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ORIGINAL ARTICLE

Insulin resistance and adipose-derived hormones in young men with untreated obstructive sleep apnea

Trent A. Hargens · Stephen G. Guill · Anthony S. Kaleth · Sharon M. Nickols-Richardson · Larry E. Miller · Donald Zedalis · John M. Gregg · Frank Gwazdauskas · William G. Herbert

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Abstract
Purpose Obstructive sleep apnea (OSA) increases the risk for insulin resistance (IR). The mechanisms that link the two are not clear and are frequently confounded by obesity. OSA is associated with alterations in adipose-derived hormones (adipokines) that increase IR; however, previous studies have focused on middle-aged and older adults. The objective of this study was to determine if IR and alterations in adipokines exist in young men with OSA, independent of obesity.
Methods Subjects were assigned into the following groups based on body mass index and presence of OSA: obese with OSA (OSA, $n=12$), obese without OSA (NOSA, $n=18$), and normal weight without OSA (CON, $n=15$). Fasting blood was obtained for batch analysis of biomarkers of IR. The homeostasis model assessment (HOMA) method was used to assess IR.
Results HOMA and leptin were higher in the OSA group than the CON group. There were no differences in insulin, tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) between the OSA and NOSA groups. Adiponectin was lower in the OSA group vs. NOSA and CON; however, when controlled for central abdominal fat (CAF), the difference was nullified. When controlled for total body adiposity, however, CAF was 24 % higher in the subjects with OSA vs. subjects without OSA.
Conclusions These findings suggest that excess CAF in young men with OSA may contribute to risk for type 2 diabetes indirectly by a degree that would otherwise not be reached through obesity, although further research is needed.

Keywords Obstructive sleep apnea · Insulin resistance · Adiponectin · Leptin · Obesity

T. A. Hargens
Department of Kinesiology, James Madison University, Harrisonburg, VA 22807, USA

T. A. Hargens (✉) · S. G. Guill · W. G. Herbert
Laboratory for Health and Exercise Sciences, Department of Human Nutrition, Foods and Exercise, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA
e-mail: hargenta@jmu.edu

A. S. Kaleth
Department of Kinesiology, Indiana University-Purdue University, Indianapolis, IN, USA

S. M. Nickols-Richardson
Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA

L. E. Miller
Miller Scientific Consulting, Inc., 26 Portobello Road, Arden, NC 28704, USA

D. Zedalis
Edward Via Virginia College of Osteopathic Medicine, Blacksburg, VA, USA

J. M. Gregg · W. G. Herbert
Health Research Group, LLC, Rockbridge Baths, VA, USA

F. Gwazdauskas
Department of Dairy Science, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA

Introduction

Obstructive sleep apnea (OSA) is a chronic sleep disorder that may affect as many as one in five middle-aged adults

[1]. OSA is characterized by repetitive bouts of upper airway collapse during sleep, resulting in intermittent periods of hypoxia, hypercapnia, fragmented sleep, and heightened sympathetic nervous system activity [2]. If left untreated, OSA increases the risk for chronic cardiovascular and metabolic disorders, such as hypertension [3], diabetes [4], and metabolic syndrome [5]. Although the influence of obesity likely exaggerates this risk, considerable evidence suggests an independent relationship exists between OSA and many of these conditions [3–5]. Early studies attempting to determine if the relationship between OSA and insulin resistance is independent of obesity were conflicting [5, 6]. However, recent well-controlled investigations demonstrated a higher insulin resistance in middle-aged, obese subjects with OSA than that observed in controls of similar age and body habitus [6, 7].

The mechanisms linking OSA and insulin resistance remain unclear. However, low-grade systemic inflammation, as evidenced by elevated serum C-reactive protein, has been suggested as a potential mediator [8]. Additional studies have demonstrated an upregulation of glucose and insulin-regulating hormones produced by adipose tissue (adipokines), such as the proinflammatory interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) [9], and leptin [10]. Conversely, reductions in adiponectin, a potent anti-inflammatory adipokine with insulin-sensitizing effects [11] have been reported in middle-aged adults with OSA [12, 13] and may be an additional link between insulin resistance and OSA. A previous in vitro investigation demonstrated a suppression of adiponectin expression due to a surge of catecholamines [14], a typical physiological consequence of increased sympathetic drive experienced in untreated OSA [15], leaving the authors to suggest this phenomenon as a likely link to catecholamine-induced insulin resistance [14].

