Spring 5-4-2019

Relationship between Binge Eating Disorder and Circadian Chronotype

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RELATIONSHIP BETWEEN BINGE EATING DISORDER AND CIRCADIAN CHRONOTYPE

By

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A THESIS

Presented to the Faculty of

The University of Nebraska Graduate College

In Partial Fulfillment of the Requirements

For the Degree of Master of Science

Medical Sciences Interdepartmental Area Graduate Program

Clinical & Translational Research

Under the Supervision of Professor Laura Bilek

University of Nebraska Medical Center

Omaha, Nebraska

December 2018

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ACKNOWLEDGEMENTS

After a long academic hiatus, I was able to return to the University of Nebraska Medical Center via the Medical Studies Interdisciplinary Program and learn how to become a scientist. I am grateful to UNMC to allow me this opportunity.

The ability to take advantage of this opportunity was due to a meeting with Dr. Laura Bilek. She is my advisor and has guided me throughout the process of this master's program over the last 4 years. She demonstrated a great deal of patience and is a very kind and insightful mentor. The time that she extended to me and guidance was invaluable, and I could not have completed this degree without her.

The other members of my team were John Graham Sharp and Tim McGuire. The four of us plus Donald Johnson frequently met and had long discussions about obesity, circadian rhythms, perivascular adipose tissue, autophagy and often were led into all types of scientific discussions. It was great fun and I am so appreciative for the time and nurturing that occurred in these meetings.

Teresa Hartman and the library staff at UNMC were very helpful.

Belinda is my spouse and she always encourages me to do the best things in life. Her insight and encouragement were the main impetus to this study and degree program.

ABSTRACT

RELATIONSHIP BETWEEN BINGE EATING DISORDER AND CIRCADIAN CHRONOTYPE

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UNIVERSITY OF NEBRASKA, 2018

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Binge eating disorder (BED) is a common condition in the general population and is more common in individuals with obesity. The later timing of food intake has been associated with an increase incidence of obesity. The purpose of this study was to evaluate the relationship between circadian chronotype and BED in a population of individuals with obesity. The sample consists of a retrospective review of 170 subjects presenting to an obesity medicine clinic who had been clinically evaluated for BED and chronotype.

No significant correlation was found between BED and a late chronotype in this population. In a secondary analysis no significant difference in degree of weight loss was related to the presence or absence of BED or an earlier or later chronotype. This retrospective study does not support the relationship of binge eating disorder and circadian chronotype.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

BED	Binge Eating Disorder
BMI	Body mass index
BMAL1	Aryl hydrocarbon receptor nuclear translocator-like protein 1
CLOCK	Circadian Locomotor Output Cycles Kaput
CRY	Cryptochrome protein
DSM-V	Diagnostic and Statistical Manual Edition V
IR	Insulin resistance
MEQ	Morningness-Eveningness Questionnaire
OSA	Obstructive sleep apnea
PER	Period protein
T2DM	Type 2 diabetes mellitus
TTFL	Transcriptional and translational feedback loop

CHAPTER 1: INTRODUCTION

BINGE EATING DISORDER

Binge eating disorder (BED) is a common condition observed in obesity treatment programs. Lifetime prevalence of BED in the general population in the United States is estimated to be 2.0-3.5%.[1] BED is found in higher prevalence in individuals seeking treatment of obesity and may impact the effectiveness of weight loss interventions.

BED was named as a diagnostic category in the Diagnostic and Statistical Manual V (DSM-V). This disorder is characterized by recurrent episodes of binge eating in which an individual eats a larger amount of food than normal in a discrete period of time with a sense of lack of control. BED also requires at least one episode of binge eating per week over the last three months. The binge eating episodes must cause a degree of marked distress in the individual and have at least three of the following five characteristics: eating large amounts of food when not hungry, eating much more rapidly than normal, eating until uncomfortably full, eating alone because of embarrassment, and having feelings of disgust or guilt about the overeating episode. BED also requires no associated purging behavior related to the binging.[2]

Several diagnostic scales are available for the evaluation of BED. The Eating Disorder Examination, Yale-Brown Obsessive-Compulsive Scale Modified for Binge Eating, the Questionnaire on Eating and Weight Patterns, and the Eating Disorder Assessment for DSM-V are examples of scales that have been validated for BED. The time to perform and evaluate these scales can be a limitation to their use in clinical settings. Utilizing a brief scale for characteristics of BED specified by the DSM-V criteria

and confirming this with clinician interview can be used clinically in an abbreviated way to diagnose binge eating disorder.

