CIRCADIAN RHYTHMS DISRUPTIONS AND EATING DISORDERS: CLINICAL IMPACT AND POSSIBLE PSYCHOPATHOLOGICAL CORRELATES

Giulia Menculini, Francesca Brufani, Valentina Del Bello, Patrizia Moretti & Alfonso Tortorella
Division of Psychiatry, Department of Medicine, University of Perugia, Perugia, Italy

SUMMARY

Background: A link between abnormalities in circadian rhythms and the development of eating disorders was extensively hypothesized, mainly in consideration of the influence of the circadian clock on eating behavior. The present review is aimed at summarizing the evidence about biological rhythms disruptions in eating disorders, possibly clarifying their impact on the psychopathological profile of such patients.

Methods: Electronic database MEDLINE/PubMed/Index Medicus was systematically searched for original articles examining the prevalence of circadian rhythms disruptions in eating disorders (anorexia nervosa, bulimia nervosa, binge eating disorder).

Results: Studies included in the review confirmed the hypothesis of a high prevalence of circadian disruptions in eating disorders. The analyzed research mainly focused on sleep-wake cycle, rest-activity abnormalities and hormonal secretion, whilst literature about other circadian rhythms was scanty. Altered biological rhythms presented higher association with specific psychopathological features, but such relationship was assessed in few studies.

Conclusions: Circadian rhythms disruptions were confirmed to be relevant aspects in the context of eating disorders. Further research is needed in order to clarify the role of biological rhythms in such illnesses, in the attempt to address adjunctive treatment strategies with the possible focus of circadian abnormalities.

Key words: circadian rhythms - biological rhythms - eating disorders - anorexia nervosa - bulimia nervosa - binge eating disorder

INTRODUCTION

Eating disorders (EDs) are complex psychiatric conditions that involve patients’ global functioning and present a complex etiopathogenesis, encompassing both psychological and biological aspects (American Psychiatric Association 2013). Over the last decade, several studies focused on circadian rhythms and their alterations in patients suffering from EDs. Circadian rhythms disruptions already demonstrated to play a significant role in several psychiatric disorders, possibly being correlated to their pathophysiology (Cretu et al. 2016, Allega et al. 2018). The hypothesis of a possible disruption in biological rhythms also in EDs arises from the fact that the circadian pacemaker is connected with metabolic and hedonic centers, controlling both feeding and other activities (Mendoza 2018). Subsequently, all circadian rhythms, i.e. sleep-wake rhythm, activity levels, social patterns, hormonal secretion, and not only those related to eating behaviors, can potentially be altered in patients affected by EDs. It was hypothesized that patients with abnormalities in eating attitudes display predominantly phase-delayed circadian rhythms of various behavioral and neuroendocrine factors, and that the timing of key rhythms involved in food intake and metabolism would be altered (Goel et al. 2009). This was already demonstrated in animal models, where changes in food intake resulted in a fragmentation of sleep and a reduction of slow wave sleep (Lauer & Krieg 2004). In addition, circadian disruptions may represent not only relevant symptomatological features in EDs, but also possible modulators of some clinical aspects of such disorders, which could be i.e. demonstrated by the link between insomnia and poorer treatment outcomes (Allison et al. 2016). Notwithstanding the potential interest of circadian dysruptions in EDs, an extensive assessment of their impact on this complex group of disorders is still lacking. Subsequently, the aim of the present review is to summarize the evidence about circadian abnormalities in the main EDs, focusing on their prevalence and possible influence on clinical and psychopathological features.

METHODS

We conducted a systematic search of the electronic database MEDLINE/PubMed/Index Medicus using the following search string: (((anorexia nervosa) OR bulimia nervosa) OR binge eating) OR eating disorders) AND (((circadian rhythms) OR biological rhythms) OR sleep-wake cycle). Two independent investigators (GM and FB) performed the literature search, title/abstract screening and full text screening. The reference list of selected articles underwent further screening in order to search for additional literature. We included in the present review original studies reporting data about the prevalence and the possible clinical impact of circadian rhythms disruption in the main EDs, namely anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED). Only research conducted in the past 15 years was considered for inclusion (screening period: 1st January 2004 - 31st May 2019). Articles presenting
the present review.

