No Association Between Leptin Levels and Sleep Duration or Quality in Obese Adults

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Previous research in lean subjects has found lower leptin levels associated with shorter sleep duration. Since leptin levels are higher and some of the actions of leptin are impaired in obese individuals, one cannot assume that sleep will be similarly associated with leptin in obese individuals. The aim of this paper was to examine the cross-sectional association between habitual sleep duration and quality and plasma leptin levels in a sample of 80 obese men and premenopausal women aged 18–50 years. Leptin levels (ng/ml) were assayed on a fasting blood sample taken in the morning. We calculated a relative leptin level by dividing leptin by body fat percentage. Sleep duration and sleep efficiency were measured by 2 weeks of wrist actigraphy and respiratory disturbance index (RDI), a measure of sleep disordered breathing, was assessed by a portable screening device on a single night. Mean leptin levels and body fat percentage were higher in women than men ($P < 0.001$), however, mean RDI was higher in men ($P = 0.01$). There were no significant associations between relative leptin level and any of the sleep measures, including sleep duration, sleep efficiency, and sleep disordered breathing. There was also no difference between men and women in the association between sleep and leptin. In conclusion, contrary to what has been reported in other studies, measures of sleep duration and quality were not associated with leptin levels in our sample of obese adults.

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Obesity increases the risk of cardiovascular disease and diabetes, reduces life expectancy and impairs quality of life. In 2005, over 390 million people worldwide were obese, which is projected to increase to as many as 1.1 billion people by 2030 (1). Given these vast numbers, we need to understand better the consequences of obesity for health, with the ultimate goal of improving the lives of millions of people.

One area that has received much attention recently is the action of leptin in obese individuals. Some of the actions of leptin that are observed in lean individuals appear to be impaired in obesity. For example, leptin works as a satiety signal in lean adults and higher levels have been associated with reduced food intake (2). Leptin is secreted by the adipocyte and levels are directly proportional to the degree of adiposity. As such, leptin levels are much higher in obese individuals than in lean, but despite this higher level, appetite, and food intake are not reduced, a phenomenon known as "leptin resistance"(2). There is evidence to suggest, however, that not all of leptin's actions are altered in obesity. The stimulatory effect of leptin on the sympathetic nervous system and subsequently increased blood pressure (3), for example, appears intact (4,5), which may explain the association between higher leptin levels and increased risk of hypertension in obese adults (4,6). Thus, hyperleptinemia in obese individuals could have important consequences for cardiovascular health independently of body weight.

Two laboratory studies that restricted time available for sleep for two or six nights observed reduced levels of leptin compared to extended bedtimes (7,8). Other studies of only one or two nights of sleep restriction did not see an effect on leptin (9,10). A few observational, epidemiologic studies have also examined the association between sleep duration and leptin levels. The Wisconsin Cohort study, which included individuals aged 30–60 years, reported a positive association between leptin levels and habitual sleep duration based on diaries indicating that shorter sleepers had lower levels of leptin compared to people sleeping more, even after adjustment for BMI (11). None of the studies above examined the association between sleep and leptin specifically in obese subjects.

Assuming that metabolic and hormonal associations observed in lean individuals will generalize to obese individuals is inappropriate. Since leptin levels are higher and some actions of leptin are impaired in obese individuals, sleep duration may not be associated with leptin in obese subjects. The aim of this paper was to examine the association between habitual sleep and leptin levels in a sample of obese adults.

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METHODS AND PROCEDURES

Study cohort

These cross-sectional analyses included participants who were enrolled in the Sleep Extension Study, which is conducted at the National Institutes of Health Clinical Center. This study is an ongoing randomized, prospective, intervention trial of obese (BMI 29–55 kg/m^2) men and premenopausal women aged 18–50 years who report sleeping less than 6.5 h per night on average (12). After telephone interviews, eligible participants were invited into the clinic for a screening examination, which included a history and physical examination, electrocardiogram, clinical blood work, anthropometric measures, and validated sleep questionnaires (12). Finally, participants were provided with a wrist actigraphy monitor to assess habitual sleep duration for 2 weeks. The analyses presented here examine these baseline data, which were collected prior to any intervention, and our analytic sample included 80 participants at the time of this analysis (August 2010). This study was approved by the institutional review board at the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) and signed informed consent was obtained from all participants.