OSA is not uncommon in adolescents and younger adults [16]. Studies attempting to examine the relationship between OSA and insulin resistance in young men, however, are currently lacking and may provide an early indication of the pathogenesis of insulin resistance in OSA. Thus, the purpose of the current study was to determine if insulin resistance, quantified by the homeostasis model of assessment (HOMA) of insulin resistance and a proinflammatory phenotypic expression of adipokines, exists in young men with OSA. A secondary aim was to determine if evidence of insulin resistance in these young men was related independently to the presence of OSA or if an additive influence was evident when obesity was coupled with OSA. This study design was unique, as the potential confounding effects of regular participation in physical activity, use of medications, and presence of chronic cardiovascular and metabolic disorders were controlled by subject eligibility criteria.

Materials and methods

Subjects

Subjects were 18- to 26-year-old males, who responded to flyers, newspaper advertisements, and e-mails sent throughout the campus of Virginia Tech. Exclusion criteria were (a) habitual use of tobacco products within the past year; (b) regular participation in physical activity during the previous 6 months, defined as ≥3 days per week for ≥30 min per day; (c) diagnosed or medically treated cardiovascular or metabolic disease; and (d) regular use of medications known to alter vascular function or inflammation. The initial assessment of subjects included measurement of height and weight to determine body mass index (BMI) and assessment of OSA via an unattended home sleep evaluation test. Accordingly, subjects who qualified for the study were assigned to one of three groups: (1) overweight with OSA (BMI >25.0 kg/m^2, apnea–hypopnea index (AHI) >5.0, labeled OSA), (2) overweight without OSA (BMI >25.0 kg/m^2, AHI <5.0, labeled NOSA), and (3) normal weight without OSA (BMI <25.0 kg/m^2, AHI <5.0, labeled CON). The resulting subject sample (67 % overweight-to-obese) is consistent with the prevalence of overweight and obesity estimated among adults in the United States of America [17]. All subjects provided a written informed consent, and the protocol was authorized by the Institutional Review Board of Virginia Tech.

OSA evaluation

Subjects underwent an unattended, limited home sleep evaluation to screen for OSA, utilizing a validated device (Embletta PDS, Broomfield, CO) [18]. The Embletta recorded the following measures during sleep: snoring, airflow, oxygen saturation, heart rate, thoracic breathing effort, and abdominal breathing effort. Subjects were given written and oral setup instructions and wore the device for at least 6 h during one weeknight of sleep in their home. Data were manually scored by a registered sleep technologist and confirmed by a sleep physician. OSA severity was assessed by the AHI, which is the average number of apneas and hypopneas per hour of sleep. Apneas and hypopneas were scored according to the recommendations set forth by the American Academy of Sleep Medicine [19]. Daytime sleepiness was assessed via the Epworth Sleepiness Scale (ESS) [20, 21].

Evaluation of adiposity

All anthropometric measures were obtained while subjects were in lightweight clothing and socks. The BMI was defined as body weight in kilograms divided by height in meters squared. Height and weight were obtained according

to standardized procedures as set for by the American College of Sports Medicine [22]. Neck circumference was measured at the laryngeal prominence, between the midanterior neck and midcervical spine. Total body fat was quantified using dual energy X-ray absorptiometry (DXA) (Hologic QDR 4500A. Bedford, MA). Central abdominal fat (CAF) was measured from total body DXA by the method of Kamel et al., as described previously [23]. Test–retest reliability for CAF as conducted by the same investigator who performed all other DXA measurements is 3.32 %. To eliminate interobserver variability, all measurements from the DXA were obtained and analyzed by one investigator. Test–retest reliability for total fat mass and body fat percentage with this DXA unit has been previously reported [24].