RESULTS

Literature search results

The database search initially yielded 672 records. Among these, 21 were selected after performing title-abstract screening. Further evaluation led to the exclusion of 3 articles. Two more papers were deemed eligible for inclusion in the review after hand-screening of relevant references. Subsequently, the full text examination identified 20 papers which were included in the present review.

Content results

Hormonal circadian patterns

Patterns of circadian hormone secretion in patients with EDs were evaluated in ten of the included studies, with the measurement of blood and salivary levels at different times of the day (Misra et al. 2005, Germain et al. 2007, dos Santos et al. 2007, Germain et al. 2009, Germain et al. 2010, Monteleone et al. 2011, Galusca et al. 2012, Ostrowska et al. 2013, Galusca et al. 2015, Germain et al. 2016). Thirteen hormones were taken into account in the selected articles (see Table 1), mainly regulating food intake and appetite. The circadian rhythm of such molecules was significantly decreased/absent or dysregulated in subgroups of patients affected by EDs, with frequent abnormalities in their daily mean blood/salivary concentration. An exception was demonstrated for orexigenic neuropeptide 26RFa, which showed a circadian profile similar in BN and controls, whilst it was significantly decreased in all-type AN (Galusca et al. 2012). A similar result was found for obestatin and ghrelin, which showed abnormalities only in AN patients but not in BN (Germain et al. 2010). Studies considering also constitutional thinness demonstrated that some abnormalities were detectable as well in these subgroups for the analyzed hormones (Germain et al. 2007, Germain et al. 2009, Germain et al. 2016).

Sleep-wake rhythm

Sleep-wake disruptions in EDs were examined in eight of the included studies, by analyzing sleep architecture (Tzichinsky & Latzer 2006, Sauchelli et al. 2015, Tanahashi et al. 2017, Asaad Abdou et al. 2018, Kandeger et al. 2018, Roveda et al. 2018) and sleep quality (Lundgren et al. 2008, Sauchelli et al. 2015, Tromp et al. 2016, Asaad Abdou et al. 2018). Studies considering obese patients with and without BED showed that patients with BED did not present sleep architecture abnormalities when compared to obese subjects (Roveda et al. 2018), with the whole obese group showing more significant sleep disturbances. Despite this, in another study the BED subgroup demonstrated abnormalities in specific parameters, such as minutes of wakefulness during sleep (Tzichinsky & Latzer 2016). One study, using a structured questionnaire and polysomnography, also demonstrated higher rates of parasomnias and daytime hypersonomnia in AN and BN, as well as abnormalities in indexes such as sleep latency, sleep efficiency and arousal (Asaad Abdou et al. 2018). When comparing different AN subtypes, binge eating-purging type presented with worse sleep quality, abnormal sleep duration and more disrupted circadian rhythm (Sauchelli et al. 2015, Tanahashi et al. 2017). Furthermore, insomnia and sleep parameters abnormalities were linked to a higher severity of depressive symptoms in EDs (Asaad Abdou et al. 2018) and presented an indirect influence on disordered eating attitudes (Kandeger et al. 2018).

Chronotype/circadian preference

Four of the selected studies analyzed patterns of activities in EDs, with a particular focus on circadian preferences (Natale et al. 2008, Harb et al. 2012, Roveda et al. 2018, Kandeger et al. 2018). Studies assessing chronotype found a significant association with evenness, both when the sample was composed of patients with all-type EDs (Natale et al. 2008) and only with diagnosis of BED (Harb et al. 2012). In this subgroup of patients, levels of daytime activity also resulted to be reduced (Roveda et al. 2018). On the other side, a study assessing eating patterns and diurnal preference in a sample of students did not find any significant correlation between chronotype and disordered eating attitudes (Kandeger et al. 2018).

Other circadian rhythms

One study assessed circadian eating patterns and mood variations among patients with diagnosis of BN, by means of self-administered instruments (Lundgren et al. 2008). Dysregulated eating behaviors presented a significant circadian component, with the prevalence of night-time eating and morning anorexia. Similarly, mood variations across the day were strongly prevalent, with a higher rate of depression during the evening/night.