Anecdotally binge eating episodes occur later in the day. This was observed in the 170 patients in this trial, although not studied in an observational trial. It is less common to see binge eating occur early in the day soon after awakening. Binge eating episodes more commonly occur in-between the mid-day meal and the evening meal, after the evening meal, or within the meal setting.

Binge eating disorder has a stronger correlation in obesity compared to individuals with normal weight. Kessler *et al* reported in the World Mental Health data base the odds ratio of lifetime prevalence of BED in normal and overweight populations to be 1.0 and 1.3. In individuals with BMI of 30-34.9 and 35-39.9 the odds ratios rose to 3.1 and 3.0 respectively. In the BMI class of 40 and greater the odds ratio of BED was 6.6. The odds ratio of BED in a study by Hudson *et al* was 1.9 for a BMI of 30-39.9 and 4.9 for a BMI of 40 or greater. This was a face to face survey of U.S. households of 9282 adults.[3] Wadden *et al* reviewed epidemiologic studies and found the diagnosis of BED in subjects being assessed for bariatric surgery to range from 5-25% using strict BED criteria and structured clinical interviews.[4]

Successfully treating BED is beneficial in both the treatment of weight loss and in maintenance of weight loss. Treatments of BED currently include cognitive behavioral therapy and/or the FDA approved medication lis-dexamphetamine.[5] Several medications have been used off-label by practitioners for the treatment of BED including topiramate, phentermine, phentermine-topiramate combinations, bupropion and naltrexone as well as other medications.[5] Bariatric surgery has demonstrated effectiveness in ameliorating BED in patients.[6]

CIRCADIAN CHRONOTYPE

The circadian system occurs in all organisms from unicellular to plants to humans. In the last few decades there has been a large advance in understanding of the molecular elements and functioning of the circadian system.

In humans the circadian system is composed of a central pacemaker located in the suprachiasmatic nucleus of the hypothalamus that centrally coordinates control of most physiologic and behavioral functions. Light input from the retinal hypothalamic tract provides light and dark information that the central pacemaker uses to coordinate multiple components of physiology into repeating 24-hour cycles. This includes sleep/wake cycles, hormonal regulation, body temperature control and many of our metabolic homeostatic systems.

The structure of the circadian architecture is based on a DNA transcriptional-translational feedback loop (TTFL) that regulates the circadian clock not only in the suprachiasmatic nucleus but peripherally the molecular “clock” mechanisms are replicated in most cells in the human body. Two proteins, CLOCK and BMAL1, are the core of the clock signaling in humans. They dimerize into a transcription factor that codes for their own repressors (PER and CRY). PER and CRY dimerize in the cytoplasm and enter the nucleus to repress the CLOCK:BMAL1 complex. They are degraded cyclically in the cytoplasm through an ubiquitination process. This creates a cycling effect of activation and repression that is the basis for the 24-hour circadian cycle. ROR and REV-ERB*a* are other looping regulators that control timing and repress other molecular regulators of the circadian system including several ubiquitases, phosphatases and kinases. There is also post-translational and post-transcriptional modulation of the circadian signaling cycles.[7]

The circadian system can be modulated by external inputs called Zeitgebers. Such inputs as timing of sleep, meal timing, and ambient temperature can modulate the functioning of the clock in the peripheral clocks of cells and organs as well as through the central pacer in the suprachiasmatic nucleus. Control of the circadian signaling can also occur through post-translational and post-transcriptional control.[7]

The awake-sleep cycle in humans is a circadian characteristic known as chronotype. This cycle can be categorized as early, intermediate or late chronotype depending on an individual's preferred time of awakening and going to sleep. Individuals with an early chronotype tend to wake up earlier in the day and have a tendency for sleep onset earlier in the evening. This is in contrast to individuals with late chronotypes who have wake and sleep times naturally shifted to later in the day.[8]

Individuals with different chronotypes not only have preferred sleep and wakening times but have been shown to have different timing of macronutrient intakes. Later times of meal ingestion have been shown to affect body composition to a more obese phenotype. Later meal ingestion has been shown to affect peripheral circadian signaling as well.[9] Animal studies show changes in peripheral and central circadian signaling and feedback by altered timing of meal ingestion.[10] A study in humans also showed effects on the clock gene PER2 expression in whole blood as a result of shifted meal timing.[11]