Phlebotomy and adipokine analysis

Subjects reported between 0,600 and 1,000 h to have fasting blood drawn via cubital venipuncture. Testing conditions included (a) at least 6 h of sleep, (b) no food intake for the previous 8 h, and (c) no alcohol or caffeine intake for the previous 24 h. Whole blood was centrifuged for 10 min at 2,500 rpm to isolate serum, which was immediately frozen at −80 °C for batch analysis at the completion of the study. Leptin was measured via radioimmunoassay (Linco Research, St. Charles, MO; coefficient of variation (CV) = 7.2 %). IL-6 and adiponectin were quantified via a custom, multiplex sandwich ELISA (SearchLight, Pierce Biotechnology, Rockford, IL; CV = 9.2 %). Serum TNF-α was measured using a high sensitivity ELISA kit (Quantikine HS, R&D Systems, Minneapolis, MN; CV = 8.6 %). Fasting insulin was measured using radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA; CV = 9.8 %). Fasting blood glucose was assessed using a reflectance photometry (Cholestech LDX, Hayward, CA). Total error for glucose using this method reported by the manufacturer is reported to be less than ±11 %. The HOMA for insulin resistance was used to quantify insulin resistance and is a calculation based on fasting insulin and glucose (insulin resistance = [fasting insulin × fasting glucose]/22.5) [25].

Statistical analysis

Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL). One-way ANOVA was used to make group comparisons for measures of interest. Central abdominal fat and BMI were treated as covariates for the primary study variables of interest. Relationships between variables characterizing insulin resistance, OSA severity, and adiposity were assessed using Pearson product moment of correlation. Data are reported as mean ± SE. Statistical significance was determined a priori for all experimental analyses as a p value<0.05.

Results

Subject characteristics and biochemical markers of insulin resistance are presented in Table 1. Per study design, both the NOSA and CON groups had AHI values <5.0. The mean AHI in the OSA group was indicative of a moderately severe disease [19]. There were no differences between groups in regard to age and excessive daytime sleepiness. HOMA, insulin, and leptin were higher in both the OSA ($p<0.001$, $p<0.01$, and $p<0.001$, respectively) and NOSA ($p<0.05$, $p<0.05$, and $p<0.001$, respectively) groups compared to the CON group. No differences were observed between the OSA and NOSA groups, suggesting that the primary mediator of insulin resistance in this younger cohort may be measures of obesity and adiposity, and not OSA. In contrast, serum adiponectin was lower in the OSA group compared to NOSA ($p<0.05$) and CON ($p<0.05$) groups. There was no difference between any group for glucose, TNF-α or IL-6 ($p>0.05$). After controlling for CAF, there were no group differences for any biochemical marker.

Body composition data are presented in Table 2. The OSA and NOSA groups had higher BMI, neck circumferences, and overall fat mass than the CON group ($p<0.05$). The OSA group had a higher percent body fat ($p<0.05$) and CAF (Fig. 1, $p<0.05$) compared to the NOSA and CON groups. After controlling for BMI, CAF levels remained 24 % higher in OSA subjects than non-OSA subjects (Fig. 2, 7.5±0.4 vs. 6.1±0.2 kg, $p<0.01$). Across all subjects, CAF and total fat mass showed similar moderate to high correlations with HOMA (CAF $r=0.68$, $p<0.001$; fat mass $r=0.70$, $p<0.001$), insulin (CAF $r=0.72$, $p<0.001$; fat mass $r=0.72$, $p<0.001$), and leptin (CAF $r=0.84$, $p<0.001$; fat mass $r=0.88$, $p<0.001$). AHI was positively correlated with BMI ($r=0.40$, $p<0.01$), total fat mass ($r=0.37$, $p=0.01$), and CAF ($r=0.45$, $p<0.01$). AHI was correlated to insulin ($r=0.33$, $p=0.03$), leptin ($r=0.30$, $p=0.04$), and adiponectin ($r=-0.29$, $p=0.05$).

Discussion

This study is the first to our knowledge to explore the relationship between insulin resistance and previously undiagnosed OSA in young obese men who are sedentary and free of cardiovascular and metabolic disorders. Though there were no differences between the OSA and NOSA groups in regard to BMI or fat mass, the OSA group had 24 % more CAF than subjects without OSA ($p<0.05$). Serum adiponectin concentration was lower only in subjects with OSA ($p<0.05$). Analysis that removed the influence of CAF revealed that differences in adiponectin between groups were due primarily to the presence of excessive CAF. Excess CAF has been shown by others, in obese

