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CLINICAL REVIEW

Obstructive sleep apnea and energy balance regulation: A systematic review

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SUMMARY

Obesity and obstructive sleep apnea (OSA) have a reciprocal relationship. Sleep disruptions characteristic of OSA may promote behavioral, metabolic, and/or hormonal changes favoring weight gain and/or difficulty losing weight. The regulation of energy balance (EB), i.e., the relationship between energy intake (EI) and energy expenditure (EE), is complex and multi-factorial, involving food intake, hormonal regulation of hunger/satiety/appetite, and EE via metabolism and physical activity (PA). The current systematic review describes the literature on how OSA affects EB-related parameters. OSA is associated with a hormonal profile characterized by abnormally high leptin and ghrelin levels, which may encourage excess EI. Data on actual measures of food intake are lacking, and not sufficient to make conclusions. Resting metabolic rate appears elevated in OSA vs. controls. Findings on PA are inconsistent, but may indicate a negative relationship with OSA severity that is modulated by daytime sleepiness and body weight. A speculative explanation for the positive EB in OSA is that the increased EE via metabolism induces an overcompensation in the drive for hunger/food intake, which is larger in magnitude than the rise in EI required to re-establish EB. Understanding how OSA affects EB-related parameters can help improve weight loss efforts in these patients.

Introduction

Obesity is a well-established leading risk factor for obstructive sleep apnea (OSA), and OSA itself may promote further weight gain [1]. Although the reasons underlying this reciprocal relationship remain uncertain, evidence from observational and laboratory-based studies demonstrates a relationship between sleep and factors regulating body weight, such as food intake and physical activity (PA) [2]. Sleep disruptions characteristic of OSA are expected to be associated with behavioral, metabolic, and/or hormonal changes favoring weight gain and/or difficulty losing weight. Supporting evidence comes from the finding that newly diagnosed OSA patients have a history of weight gain vs. sex, age, and body mass index (BMI)-matched controls over the year prior to diagnosis [3]. Furthermore, compared to BMI-matched non-OSA individuals, OSA patients with visceral obesity had a smaller decrease in BMI and fat mass in response to a lifestyle intervention for weight loss [4].

When examining the effects of OSA on obesity, it is important to consider the factors regulating energy balance (EB). Body weight gain is expected as a consequence of excessively increased food intake and/or reduced PA [5]. Body weight stability is achieved when energy intake (EI) is equal to energy expenditure (EE). Thus, EB is the quantifiable relationship between the intake and output of energy from the body.

The current goal is to explore if OSA alters behavior, hormones, and/or metabolism to encourage an energy imbalance, such that EI is increased relative to EE, and to examine the functional implications of the disorder on EB regulation. This report will focus on investigations of outcomes like food intake, the hormonal regulation of hunger/appetite/satiety, PA levels, and energy metabolism in OSA patients, to determine if there is a dysregulation of EB-related parameters in these patients. A particular focus will be on methodological differences among studies, and how these may contribute to discrepancies.

Methods

Search strategy

A systematic literature review was conducted to identify manuscripts which investigated aspects of EB regulation, namely

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Glossary of terms

AHI	apnea-hypopnea index
BMI	body mass index
CPAP	continuous positive airway pressure
EB	energy balance
EE	energy expenditure
EI	energy intake
EDS	excessive daytime sleepiness
ESS	Epworth sleepiness scale
IC	indirect calorimetry
NOS	Newcastle-Ottawa scale
NPY	neuropeptide Y
OSA	obstructive sleep apnea
PA	physical activity
PSG	polysomnographic
RDI	respiratory disturbance index
RMR	resting metabolic rate
REM	rapid eye movement
SMR	sleeping metabolic rate
SWS	slow wave sleep
WRIC	whole-room indirect calorimetry

parameters related to either EE or EI, in OSA patients. The web-based literature search included PubMed/MEDLINE and Embase databases. Search terms were selected to reflect the condition and outcome parameters. For the condition, search terms included: sleep apnea OR sleep apnoea OR sleep disordered breathing OR CPAP (continuous positive airway pressure) OR positive airway pressure. For EI, search terms included: caloric intake; food intake; food preference; dietary quality; macronutrient; hunger; appetite; satiety; hunger hormone; appetite hormone; satiety hormone. For EE, search terms included: energy expenditure; thermogenesis; energy metabolism; physical activity. Terms were searched in all possible combinations using Boolean Logic operators. Additionally, a manual search of bibliographies of included articles was conducted to identify relevant references which may not have been found by the automated search. Obtained references were indexed and managed using EndNote X7 (Thompson Reuters, New York, NY).

