badoud et al., 2015).

The prevalence of obstructive sleep apnea (OSA) increases with escalating BMI and has also been linked to various cardiometabolic abnormalities (Luciano et al., 2013). OSA may exert negative effects on the CV system through multiple mechanisms including hypoxemia, sleep disruption, activation of the sympathetic nervous system, and inflammatory activation (Zamarron et al., 2013). In spite of this proposed connection, the contribution of these OSA-related deleterious effects in determining the MHO vs. MAO phenotype is currently unknown. Furthermore, the prevalence of OSA in these two obese subsets is not well established.

In this study, we hypothesized that if OSA independently contributes to metabolic disease and heightens CV risk, then obese individuals with OSA will have a greater cardio-metabolic disease burden compared to BMI-matched patients without OSA. We further hypothesized that subjects with OSA who are non-compliant and poorly controlled with continuous positive airway pressure (CPAP) will also have a greater incidence of cardio-metabolic disease, be more likely to be categorized as MAO, and have heightened insulin resistance and impaired beta (β)-cell function compared to well-managed CPAP compliant patients.

2. Materials and methods

2.1. Selection and description of participants

We prospectively recruited obese patients scheduled to undergo bariatric surgery at The Ohio State University Center for Minimally Invasive Surgery. All patients had formal testing for OSA with polysomnography and analysis was performed prior to surgical intervention. A diagnosis of OSA was defined by either the presence of 1) greater than 4 predominantly obstructive respiratory events per hour of sleep by polysomnography (obstructive and mixed apneas, hypopneas, or respiratory effort related arousals) with one or more symptoms or OSA-related comorbidities, or 2) greater than 14 predominantly obstructive respiratory events per hour of sleep in the absence of associated symptoms or comorbidities (American Academy of Sleep Medicine, 2014). Subjects were further stratified into subgroups by 1) the absence (negative polysomnography) or presence (positive polysomnography or use of CPAP) of OSA, and 2) the absence or presence of 4 cardio-metabolic abnormalities: hypertension (blood pressure $\geq$ 130/80 mmHg and/or treatment with antihypertensive medications), T2DM/prediabetes (glycated hemoglobin $\geq$5.7% and/or treatment with diabetes medications), dyslipidemia (triglycerides $\geq$ 150 mg/dL, LDL > 130, HDL < 50 for women and <40 for men, and/or treatment with lipid lowering medications), and fatty liver disease. Metabolically healthy obese (MHO) participants were defined as having $\leq$ 1 of these cardio-metabolic disorders.

2.2. Experimental procedures

Individual CPAP compliance reports were available and reviewed for a subset of 38 subjects with OSA. A standard compliance report provides detailed information about device settings, pressure and leak values, apnea and hypopnea events per hour, and usage data including the number of days a patient uses the device for greater than or less than 4 h, average daily use, total hours used, and median daily usage. We defined CPAP compliant patients as usage >4 h per night on 70% of nights.

Blood samples were collected and analyzed for glucose, insulin, and adiponectin levels by ELISA (Millipore, Billerica, MA). The homeostasis model assessment for estimated insulin resistance (HOMA-IR) and beta-cell function (HOMA-β) were calculated as follow:

$$\text{HOMA-IR} = \text{Glucose (mg/dL) x Insulin / 405}$$

$$\text{HOMA-}\beta = 360 \times \text{Insulin/Glucose (mg/dL)} - 63\%$$

2.3. Statistical analysis

Data were examined for normality according to the Shapiro-Wilks criteria. Continuous variables were compared by subject group through one-way ANOVA for normally distributed variables and Mann-Whitney *U* test for non-normally distributed variables. Ordinal variables were analyzed by group via the Chi-Square test. Further analysis was performed using analysis of covariance (ANCOVA), with BMI, age and gender as independent covariate or confounding variables. For association analyses, Pearson's correlations were used for normally distributed data and Spearman's correlations for non-normally distributed data. Multivariate linear regression with age, gender and BMI as independent variables was performed for significant correlations. A p-value of $\leq$0.05 was considered statistically significant. All data are presented as means $\pm$ standard deviation.

2.4. Study approval

This study was approved by the Human Research Protection Office at The Ohio State University School of Medicine in Columbus, OH. All study subjects provided written informed consent before screening and participation in the study.

3. Results

3.1. Prevalence of OSA and cardio-metabolic abnormalities

A total of 83 patients (BMI 49 $\pm$ 9 kg/m2) were included in the overall analyses: Of this total cohort, fifty-seven (~69%) patients had OSA and twenty-six (~31%) patients did not have OSA. Patients with OSA were older, heavier, and more likely to be male, but there were no significant racial differences between the two cohorts (Table 1). While a greater proportion of patients with OSA (79%) compared to those without OSA (54%) had $\geq$ 2 cardio-metabolic abnormalities ($\chi 2 = 5.47$, $p < 0.02$) (Fig. 1), when adjusted for age, gender and BMI by covariate analysis this difference was nonsignificant ($p = 0.36$). Among all cardio-metabolic complications, HTN was more common in patients with OSA ($\chi 2 = 6.70$; p-value = 0.01), but when adjusted for age, gender and BMI this difference was also nonsignificant ($p = 0.29$). There were no significant differences in the presence of T2DM, dyslipidemia, fatty liver disease, or abnormal liver function tests (LFTs) in those with vs. without OSA.