Chronotype is determined by the rise in melatonin levels that occurs two hours prior to the normal time an individual has onset of sleep. This can be measured either by determining serum or salivary levels showing the daily rise of melatonin in the evening. Economically this would be difficult to measure in an outpatient clinical setting. Chronotype can also be determined using the validated scale Morning Evening-

ness Questionnaire (MEQ), which is a self-reported scale which categorizes individuals through quintiles from a definite morning through a definite evening chronotype.[12]

CIRCADIAN DYSYNCHRONY

Dysynchrony of the circadian system can have deleterious metabolic effects. Mouse knock-out models of individual components of the TTFL frequently have obesity and metabolic dysfunction.[13]

Meal timing is a circadian zeitgeber, and experimental studies in animals show shifting times of meal ingestion can result in signs of metabolic syndrome and weight gain. These results have been seen in human studies as well. Later time of food intake can lead to less effective weight loss during weight loss trials as well as increased weight gain. Signs of insulin resistance can be seen in short-term studies that shift feeding times to later in the day. Late chronotypes have been observed to ingest more macronutrients later in the day.[14]

Sleep onset can be a powerful zeitgeber as well, causing dysynchrony in circadian signaling and human disease. In humans a common example of circadian dysynchrony is seen in chronic shift workers. In this population of workers, dysynchrony is associated with increased risks of obesity, cardiovascular disease, metabolic syndrome, Type 2 diabetes and an increased risk of malignancies. Shift work disorder is associated with short sleep and frequently shifted time of food ingestions. These associations may occur without a concurrent increase in calorie intake.[15]

STUDY PURPOSE

A previous study by Harb et al demonstrated in a cross-sectional study of a predominately overweight but not obese sample, an association of binge eating disorder with later chronotype.[16]

The objective of this study was to assess if there is a relationship between BED and late chronotype in patients with obesity. If a positive association exists then therapeutic interventions based on an individual circadian chronotype may be beneficial both in the treatment of BED but also obesity and related comorbidities. A secondary objective was to determine if either the presence or absence of BED and having a late chronotype has an effect on weight loss outcomes in a 16-week obesity treatment study.

CHAPTER 2: METHODS

PARTICIPANTS

Retrospective chart analysis was conducted on 170 patients with obesity presenting to Nebraska Bariatric Medicine, an obesity medicine clinic, from July 1, 2017 to December 31, 2017. The clinic is staffed by a board-certified obesity medicine physician. Most patients are referred to the clinic by other health care providers and are treated with behavioral and pharmacologic modalities. Some of the patients are self-referred. Common reasons for referral into the clinic are medical issues complicated by obesity such as degenerative joint disease with a need for weight loss prior to joint arthroplasty, diabetes, obstructive sleep apnea, congestive heart failure and chronic renal failure. Patients were in the age group of 19-70.

PROCEDURES

The study protocol was approved by the University of Nebraska Medical Center IRB (482-18-EP) with oversight to the study ceded by Catholic Health Initiatives IRB (1244485-1). The study population was obtained from Nebraska Bariatric Medicine in Lincoln, Nebraska which is part of the Catholic Health Initiatives health system.

MEASURES

Chronotype was an independent variable and assessed in all clinic patients at the initial visit with the MEQ, a patient self-assessment scale. The questionnaire includes 19 questions that determine an individual's peak time of alertness during their day and patterns of sleep and wakefulness. Patients were categorized as a late chronotype with a score of 42 or less on the MEQ. Scores greater than 42 were categorized as a non-late chronotype.

BED was diagnosed using a brief written questionnaire completed by the patient. The questionnaire has the patient rate on a graded scale if he or she experiences episodes of eating larger amounts of food and has a sense of loss of control during those eating episodes. Frequency of eating with lack of control is assessed, and a checklist of confirmatory characteristics is included. Three of these characteristics during binging need to be present to confirm the diagnosis and include the following:

Eating more rapidly than normal

Eating until uncomfortably full

Eating larger amounts of food when not hungry

Eating alone because of embarrassment

Feeling depressed or guilty about the overeating

Feeling upset about the uncontrolled eating or weight gain

Binging needs to occur at least once of week over the three months prior to the initial visit. The questionnaire also asks if the patient has any purging behaviors. These diagnostic criteria from the DSM-V for BED are then confirmed by the physician during the initial history and physical examination. The questions for chronotype and binge eating disorder are included on an intake form completed by all clinical patients at their initial visit.