Sleep measures

Habitual nocturnal sleep duration and quality was estimated using wrist actigraphy monitors (Actiwatch-64; Mini Mitter/Respironics/Philips, Bend, OR), which are noninvasive devices similar in size to a wristwatch. These devices have been validated against polysomnography, with correlations for sleep duration ranging from 0.82 in insomniacs to 0.97 in healthy subjects (13). Participants in this study wore the wrist actigraphy monitor continuously for ~2 weeks (median 14 days, range 9–15 days). Two measures from the actigraphy data were used: sleep duration (amount of actual sleep obtained) and sleep efficiency (percentage of time in bed spent sleeping), which represents sleep quality. Sleep disordered breathing was assessed over one night using a portable screening device (Apnea Risk Evaluation System; Advanced Brain Monitoring, Carlsbad, CA). Data were automatically scored and then reviewed by a technician. The device provides an estimate of the respiratory disturbance index (RDI), which is the number of apneas and hypopneas per hour of sleep (14). This device has been validated against polysomnography and demonstrated high sensitivity and specificity (15). RDI was also dichotomized at <15 or ≥15 events per hour.

Leptin measurement

Morning fasting blood was drawn between 8:00 AM and 10:00 AM for most participants. Plasma leptin was assayed using a human leptin radioimmunoassay kit (Linco Research, St Charles, MO) with a sensitivity of 0.5 ng/ml and an intra-assay coefficient of variation of 8.3%. We calculated a relative leptin level by dividing leptin by body fat percentage.

Covariates

Covariates in these analyses included age (years), sex (0 = male) and total body fat. Body fat percentage was estimated using dual energy X-ray absorptiometry (DXA QDR 4500 machine; Hologic, Bedford, MA).

Statistical analysis

Statistical analysis comprised two steps. First, descriptive statistics for leptin levels, sleep measures, and demographic variables were calculated for the cohort as a whole and separately by sex. Statistical tests used to compare men and women included: *t* test for difference in means, Fisher's exact test for difference in frequency, and Pearson χ^2 test for difference in counts. Second, linear regression was used to predict relative leptin levels from each sleep measure alone (unadjusted) and with adjustment for the covariates. A separate model was used for each sleep measure: sleep duration, sleep efficiency, and RDI. An interaction term between sex and the sleep measure was added to the regression models to determine if the association between sleep and leptin differed by sex. All analyses were performed using SAS (version 9.1.3; SAS Institute, Cary, NC) and JMP (version 8.0; SAS Institute , Cary, NC).

RESULTS

Table 1 describes the study sample. Mean sleep duration, leptin level, and body fat percentage were all higher in women than men. Mean RDI was higher in men and a larger percentage of men were above the clinical cut-off for sleep disordered breathing. In unadjusted and adjusted regression models predicting leptin levels, no significant association was observed between any of the three sleep measures and relative leptin level (all $P > 0.20$). Using the dichotomized RDI variable instead of RDI as a continuous measure did not alter the results. None of

Table 1 Characteristics of the study population (updated 19 May 2011)