Table 1 Subject characteristics and biochemical markers of insulin resistance

Measure	OSA (n=12)	NOSA (n=18)	CON (n=15)	p value
Age (years)	22.8±0.8	22.5±0.7	21.1±0.6	0.22
AHI (events/h)	25.4±5.4$^{*, **}$	2.2±0.3	2.0±0.3	<0.001
ESS (x/24)	7.8±1.1	8.3±0.8	6.4±0.6	0.21
Glucose (mg/dl)	86.8±2.6	92.6±2.2	85.3±2.9	0.10
HOMA-IR	3.6±0.4**	3.0±0.6***	1.4±0.2	<0.01
Insulin (μU/l)	16.9±1.8*	12.5±2.3***	6.4±0.8	<0.01
TNF-α (ng/ml)	0.95±0.07	0.86±0.05	0.86±0.05	0.45
IL-6 (ng/ml)	6.4±2.2	6.7±2.2	7.2±1.6	0.96
Leptin (ng/ml)	11.9±1.0*	9.7±1.4*	4.1±0.5	<0.001
Adiponectin (μg/ml)	10.0±0.8$^{***, ****}$	13.9±1.4	14.5±1.3	0.05

HOMA-IR homeostasis model assessment of insulin resistance, *TNF-α* tumor necrosis factor alpha, *IL-6* interleukin-6
$^{*}p$<0.001 (vs. CON); $^{**}p$<0.01 (vs. CON); $^{***}p$<0.05 (vs. CON); $^{****}p$<0.05 (vs. NOSA)

individuals with or without OSA to be inversely related to decreased circulating adiponectin and directly related to increased insulin resistance [26–28]. We postulate that, given the younger age of our subjects, the subjects with OSA likely have had clinically significant disease for a shorter time period. As a result, the influence of OSA on biochemical markers of insulin resistance is lessened, compared to middle-aged and older adults with OSA. Given that, the initial pathogenesis of insulin resistance is more likely due to obesity and CAF in particular.

Recently, several well-controlled studies have reported the finding of insulin resistance in middle-aged adults with OSA that is independent of the effects of obesity [6, 7, 29]. Investigations by Ip [6] and Vgontzas [29] both found higher insulin resistance (HOMA) in overweight, middle-aged adults with OSA than in controls. Neither study controlled for CAF in their analysis. Ip did not assess CAF, only BMI, whereas Vgontzas assessed visceral fat through CT scanning. In addition, both studies included subjects diagnosed with and on medication for HTN. The current study did not find differences in glucose, insulin, or insulin resistance between obese groups with and without OSA when data were adjusted to remove the influence of CAF. These findings suggest that OSA does not exert an independent effect on insulin resistance in this younger cohort of adult men. Perhaps, pathogenic effects of OSA and obesity are synergistic, and only after these comorbid conditions have been sustained for many years does a distinct etiologic contribution from OSA on insulin resistance manifest.

Another aspect of importance in the current study was to examine serum concentrations of several adipokines, previously implicated in the regulation of insulin in relation to the presence of OSA. Ciftci and colleagues [9] reported higher serum concentrations of both IL-6 and TNF-α in overweight, middle-aged subjects with OSA (mean age = 49.6 years) than in controls matched for age (mean age = 47.2 years), BMI, and daytime sleepiness. In contrast, in the current study, we found no evidence of differences in either IL-6 or TNF-α in young men with previously undiagnosed OSA. Ciftci did not assess CAF in their study, so the impact of that on their findings cannot be determined. Regression analysis done by Ciftci did report that TNF-α was independently associated with AHI, but not BMI. They concluded that it was likely the severity of OSA and the repeated hypoxemia that results from apnea and hypopnea events that triggers the increased levels of inflammatory adipokines, rather than any obesity or other body composition variable. We found AHI to be related to leptin and adiponectin, but no relationship between AHI and IL-6 and TNF-α in our younger cohort. This suggests that OSA alone does

Table 2 Body composition

Measure	OSA (n=12)	NOSA (n=18)	CON (n=15)	p value
BMI (kg/m^2)	32.4±1.0*	31.6±1.1*	22.2±0.3	<0.001
Neck (cm)	40.7±0.6*	40.8±0.8*	36.3±0.4	<0.001
Body fat (%)	29.8±1.0$^{*, **}$	26.2±1.2*	18.5±1.2	<0.001
Total fat mass (kg)	30.6±2.0*	26.7±2.1*	13.2±1.0	<0.001
CAF (kg)	9.1±0.7$^{*, **}$	7.3±0.6$^{*, ***}$	3.4±0.3	<0.001

AHI apnea–hypopnea index, *ESS* Epworth Sleepiness Scale, *BMI* body mass index, *Neck* neck circumference, *CAF* central abdominal fat
$^{*}p$<0.001 (vs. CON); $^{**}p$<0.05 (vs. NOSA); $^{***}p$<0.001 (vs. NOSA)