All participants had initial demographic information including age, BMI calculated by the Quetelet index (weight in kilograms divided by height in meters squared), blood pressure, resting heart rate, height and weight. Weight, BMI, blood pressure and resting heart rate were reassessed after 16 weeks of weight loss treatment in the clinic. Comorbid conditions of hypertension, insulin resistance, type 2 diabetes, obstructive sleep apnea and chronic insomnia were also assessed in all patients.

Treatment consisted of a behavioral intervention plan as well as weight loss pharmacotherapy in patients if indicated. The behavioral plan included use of a breakfast meal replacement, monitoring daily diet intake usually using a phone application, learning to restrain amounts within a meal, and mindful eating patterns. Medications commonly used in the clinic included phentermine, topiramate, bupropion, naltrexone and metformin. Patients were scheduled for monthly clinic follow-up for 16 weeks.

STATISTICAL ANALYSES

Descriptive statistics were performed to describe the baseline characteristics of the study patients. Frequencies were calculated for sex, BED, non-BED, late and non-late chronotype.

Chi-square analysis was used to evaluate the relationship between BED and chronotype. The 2-tailed student t test was used to determine if there was a significant difference in weight change at 16 weeks in the group of patients with or without binge eating and in the group with late or non-late chronotype.

SPSS version 25.0 (SPSS, Chicago, IL) was used for all analysis. Statistical significance was set at $p < 0.05$.

CHAPTER 3: RESULTS

The patients (n = 170, range 19-70) had a mean age of 49.1 years (S.D. 11.7). 80% of the patients were female and 20% male. In the study population 67.1% had insulin resistance, 47.9% had obstructive sleep apnea, 50.0% were treated for hypertension and 23.5% had type 2 diabetes mellitus. Self-reported hours of sleep by the patients was recorded and 57.4% of the patients reported 7 hours of sleep a night or more.

In the study population 41.2% of the patients were diagnosed with BED and 58.8% did not have BED. Late chronotype was seen in 12.1% of the sample and 87.9% had a non-late chronotype. Descriptive characteristics are shown in **Table 1**.

Table 1
Demographic characteristics of the sample population (N = 170)

Patient characteristics	Mean (S.D.)
Age (years)	49.1 (11.7)
Sex—n (%)	
Female	136 (80.0%)
Male	34 (20.0%)
Weight—lbs.	281.4 +/- (65.9)
Body mass index (kg/m^2)	45.1 +/- (9.0)
Initial weight	
Female	268.0 +/- (4.6)
Male	334.6 +/- (14.2)
BED—n (%)	70 (41.2)
Non-BED—n (%)	100 (58.8)
Initial weight BED	279.0 +/- (7.9)
Initial weight non-BED	283.0 +/- (6.62)
MEQ	55.5 +/- (11.1)
Initial weight late chronotype	291.3 +/- (54.8)
Initial weight non-late chronotype	282.3 +/- (69.2)
Insulin resistance—n (%)	56 (32.9)
Initial weight IR	290.3 +/- (71.3)
Initial weight non-IR	263.2 +/- (49.0)
Obstructive sleep apnea—n (%)	81 (47.6)
Initial weight with OSA	309.3 +/- (8.2)
Initial weight without OSA	256.2 +/- (4.8)
Hypertension—n (%)	85 (50)
Type 2 DM—n (%)	40 (23.5)
Initial weight with T2DM	301.3 (14.2)
Initial weight without T2DM	274.2 (4.9)
Sleep > 7 hours n (%)	97 (57.4%)
Initial weight with sleep > 7 hours	284.1 +/- (7.1)
Initial weight with sleep < 7 hours	278.8 +/- (7.2)

There was no significant difference in either BED or late chronotype with the presence or absence of IR, OSA or T2DM.

Two patients were not included in the analysis of BED with chronotype due to incomplete data. The MEQ was not completed in these patients. For 168 patients who were evaluated for BED and had completed the MEQ, Pearson Chi-square analysis was performed to evaluate their relationship. The 2-sided significance had a *p* value of .412 which demonstrated no significance incidence for BED and late chronotype. **Table 2**