DISCUSSION

The results of the present review, as expected, demonstrated high rates of biological rhythms dysregulation in patients with EDs, when considering sleep/wake cycle, activity patterns/chronotype and hormone secretion. Abnormalities in the circadian concentrations of the studied hormones, especially molecules controlling food intake (i.e. NYY, GLP-1, leptin, ghrelin, obestatin,
Table 1. Summary of the included studies assessing circadian rhythms in EDs

<table>
<thead>
<tr>
<th>References</th>
<th>Study Design</th>
<th>Sample</th>
<th>Analyzed circadian rhythm</th>
<th>Circadian rhythm assessment measure(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asaad Abdou et al. 2018</td>
<td>Observational, prospective, cross-sectional study</td>
<td>23 females with AN or BN (age 18-45) 20 controls matched for age and sex</td>
<td>Sleep architecture</td>
<td>Structured Sleep Disorder Questionnaire PSG</td>
</tr>
<tr>
<td>Kandeger et al. 2018</td>
<td>Observational prospective study</td>
<td>383 students (60.1% females), mean age 21.1 (±0.1), who were screened for disordered eating attitudes (4.2% met the criteria)</td>
<td>Chronotype/circadian preference, sleep architecture</td>
<td>MEQ, Insomnia severity index</td>
</tr>
<tr>
<td>Roveda et al. 2018</td>
<td>Observational, prospective, cross-sectional study</td>
<td>8 obese females 8 obese females with BED</td>
<td>Rest-activity circadian rhythm and sleep architecture</td>
<td>Actigraphy and Actiwatch Sleep Analysis Software</td>
</tr>
<tr>
<td>Tanahashi et al. 2017</td>
<td>Observational, prospective, cross-sectional study</td>
<td>12 AN binge-eating-purging type 8 AN restricting type</td>
<td>Sleep quality and sleep architecture</td>
<td>PSQI</td>
</tr>
<tr>
<td>Germain et al. 2016</td>
<td>Observational, prospective, cross-sectional study</td>
<td>10 restrictive type AN women 5 binge-purging type AN women 15 recovered restrictive type AN women 4 BN women 10 constitutional thinness women 7 healthy obese women 10 normal weight women</td>
<td>Plasmatic IL-7 rhythm</td>
<td>24-hour sampling of IL-7 (12 measurements), leptin and cortisol (6 measurements)</td>
</tr>
<tr>
<td>Tromp et al. 2016</td>
<td>Observational prospective study</td>
<td>574 young adults, 12% with EDs (screened positive at ESP)</td>
<td>Sleep quality and daytime functioning</td>
<td>SLEEP-50 questionnaire subscales for sleep apnea, insomnia, circadian rhythm disorder and daytime functioning</td>
</tr>
<tr>
<td>Galusca et al. 2015</td>
<td>Observational, prospective, cross-sectional study</td>
<td>23 AN young women 22 CT young women 14 normal weight age-matched controls</td>
<td>Plasmatic NPY and αMSH rhythm</td>
<td>24-hour sampling of NPY, αMSH (12 measurements), leptin, GH and cortisol (6 measurements)</td>
</tr>
<tr>
<td>Sauchelli et al. 2015</td>
<td>Observational, prospective, cross-sectional study</td>
<td>48 AN patients 98 healthy weight controls</td>
<td>Sleep quality, sleep architecture</td>
<td>PSQI</td>
</tr>
<tr>
<td>Ostrowska et al. 2013</td>
<td>Observational, prospective, cross-sectional study</td>
<td>86 females (13-18 years) with AN and 21 healthy subjects (13-17 years)</td>
<td>Melatonin rhythm</td>
<td>Melatonin blood samples (2 measurements)</td>
</tr>
<tr>
<td>Galusca et al. 2012</td>
<td>Cross-sectional study</td>
<td>19 restrictive AN women 10 binge-purging AN women 14 CT women 10 bulimic women 10 normal-weight age-matched controls</td>
<td>Orexigenic neuropeptide 26RFa rhythm</td>
<td>24-hour sampling of 26RFa (12 measurements), leptin, GH, cortisol (6 measurements)</td>
</tr>
<tr>
<td>Harb et al. 2012</td>
<td>Cross-sectional study</td>
<td>100 subjects (77% females), mean age 39.5 (±11.7) years, 66% overweight. 43% presented binge eating, 27% abnormal eating attitudes/behaviors, 18% night eating behavior.</td>
<td>Chronotype/circadian preference</td>
<td>MEQ</td>
</tr>
</tbody>
</table>