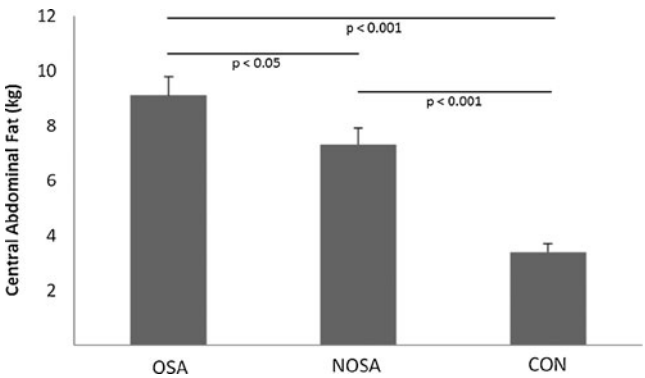

Fig. 1 Central abdominal fat by group. *OSA*, overweight subject group (body mass index >25 kg/m^2) with OSA; *NOSA*, overweight subject group without OSA; *CON*, normal weight subject group without OSA

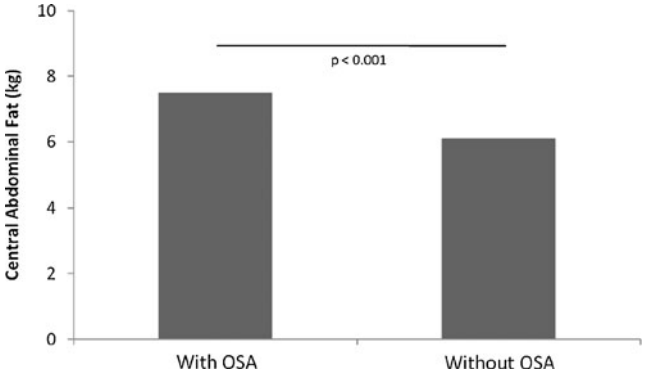

Fig. 2 Central abdominal fat in overweight subject groups, controlled for the influence of body mass index

not independently influence these markers in a younger OSA group.

Leptin, a hormone which regulates appetite and energy expenditure, has consistently been reported as elevated in OSA [10, 25, 30–32]. More recently, Sánchez-de-la-Torre et al. [33] reported no effect of OSA on leptin levels in middle-aged men but rather obesity was the primary mediating factor in leptin. Similar to Sánchez-de-la-Torre et al., we found serum leptin was not different between the OSA and NOSA groups after adjustment for CAF. In contrast to Sánchez-de-la-Torre et al., we were able to examine the association of CAF to adipokines levels, whereas they were only able to examine adipokine levels to BMI. We found that CAF, rather than total adiposity expressed as BMI, was the primary mediating factor. We were, however, able to extend their conclusions to a younger adult OSA group that adiposity, not OSA, was more related to leptin levels. One recent study by Canapari and colleagues [34] did examine OSA, adiposity, and leptin in obese children (mean age 12.6 ±3.0 years). They reported that leptin levels in the OSA group were significantly higher than the control group. The OSA group was significantly more obese than the control group, and there was a trend for greater visceral fat as well, which was not controlled for in their analysis.

Previous investigations have also demonstrated reduced levels of adiponectin in middle-aged adults with OSA [12, 13, 35]. Zhang and colleagues [13] found that serum concentration of adiponectin was nearly 30 % lower in the middle-aged, overweight subjects with OSA than the overweight controls. Kanbay et al. [12] reported similar findings in obese middle-aged adults with severe OSA, showing adiponectin levels 45 % lower than in nonapneic controls of similar age and body habitus. Furthermore, Lam and colleagues demonstrated that hypoadiponectinemia was directly related to sympathetic activation and severity of OSA [36]. In contrast, Sánchez-de-la-Torre et al. [33] found that, similar to what they report for leptin, adiponectin was not effected by OSA. After controlling for the effects of CAF, the current study did not reveal differences in adiponectin between any of the study groups. These findings contradict previous investigations in middle-aged adults by Zhang [13], Kanbay [12], and Lam [36]. Subjects in the current study, however, were younger and had less severe OSA than previous investigations. Our results suggest that a suppression of adiponectin in younger males with OSA is more related to the presence of excessive CAF than OSA, an argument that was strengthened when data were adjusted to control for BMI. These findings are consistent with those of Steffes [26], who demonstrated that central fat is most responsible for production and circulation of adiponectin.