Eligibility criteria

The following criteria were required for selection: 1) original research investigations; 2) conducted in humans; 3) conducted in adults; 4) include patients diagnosed with OSA of at least mild severity (apnea hypopnea index [AHI] $\geq$5 events/h) based on polysomnography (PSG). Studies were included if they were between-group comparisons of OSA patients vs. controls or if they included a group of OSA patients without a control group and examined them using regression analysis.

Studies were excluded if they were in diagnosed OSA patients but did not include a relevant EB-related parameter (i.e., food intake, hunger/appetite, EE, energy metabolism, PA), if they did not include a PSG-based diagnosis of OSA, and if they examined the effects of CPAP but did not include an examination of OSA vs. control at baseline.

To help reduce risk of source selection bias, there were no restrictions on date or country of origin of research/publication. Specified EB-related parameters could be secondary/minor outcomes within reports. Reviews, commentaries, editorials, letters to the editor, and case reports were not included. In addition to a "forward" (i.e., utilizing databases and search terms) search strategy, a "backward" or ancestry search strategy was utilized such that the reference list of all relevant reports was searched to include references missed by automatic search. Despite these efforts, having a single author conduct the literature search and data extraction might have unintentionally led to some degree of selection bias.

Data items

To be selected, studies must have included at least one relevant EB-related parameter within OSA patients. For EI, this included circulating hormones known to regulate hunger/satiety/appetite, and measures of food intake or habitual dietary patterns. For EE, this included measures from indirect calorimetry (IC), accelerometry, and questionnaires on PA levels.

Reviewing procedure and data extraction

Database searches were first conducted in December 2015. In May 2016, the search was conducted again to identify references published between December 2015 and May 2016. All obtained references were reviewed, and if retained, data extraction was conducted by a single author. The first level of review was title and abstract screening. Irrelevant references were removed. Potentially relevant studies were further assessed by obtaining and reading the full text and checking against the pre-specified eligibility criteria.

For each reference, the following variables were systematically extracted and entered into a summary table: 1) authors; 2) year of publication; 3) journal; 4) sample size; 5) criteria and cut-offs used to define OSA and control; 6) age and BMI; 7) study design; 8) outcomes; 9) time of assessment and if done under fasting conditions; 10) statistical approaches; 11) findings, including individual outcome variables (e.g., means, confidence intervals) and whether any confounder adjustments were added to statistical analyses. The principal summary measures were between-group differences in means for outcomes (OSA vs. controls), and regression results indicating relationships between OSA severity and EB-related outcome variables. A summary of the studies screened, assessed for eligibility, and included is presented in Fig. 1. Additionally, a Newcastle-Ottawa scale (NOS) score was assigned for case–control studies, [6]. NOS scores (up to nine stars, with increasing number for increasing quality of non-randomized studies) are indicated in Tables 1–3.

Results

Food intake and preference

Main findings

Food preference was studied in a group of patients undergoing screening for OSA, with the fiber-liking and fat-liking subscales of the Liking Scale completed in the morning following the diagnostic study [7]. In a hierarchical multiple regression model including sex and BMI, liking for high-fat food was associated with greater OSA severity, based on respiratory disturbance index (RDI) [7]. In terms of actual food intake, based on questionnaire, Vasquez et al. reported baseline findings from participants (n = 305) in the apnea positive pressure long-term efficacy study (APPLES) trial of responses to a Food frequency questionnaire [8]. After adjusting for age, BMI, and Epworth sleepiness scale (ESS) score, individuals with RDI $\geq$50 events/h consumed significantly more cholesterol per day than those with RDI <50 events/h, and consumption of protein, total fat, and saturated fatty acids was increased in women with RDI $\geq$50 events/h vs. RDI <50 events/h [8].