



Salud mental

ISSN: 0185-3325

ISSN: 0186-761X

Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz

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Salud mental, vol. 44, no. 1, 2021, January-February, pp. 25-30

Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz

DOI: 10.17711/SM.0185-3325.2021.005

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The role of circadian rhythms in individuals with attention deficit hyperactivity disorder and obesity: A narrative review

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Received: 3 April 2019

Accepted: 5 February 2020

Citation:

Galicia, F., Zavaleta Ramírez, P., Villavicencio, L., de la Peña, F. R., Garza Gallegos, K., Arias Caballero, A., Fera, M., ... Palacios-Cruz, L. (2021). The role of circadian rhythms in individuals with attention deficit hyperactivity disorder and obesity: A narrative review. *Salud Mental*, 44(1), 25-30.

DOI: [10.17711/SM.0185-3325.2021.005](https://doi.org/10.17711/SM.0185-3325.2021.005)



ABSTRACT

Background. A relationship between attention deficit hyperactivity disorder (ADHD) and obesity has been consistently documented. Obesity and metabolic syndrome have been associated with misalignment between daily activities and circadian rhythm. ADHD patients have a high prevalence of delayed sleep phase syndrome, which is a circadian rhythm disorder. Understanding this relationship is important for the evaluation of obese population at risk. **Objective.** The aim of this narrative review was to summarize the information updated until 2019 about the role of circadian rhythms in obese ADHD individuals. **Method.** A search was performed in MEDLINE, EMBASE, and Google Scholar database. The terms ADHD, obesity, circadian rhythm, sleep disorders, adolescent, adult, Adolesc, circadian, attention deficit hyperactivity disorder, and child were combined with logical functions. **Results.** A total of 132 articles were reviewed. Evidence showed that ADHD subjects have an increased risk to present obesity and circadian rhythms disorders. Some possible pathways for this relationship have been hypothesized including obesity as a risk factor, an underpinned common biological dysfunction, and behavioral and cognitive features of individuals with ADHD. As most of the articles are methodologically cross-sectional, it is not possible to establish causative associations. **Discussion and conclusion.** This review points out the importance of early recognizing and treating circadian rhythms disorders and obesity in ADHD patients. Future studies must be carried out with a longitudinal design to establish the effect of each comorbidity in the treatment of individuals with ADHD.

Keywords: Attention deficit hyperactivity disorder, circadian rhythms, obesity.

RESUMEN

Antecedentes. La relación entre el trastorno por déficit de atención con hiperactividad (TDAH) y la obesidad se ha documentado consistentemente. Por otro lado, el síndrome metabólico y la obesidad se han asociado con un desfase del ritmo circadiano. En poblaciones clínicas con TDAH se han encontrado una alta prevalencia del trastorno de fase de sueño retrasada, el cual es un trastorno del ritmo circadiano. Entender la relación entre estos padecimientos es importante para evaluar la población en riesgo de obesidad. **Objetivo.** Resumir la información actualizada hasta 2019 sobre el rol del ritmo circadiano en individuos obesos con TDAH. **Método.** Se realizó una búsqueda de artículos en las bases de datos MEDLINE, EMBASE y Google Scholar. Los términos TDAH, obesidad, ritmos circadianos, trastornos del sueño, adolescentes, adultos y niños se combinaron con operadores lógicos. **Resultados.** Se revisaron un total de 132 artículos. La evidencia demostró que los sujetos con TDAH tienen un alto riesgo de sufrir obesidad y ritmos circadianos alterados. Existen algunas hipótesis para establecer esta relación, incluyendo la obesidad como factor de riesgo para TDAH, la disfunción biológica común entre estos trastornos y las características conductuales y cognitivas de los individuos con TDAH. Sin embargo, como la mayoría de los artículos son transversales, no es posible establecer una asociación causal. **Discusión y conclusión.** Esta revisión señala la importancia del reconocimiento temprano y tratamiento de los trastornos del ritmo circadiano y obesidad en pacientes con TDAH. Estudios futuros deben realizarse de manera longitudinal para establecer el efecto de estas comorbilidades en el tratamiento de los individuos con TDAH.