	All (*n* = 80)	Female (*n* = 60)	Male (*n* = 20)	Difference
	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	*P* value
Age (years)	41.1 ± 6.8	41.6 ± 6.4	39.3 ± 7.9	0.1747[c]
BMI (kg/m^2)	38.2 ± 6.4	38.4 ± 6.2	37.5 ± 6.9	0.6247[c]
Body fat (%)	41.1 ± 7.0	43.8 ± 4.9	33.0 ± 6.0	<0.0001[c]
Leptin (ng/ml)	48.2 ± 23.9	56.2 ± 21.4	24.3 ± 12.2	<0.0001[c]
Relative leptin	112.4 ± 43.9	126.1 ± 39.0	71.2 ± 29.8	<0.0001[c]
Objective sleep duration	6.15 ± 0.78	6.23 ± 0.73	5.90 ± 0.88	0.0943[c]
Objective sleep efficiency (%)[a]	79.4 ± 8.2	79.8 ± 8.1	78.4 ± 8.4	0.5407
RDI (events/hour)[b]	9.33 ± 11.99	7.39 ± 8.38	16.14 ± 19.01	0.0109[d]
RDI (<15)[b]	77.8% (49)	83.7% (41)	57.1% (8)	0.0634[e]
Race/ethnicity				0.1874[d]
Non-Hispanic black	57.5% (46)	63.3% (38)	40.0% (8)	
Non-Hispanic white	38.7% (31)	33.3% (20)	55.0% (11)	
Other	3.8% (3)	3.4% (2)	5.0% (1)	

[a]*n* = 78. [b]*n* = 63. [c]*t*-test for means. [d]χ^2 test. [e]Fisher's exact test.

the interaction terms between sex and sleep were significant, which indicated that there were no differences between men and women in the association between sleep and leptin.

DISCUSSION

We did not find a significant cross-sectional association between leptin level and habitual sleep duration, sleep quality or sleep disordered breathing in this sample of obese adults. These results are inconsistent with what has been reported in some other studies. For example, two experimental studies that restricted time available for sleep and controlled food intake (either constant glucose infusion or identical meals) in lean men reported lower leptin levels after sleep restriction (7,8). Another study in lean men observed no effect of two nights of 4.25 h in bed compared to 7.25 hours in bed on leptin levels (9,10), however food intake was high in both conditions (~4,000 kcal/day). The Wisconsin Sleep Cohort study, which observed a negative association between habitual sleep duration and leptin levels, included a wide range of BMI levels (median was 29.7 kg/m^2). Although they adjusted for BMI in their analyses, they did not examine the association between sleep and leptin at different levels of BMI (e.g., lean, overweight or obese). Furthermore, their measure of sleep was based on diaries rather than actigraphy. Therefore, it is not known if sleep duration would remain significantly associated with leptin level in the subset of obese participants or if they had used actigraphy to estimate sleep duration. Finally, one laboratory, compared two weeks of 5.5 h in bed to 2 weeks of 8.5 h in bed with *ad libitum* feeding in overweight subjects (BMI 24–29 kg/m^2) and saw no difference in leptin levels (16). In both conditions, however, subjects gained similar amounts of body fat (1.5–1.7 kg on average). Our study did not control for food intake, but rather examined habitual sleep duration and leptin level.

Limitations to our study include potentially fewer long sleepers than if the study had been population-based and a single measure of leptin rather than a 24-h profile. The discrepant results between studies need to be examined further to determine whether they are due to methodological differences or if they represent true physiological differences between lean, overweight and obese individuals.

Derangements in the actions of leptin in obese individuals are well-established. In particular, despite high levels of leptin due to increased adiposity, food intake is not reduced (2). Recent evidence, however, suggests that leptin's actions are not necessarily impaired across all of its domains. In particular, stimulatory effects of leptin on blood pressure are observed in obesity (4,5). Higher levels of leptin in obese individuals have been associated with increased blood pressure and increased cardiovascular disease risk (6). Therefore, higher levels of leptin in obesity may have cardiovascular consequences. Our results indicate that in obese individuals the leptin system becomes insensitive to the signals associated with sleep disturbances. Thus, the relationship between sleep and leptin may also be disrupted in obese individuals and adds another dimension, sleep, to the accepted concept of "selective leptin resistance" in obese individuals. Future studies should explore the clinical consequences of this phenomenon.

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DISCLOSURE

The authors declared no conflict of interest.

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