Table 2
Pearson's chi-squared test for frequencies of BED and chronotype

	MEQ #		
	non-late	late	Total
BED #	57	6	63
Non-BED #	74	12	86
Total	131	18	149

	Value	df	Significance (2-sided)
Pearson Chi-Square	.672	1	.412

Out of the 170 patients initially evaluated, 149 had 16-week follow-up visits. For the secondary outcome of weight loss change at 16 weeks, weight change outcome data was available for a completers rate of 87.6%. The degree of weight loss was evaluated using student t tests in both those with and without BED and in those with late and non-late chronotypes. There was no significant difference between groups for either BED or chronotype categories. Student t test evaluating weight change at 16 weeks in those with BED and without BE showed no significance with a *p* value of .435. The difference in means between those with and without late chronotype and weight change at 4 months trended closer but was not significant with a *p* value of 0.107. **Tables 3 and 4**

Table 3

16-week weight loss	Mean (S.D.)
Initial Body Mass Index (kg/m^2)	45.1 +/- (9.0)
16-week Body Mass Index (kg/m^2)	42.4 +/- (9.2)
Initial weight lbs.	281.4 +/- (65.9)
16-week weight lbs.	267.9 +/- (70.0)
Weight change 16 weeks in BED lbs.	17.2 +/- (2.1)
Weight change 16 weeks in non-BED lbs.	16.3 +/- (1.60)
Weight change 16 weeks in late chronotype lbs.	12.1 +/- (4.8)
Weight change 16 weeks in non-late chronotype lbs.	17.4 +/- (1.4)

Table 4

Independent samples test for weight loss difference in BED

	Number	Mean % weight change	Standard deviation
BED	50	.063	.051
Non-BED	61	.056	.041
% weight change (significance 2-tailed (equal variances assumed)		.435	

Independent samples test for weight loss difference in chronotypes

	Number	Mean % weight change	Standard deviation
Late chronotype	11	.038	.047
Non-late chronotype	89	.063	.046
% weight change (significance 2-tailed (equal variances assumed)		.107	

There was no significant difference in 16-week weight loss in the analysis of the groups with and without IR, OSA and T2DM or hypertension (significance with 2-tailed independent t test 0.45, 0.15, 0.18 and 0.38 respectively).

CHAPTER 4: DISCUSSION

The primary outcome in this study was an evaluation of the relationship between BED and late chronotype in a population of patients with obesity presenting for treatment. There was not an increased incidence of BED in patients with a later chonotype. The secondary outcome of the study evaluated the weight loss outcomes in this population at 16 weeks. There was no significant difference in weight loss whether the patients had BED or not and there was no effect of weight loss outcomes with the different chronotypes.

This is in contrast with the study by Harb et al, which did show a correlation with increased BED in subjects with a later chronotype. That study included a smaller sample of 100 subjects who presented to a nutrition clinic. Of the subjects in that study 66% were overweight and 18% met criteria for obesity. The rate of BED was 14.5% using the Binge Eating Scale. This study was in a population of only patients with obesity. The Harb study was a cross-sectional trial and no evaluation of weight change was studied.

The present study does have several limitations. The sample size was 170 patients but the number with late chronotype was low, slightly greater than 12%. Two patients in this trial did not complete the MEQ and 168 patients were compared with BED and chronotype.

For the secondary outcome of weight change only 87.6% of the patients had follow-up weights at 16 weeks. BED was diagnosed differently in the two studies. The Binge Eating Scale was utilized in the Harb study and clinician confirmation of BED based on DSM-V criteria used in this study. The Harb study had a BED incidence of 14.5% versus 41.2% in this study. This may reflect the differing populations as the

patients in this study were primarily referred to this clinic for significant obesity and comorbid problems. Increasing BMI is associated with increasing likelihood of BED. Different diagnostic methods may also have affected the different rates of BED.

An important outcome in this study did show that diagnosis of BED or late chronotype did not cause a difference in weight loss. The patients were all evaluated and treated with the same behavioral program but differed in pharmacologic treatment. In general patients with BED tended to be treated more frequently with topiramate versus those without BED. The completers that had 16-week follow-up data was only 87.6% and several of these patients eventually returned for follow-up at a later date. Retention is difficult in an obesity medicine clinic and patients are not always compliant with follow-up visits. Weight loss in a short-term trial such as this does not reflect long-term weight loss or weight loss maintenance.

Repeating the study with a larger sample of patients and all participants having a similar pharmacologic treatment plan could improve on the limitations of this study.

CHAPTER 5: CONCLUSION

There is not an increase in BED in patients with late chronotype in a population of patients with obesity or overweight in this retrospective analysis. In a 16-week trial the amount of weight loss attained by these patients did not vary whether the subjects had BED or had a late chronotype.

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