Palabras clave: Trastorno por déficit de atención e hiperactividad, ritmos circadianos, obesidad.

BACKGROUND

In the past years, several studies have documented the close relationship among circadian rhythms, attention deficit hyperactivity disorder (ADHD), and obesity (Vogel et al., 2015; Cortese et al., 2016; Pagoto et al., 2009).

Obesity is defined as an excess of body fat, estimated by a relationship between height and weight, specific for age and sex. Obesity in children older than two years is diagnosed when body mass index (BMI) is above the 95th percentile. In countries like the United States obesity is more common in children and adolescents (Lobstein et al., 2015).

An increase in the rates of obesity and overweight prevalence in younger populations has been observed worldwide (WHO, 2014). According to the 2018 Mexico's National Health Survey, 15% of adolescents 12 to 19 years old, that live in urban cities, have obesity. In contrast, only 13% of the adolescents of the same ages have obesity in smaller Mexican cities (Romero-Martínez et al., 2019). It is known that individuals with a psychiatric disorder are in a higher risk to develop obesity (Simon et al., 2006). Depression is the most prevalent comorbidity followed by several other psychiatric disorders including ADHD (Cortese et al., 2016; Hubel, Jass, Marcus, & Laessle, 2006; Quintero et al., 2016).

ADHD is a neurodevelopmental disorder with a 5.2% worldwide prevalence throughout the life cycle (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). In Mexico, a 1.6% prevalence has been estimated between adolescents from 12 to 17 years old in a community study (Benjet et al., 2016).

Cross-sectional studies have shown that up to 30% of adults with ADHD have obesity (Raziel, Sakran, & Goitein, 2014). In turn, longitudinal studies have found associations between childhood ADHD and obesity in later life pointing to an obesity risk that increases over time (Cortese et al., 2016; 2013b). Several studies have proposed that one of the mechanisms that interplays in the relationship between ADHD and obesity might be sleeping disorders, specifically circadian rhythms disorders and insomnia. (Weinberg & Brumback, 1990; Türkoğlu, & Çetin, 2019).

The aim of this narrative review was to gather and summarize the information updated until 2019 about the role of circadian rhythms in obese ADHD individuals.

METHOD

In order to provide an overview of the evidence regarding the role of circadian rhythms in patients with ADHD and obesity, a series of searches were performed in MEDLINE, EMBASE, and Google Scholar. We used the terms ADHD, obesity, circadian rhythm, sleep disorders, adolescent, adult, adolesc, circadian, attention deficit hyperactivity disorder, child. These terms were combined with logical functions and operators using the "OR, AND & NOT", specific

for each search engine, to reduce and specify the resulting papers.

MEDLINE search was conducted through Pubmed. More than 15 search terms were used; textual words were searched and Medical Subject Headings (MeSH) were also employed. We obtained 115 references that were downloaded. EMBASE search was carried out in Elsevier through EMBASE. Same terms were used as well as textual words, resulting in 12 additional useful references. Next, we used Google Scholar resulting in five additional downloaded articles. Finally, a total of 132 articles were used for the present narrative review: each article was reviewed and later approved by at least two of the authors.

RESULTS

Circadian rhythms

Circadian rhythm stands for endogenous rhythms entrained in a period of approximately 24 hours and are present even in the absence of external time cues (Huang, Ramsey, Marcheva, & Bass, 2011; Bailey, Udoh, & Young, 2014). The integration of circadian systems involves a widely distributed network of local tissue clocks in the brain and the periphery (Huang et al., 2011). In humans, circadian rhythms are organized and guided by suprachiasmatic nucleus (SN), also known as primary oscillator, which involves projections to hypothalamus including arcuate nucleus (ARN), paraventricular nucleus, lateral hypothalamic area, and dorsomedial hypothalamus; areas from the brainstem like ventral tegmental area and to the brainstem in the dorsomedial nucleus vagus, through medial preoptic area, and periventricular nucleus (Hastings, Maywood, & Brancaccio, 2018). Circadian systems are organized hierarchically, thus the suprachiasmatic nucleus oscillator (Moore, 2013) presides over peripheral clocks. Examples of these are the 24-hour variation of glucose, insulin, and leptin levels (Fonken & Nelson, 2014).