Notes: αMSH = Melanocyte stimulating hormone type α; AM = Anti-meridian; AN = Anorexia nervosa; BDI = Beck Depression Inventory; BED = Binge Eating Disorder; BN = Bulimia nervosa; CT = constitutional thinness; EDs = Eating disorders; ESP = Eating Disorder Screen for Primary Care; GH = Growth hormone; GLP-1 = Glucagon-like peptide 1; IGF-1 = Insulin-like growth factor-1; IL-7 = Interleukin-7; EAT = Eating Attitude Test; EDI-2 = Eating Disorders Inventory-2; MEQ = Morningness/eveningness questionnaire, reduced version; MEQr = Morningness/eveningness questionnaire; NEQ = Night eating questionnaire; NPY = Neuropeptide Y; PM = Post-meridian; PSG = Polysomnography; PSQI = Pittsburgh Sleep Quality Index; PYY = Peptide YY.
Table 1. Continues

<table>
<thead>
<tr>
<th>References</th>
<th>Study Design</th>
<th>Sample</th>
<th>Analyzed circadian rhythm</th>
<th>Circadian rhythm assessment measure(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monteleone et al. 2011</td>
<td>Cross-sectional study</td>
<td>8 AN females; 8 age-matched controls</td>
<td>α-amylase and cortisol salivary levels</td>
<td>Salivary samples 15, 30, 60 min from awakening and at 10 AM, 12 AM (before lunch), 4 PM, 6 PM, 7 PM and 8 PM (before dinner)</td>
</tr>
<tr>
<td>Germain et al. 2010</td>
<td>Cross-sectional study</td>
<td>22 restrictive type AN women; 10 binge-purging type AN women; 16 normal-weight BN women; 9 age-matched control subjects</td>
<td>Plasmatic ghrelin, obstetan, and PYY rhythm</td>
<td>24-hour sampling of leptin, GH, cortisol, obestatin, total and acylated ghrelin, and PYY (12 measurements)</td>
</tr>
<tr>
<td>Germain et al. 2009</td>
<td>Cross-sectional study</td>
<td>15 restrictive type AN young women; 9 young women restored from AN; 10 CT; 9 control subjects</td>
<td>Plasmatic obestatin and ghrelin rhythm</td>
<td>24-hour sampling of leptin, GH, cortisol, obestatin, total and acylated ghrelin (6 measurements)</td>
</tr>
<tr>
<td>Lundgren et al. 2008</td>
<td>Observational prospective study</td>
<td>31 females, diagnosis of BN</td>
<td>Eating behavior (nighttime patterns and morning anorexia) Sleep quality Circadian mood variations</td>
<td>NEQ, EDI-2, BDI</td>
</tr>
<tr>
<td>Natale et al. 2008</td>
<td>Observational, prospective, cross-sectional study</td>
<td>270 females:146 recruited in a EDs treatment centre, 240 controls</td>
<td>Chronotype/circadian preference</td>
<td>MEQr</td>
</tr>
<tr>
<td>Dos Santos et al. 2007</td>
<td>Prospective transversal controlled study</td>
<td>12 female patients with diagnosis of AN (10 restrictive type, 2 bulimic type, age: 15-35); 13 age-matched healthy and ovulatory females</td>
<td>24-hour salivary cortisol rhythm</td>
<td>Multiple salivary cortisol determinations (9 AM, 5 PM, 11 PM)</td>
</tr>
<tr>
<td>Germain et al. 2007</td>
<td>Observational, prospective, cross-sectional study</td>
<td>12 AN young women; 10 age-matched CT; 7 age-matched normal weight</td>
<td>Plasmatic PYY, GLP-1, ghrelin, leptin and GH rhythm</td>
<td>24-hour sampling of PYY, GLP-1, ghrelin, leptin GH, cortisol (every 4 hours measurements)</td>
</tr>
<tr>
<td>Tzischinsky &amp; Latzer 2006</td>
<td>Observational, prospective, cross-sectional study</td>
<td>36 obese patients (divided in obese with and without BED); 25 normal weight controls</td>
<td>Sleep architecture</td>
<td>Mini actigraphs, self-reported questionnaires (Mini-Sleep Questionnaire, Standard Technion Clinical Sleep Questionnaire) and sleep diary</td>
</tr>
<tr>
<td>Misra et al. 2005</td>
<td>Observational, prospective, cross-sectional study</td>
<td>22 AN females (12-18 years) ; 18 age-matched healthy controls</td>
<td>Plasmatic ghrelin, GH, cortisol rhythm</td>
<td>Blood samples every half hour for 12h at night</td>
</tr>
</tbody>
</table>