Obesity is a known factor in the etiology of both OSA and insulin resistance [37]. Increased abdominal adiposity appears to accelerate the development of insulin resistance [38]. Visceral fat is well vascularized and functions as a primary endocrine organ with implications for the production and release of potent hormones affecting glucose and insulin metabolism [39]. Relatively few studies have sought to examine possible relations of abdominal obesity to OSA. Vgontzas et al. [29] found visceral fat to be 50 % higher in middle-aged, overweight subjects with OSA than in controls matched for BMI and subcutaneous fat area. Findings from the current study support the increased presence of central fat in OSA. As the current study has examined a younger cohort of subjects than previous investigations, these findings suggest that a risk for insulin resistance may exist in the form of increased central adiposity and may precede changes in calculated insulin resistance in these young men.

The mechanisms involved in determining the relationship between central obesity, OSA, and insulin resistance remain unclear and equivocal. Lam et al. [36] previously demonstrated that adiponectin was suppressed in OSA independent of obesity. However, studies by both Vgontzas [27] and Makino [28] suggest that the relationship between OSA and insulin resistance is mediated by CAF. The findings in our study appear congruent with both Makino and Vgontzas and suggest that CAF is intimately tied with hypoadiponectinemia and insulin resistance in the presence of OSA. The current study is novel in that it demonstrates this relationship at a younger age than previously reported. The interaction of OSA and excessive CAF in these young men is further complicated by a suppression of the anti-inflammatory adiponectin. Hypoadiponectinemia appears to indirectly increase the future risk for cardiometabolic disorders, beyond that attributed to the effect of uncomplicated obesity alone.

Another interesting finding of the current study is that daytime sleepiness, assessed by the ESS, did not differ between groups. Excessive daytime sleepiness is a cardinal risk factor for OSA, and the ESS is a well-validated and frequently used tool to assess sleepiness [20, 21, 40, 41]. The ESS has previously been shown to correlate significantly to AHI [21, 40] but was based on results from middle-

aged to older adults. Results from the current study suggest that among younger, college–aged men, the ESS may not be able to distinguish between clinically relevant daytime sleepiness, and that typified by a lifestyle of frequent sleep restriction.

The design of the current study was unique beyond the fact that it explored insulin resistance in a young cohort of men with OSA. The exclusion criteria prohibited subjects from participating who were physically active, taking anti-inflammatory medications, using tobacco products, and living with diagnosed cardiovascular and metabolic disorders. Taken together, these criteria provided experimental control of factors that typically confound similar studies of middle-aged adults with OSA. However, the current study was constrained by potential limitations. First, the presence of OSA in this cohort was determined by unsupervised portable polygraphy testing. Portable devices such as these, however, have been validated against the gold standard and in-lab polysomnography, and each subject's test was confirmed by a certified sleep physician of the certified sleep technologist board [18]. Although the mean AHI in the OSA group was the moderate severity disease, several subjects had an AHI <10 events/hour. Including mild disease, rather than the more severe disease exclusively, may have impacted the findings of the study. In addition, CAF as measured by DXA represents all the tissue within the defined area of the abdominal region and not specifically visceral fat which has been linked to elevated disease risk [42, 43]. Given that CAF was dramatically higher in participants with obesity and even between obese participants with and without OSA, this suggests the likelihood that a substantial portion of CAF was visceral adiposity in the OSA participants. Second, this study is limited by small sample sizes. Though additional subjects would have improved statistical power, the findings of this study warrant additional investigations in this age group to determine the extent of risk for early diabetes and other chronic conditions associated with OSA later in life. The cross-sectional study design is an additional limitation in that it is difficult to conclusively examine the impact of age and disease progression on study variables, given the single time frame examined. We were, however, able to minimize these confounding influences in several areas through the use of multiple subject selection and exclusion criteria.

In conclusion, young men with previously undiagnosed OSA demonstrated higher CAF than comparable young obese and normal weight men without OSA. These differences may represent an initial indirect risk for insulin resistance attributable to untreated OSA, particularly coupled with a suppression of adiponectin. Currently, the majority of OSA cases are not diagnosed and treated, if at all, until individuals reach their mid-40s. Thus, the findings of this study merit larger scale investigations of insulin resistance in relation to OSA for this age group, as early identification of OSA may become a basis for more aggressive weight loss interventions to prevent type 2 diabetes.

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