Zeitgebers (time-givers) are time cues that phase shift circadian clocks (Bailey et al., 2014). Light is the main zeitgeber as it resets the central nervous system clock (SCN) via the retinohypothalamic tract (Bailey et al., 2014), and the one that generates synchronized rhythms of behavior and physiology (e.g. awake-sleep) through the alignment of gene oscillation of extra-SCN neurons as well as peripheral tissues (Huang et al., 2011). Furthermore, there are other zeitgebers such as food, glucocorticoid level, and body temperature which are able to reset the phase of peripheral clocks (Huang et al., 2011).

Genes of circadian clock are known to intervene in metabolic pathways of lipids, carbohydrate, and proteins. One example is the glucose homeostasis, about which it is currently known that there is a hepatocyte circadian clock with day variations for the glycogenesis and the glycogen

turnover which are independent of food intake. These oscillations are diminished in hepatocyte specific BMAL 1 knockout mice (Doi, Oishi, & Ishida, 2010; Pantazopoulos, Gamble, Stork, & Amir, 2018).

Currently there are other external factors such as the prolonged exposure to artificial light, shift work, and social demands which might be the underlying factors from which some psychopathologies may emerge or moderate other metabolic outcomes (McHill, Hull, McMullan, & Klerman, 2018; Touitou, Reinberg, & Touitou, 2017).

Obesity and circadian rhythms

Obesity and metabolic syndrome have been associated with the presence of misalignment between daily activities and the circadian rhythm. The first studies performed with “shift workers” have shown a correlation between this poor alignment and higher mortality rates due to complications of metabolic syndrome and diabetes (Arble, Ramsey, Bass, & Turek, 2010) and cardiovascular alterations (Mosendane, Mosendane, & Raal, 2008). When comparing obese “metabolically healthy” versus obese “metabolically unhealthy”, social jet lag has been found to be more prevalent in metabolically unhealthy individuals and it has also been associated with elevated glycosylated hemoglobin (Parsons et al., 2015). The circadian rhythm could affect sleep and general metabolism. For example, oscillations in cortisol and thyroid stimulating hormone levels in plasma are present when the subject sleeps as a measure to prevent the reinforcement of the activation during the night (Copinschi, Spiegel, Leproult, & Van Cauter, 2000) and these oscillations have as a candidate for their mechanism cellular molecules of the CLOCK genes, which confer advantage to the cell for anticipation, preparing the organism for an extracellular stimulus/stress prior to its appearance (Edery, 2000; Takahashi, Shimomura, & Kumar, 2008). When considering the regulation by environmental clues, light is not the only zeitgeber as aforementioned, but there are also peripheral zeitgebers that include the quantity, quality, and time of feeding. For example, an abrupt change for days in the feeding schedule gradually shifts the internal peripheral clocks (Hirota & Fukada, 2004); voluntary scheduled exercise, exogenous melatonin or serotonergic activation are also able to change the endogenous circadian rhythms. Presumably, the fact of sleeping at different light and darkness times leads to an obesogenic behavior, but evidence shows that glucose metabolism is not purely behaviorally mediated (Zee, Attarian, & Videnovic, 2013). For example, it has been found both in humans as in rodents that there is an increase in circulating glucose levels prior to awakening (Shea, Hilton, Orlova, Ayers, & Mantzoros, 2005). In the case of short-term sleep, it has been found that the individual characteristics that predict the onset of obesity are high behavioral disinhibition to eating and low calcium intake (Chaput, Després, Bouchard,

& Tremblay, 2012). A longer duration of sleep has been associated with lower levels of diastolic and systolic pressure (Grant, Franzini, Wild, & Walker, 1998). The relationship between circadian rhythms and metabolism is bidirectional. A diet high in fat lengthens the locomotor activity, alters circadian rhythms of feeding, reduces amplitude, and shifts the phase of the gene expression of gene cycles in liver and hypothalamus (Kohsaka & Bass, 2007; Huang et al., 2011).