Notes: αMSH = Melanocyte stimulating hormone type α; AM = Anti-meridian; AN = Anorexia nervosa; BDI = Beck Depression Inventory; BED = Binge Eating Disorder; BN = Bulimia nervosa; CT = constitutional thinness; EDs = Eating disorders; ESP = Eating Disorder Screen for Primary Care; GH = Growth hormone; GLP-1 = Glucagone-like peptide 1; IGF-1 = Insulin-like growth factor-1; IL-7 = Interleukin-7; EAT = Eating Attitude Test; EDI-2 = Eating Disorders Inventory-2; MEQ = Morningness/eveningness questionnaire, reduced version; MEQr = Morningness/eveningness questionnaire; NEQ = Night eating questionnaire; NPY = Neuropeptide Y; PM = Post-meridian; PSG = Polisomnography; PSQI = Pittsburgh Sleep Quality Index; PYY = Peptide YY

orexigenic neuropeptides), were shown in a relevant number of the considered studies, confirming the hypothesis of a significant biological load in the etiopathogenesis of EDs, which should thus be considered psychoneuroendocrine diseases as historically defined (Brambilla et al. 2001). The differences in circadian hormone profiles shown between AN restrictive and binge-purging subtype could present possible implications in the differential diagnosis of such subgroups (Germain et al. 2010). Moreover, the distinct profile that some studies demonstrated for AN when compared to constitutionally thin patients (Germain et al. 2007, Germain et al. 2009, Germain et al. 2016) suggests a possible link between specific psychopathological features and hormone secretion abnormalities, which should be further clarified in future studies. This could be evaluated also in consideration of the direct effect that some of the abnormally secreted hormones,
CONCLUSIONS

Circadian disruptions were confirmed to be prevalent features in eating disorders, but the literature on the topic is still scanty, focusing only on specific biological rhythms. Further research is needed in order to clarify the psychopathological correlates of such abnormalities, their implication on differential diagnosis and their role as possible risk factors, also in the attempt to address adjunctive treatment strategies.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Giulia Menculini, Francesca Brufani, Valentina Del Bello & Patrizia Moretti conceived and designed the review.

Giulia Menculini & Francesca Brufani performed the literature search.

Francesca Brufani wrote substantial part of the introduction.

Giulia Menculini wrote substantial part of methods.

Giulia Menculini & Valentina Del Bello wrote substantial part of results.

Giulia Menculini discussed results.

Patrizia Moretti & Alfonso Tortorella corrected the first draft of the manuscript.

Alfonso Tortorella supervised all phases of the study design and writing of the manuscript.

References

7. Brambilla F, Santonastaso P, Caregara L, Favaro A: Growth hormone and insulin-like growth factor 1 secre-
tions in eating disorders: Correlations with psychopa-thological aspects of the disorders. Psychiatry Res 2018; 263:233-7

Correspondence:
Patrizia Moretti, MD
Division of Psychiatry, Department of Medicine, University of Perugia
Piazzale Lucio Severi, 1 – “Ellisse” Building, 8th Floor, 06132 Perugia, Italy
E-mail: patrizia.moretti@unipg.it