An inadequate amount of sleep leads to stress in the endoplasmic reticulum of hypothalamic neurons and to alterations in neuropeptides that regulate appetite, as reduced levels of leptins, increased levels of ghrelin and reduced central biological activity of orexin, all of which converge in reduce satiety and increase of food intake (Hakim, Kheirandish-Gozal, & Gozal, 2015; Mavanji, Teske, Billington, & Kotz, 2010).

Obesity and ADHD

There are various studies underlining the importance of the correlation between ADHD and obesity. Clinical and epidemiologic studies have suggested that children with clinically diagnosed ADHD are heavier than the average child (Cortese & Tessari, 2017). Conversely, overweight children are twice as likely to exhibit elevated rates of ADHD symptoms than their average weight counterparts (Aguirre Castaneda et al., 2016). Until now, research has mainly examined ADHD as a risk factor for obesity, and there is a lack of prospective longitudinal and epidemiological studies, so the direction of the potential link remains unevaluated (Khalife et al., 2014). Nevertheless, three possible pathways have been hypothesized: 1. Obesity/overweight or factors associated with Obesity/overweight (such as sleep-disordered breathing) lead to ADHD symptoms, 2. ADHD and obesity are underpinned common biological dysfunction, and 3. ADHD contributes to obesity (Cortese & Tessari, 2017). Research has also suggested that children with ADHD have difficulties regarding motor skills (Poeta & Rosa-Neto, 2007) that in combination with altered eating patterns and decreased levels of physical fitness leaves them with an increased risk for obesity in comparison to children without ADHD (Quezada, Ahmed, Fennie, Gollub, & Ibrahimou, 2018).

Other considerations are that behavioral and cognitive features of the individuals with ADHD may contribute to obesity. This is demonstrated in studies that found a positive correlation between ADHD symptoms, impulsivity and altered eating patterns, including binge eating or emotional induced eating or seasonal affective disorder (Cortese et al., 2016; Patte et al., 2016). Even after controlling for depression or anxiety symptoms, ADHD symptoms were correlated with bulimic conducts (Cortese, Konofal, Bernardina, Mouren, & Lecendreux, 2008).

Studies that analyze the relationship of childhood disruptive disorder as a mediating factor of obesity in ADHD

individuals have found that having conduct disorder resulted in a higher BMI at all ages compared to the individuals without conduct disorder (Anderson, Cohen, Naumova, & Must, 2006). An ecologic study carried out in students in the 13 to 17 age range, found a positive correlation between ADHD scores symptoms and higher risk of obesity (OR = 1.07), but there was no association with overweight (Lam & Yang, 2007).

Regarding the adult presentation of ADHD, a study found that obesity was more prevalent in adults with ADHD than those adults that never met diagnostic criteria (29 vs. 21%, respectively) (Pagoto et al., 2009).

Circadian rhythms disruption in obese ADHD patients

As mentioned earlier, circadian rhythms are entrained in a 24-hour loop, that regulates not only sleep, but several functions in our body. It has been proposed that a disruption of these rhythms may be the link between ADHD and obesity (Vogel et al., 2015). ADHD has been related with a high prevalence of the delayed sleep phase syndrome (DSPS) (Schrader, Bovim, & Sand, 1993). This means that ADHD patients who have DSPS are prone to have a chronic sleep debt (Coogan & McGowan, 2017). Furthermore, some epidemiological and clinical studies have reported that a chronic expression of a brief sleep pattern is associated with a higher prevalence of obesity in adults (Buxton et al., 2012) and in children (Cappuccio et al., 2008).

The hypocretin/orexin system (HOS) is one of the neurobiological systems implicated in this relationship. The HOS is involved in the control of sleep/wakefulness and feeding (Chieffi et al., 2017), therefore disturbances in this system can result in a deficit of alertness, an increase in appetite, and a decrease in satiety (Nixon et al., 2015) manifested by binge eating, which are common in patients with ADHD (Pagoto et al., 2009; Vogel et al., 2015).

Mechanisms involved in Obesity, circadian rhythms and ADHD

Common neurobiological and genetic pathways are relevant when trying to explain the association between circadian rhythms, obesity, and ADHD.

A study suggests that individuals with ADHD present altered eating patterns in the presence of a reward deficiency syndrome, especially when linked to a common biological dysfunction of the 7R allele of dopamine D4 receptor (DRD4) that affects prefrontal attentional areas and brain rewards pathways (Bazar, Yun, Lee, Daniel, & Doux, 2006). This implies that individuals with altered eating patterns and ADHD may present common genetically determined dysfunctions in the dopaminergic system.

Brain-derived neurotrophic factor (BDNF) dysregulation has been studied and showed controversial results.

There are studies that underline its importance in the development of obesity and ADHD through the regulation of satiety and motor hyperactivity at least in mice models (Kernie, Liebl, & Parada, 2000), but these findings have been hard to replicate. A study found a correlation between ADHD and other neurodevelopmental disorders with obesity through 11p14.1 microdeletions, where the BDNF gene is considered to be located (Shinawi et al., 2011), that also may be linked to circadian rhythms disruptions, mediated by the presence of other psychiatric comorbidities like anxiety or depression (Chaudhury, Liu, & Han, 2015). A study that compared ADHD patients and controls found that ADHD patients had higher BMI and attributed this finding to a combination between sleep duration and unstable eating patterns (Vogel et al., 2015). Finally, a cross-sectional study found that up to 86% of children/adolescents with ADHD and a preference for morning cognitive activities or a more morningness preference circadian rhythm have normal BMI, contrary to the subjects with a preference for eveningness cognitive activities or circadian rhythm where only 7.8% of ADHD subjects had normal BMI. They also found that eveningness circadian rhythm preference was associated with obesity independently of ADHD symptoms (Türkoğlu, & Çetin, 2019). All data suggest together a complex interaction between ADHD, obesity, and circadian rhythms.

DISCUSSION AND CONCLUSION

The main finding of this review is that ADHD subjects have increased risk for obesity and other psychopathology associated. We also found a consistent link between the presence of circadian rhythm disorders and obesity in ADHD patients, but since most of them are methodologically cross-sectional, it is not possible to establish causative associations. Despite this limitation, the results can be useful for the clinician.

Several studies highlight the importance of identifying obesity and circadian rhythms disruptions in order to better treat ADHD patients. Overlooking these comorbidities may result in a low quality of life, higher health expenses, and a diminishment in life expectancy (Cortese et al., 2016).

After this review, we found that treating a person with obesity seems to have better response than to treat a person with ADHD and obesity (Pagoto et al., 2009). On the bright side, the treatment of ADHD symptoms, regardless of sex, will increase the probability of a better response in the treatment of altered eating patterns and obesity (Cortese & Castellanos, 2014). When planning for a treatment of ADHD and obesity, clinician should assess other common psychiatric disorders such as anxiety that may also interfere in the treatment response (Cortese, Faraone, Bernardi, Wang, & Blanco, 2013a).

Most studies identified in our search are cross-sectional, limiting assessment of time and how other pathways may interfere in the ADHD, circadian rhythm disorders and obesity relationship. The search was limited to English language papers which may have limited the overall scope of studies identified for this review.

Taking this limitation into account, one aspect that strengthens this review is the methodological quality, since each paper was reviewed under a specific criterion.

The information summarized in this paper points out to the importance of ADHD diagnosis from a longitudinal perspective where ADHD symptoms and lifestyle contribute to the morbidity (e.g., obesity) and long-term social impairment. Clinicians must be aware of the importance of the assessment of weight, circadian rhythm, and social cues that may contribute to enhance the relationship between ADHD and obesity. The development of prevention programs is needed in order to address risk factors for comorbidities.

Recently, new directions about the role of circadian rhythms in ADHD patients with obesity have been proposed. These studies bring new insights into sleep and the circadian regulation of metabolism. Future studies must be carried out using in a longitudinal design to establish the effect of each comorbidity in the treatment of individuals with ADHD.

Funding

None.

Conflicts of interest

Dr. Frinné Galicia Moreno has received income, per diem and support for continuing education from Laboratorios Shire/Takeda; Dr. Francisco R. de la Peña Olvera has served as an exhibitor for Laboratorios Shire/Takeda, and Eli Lilly, and has also received income, per diem and support for continuing education and/or research from Laboratorios Shire/Takeda, Eli Lilly, Springer Edit., from the Miguel Alemán Foundation and the Consejo Nacional de Ciencia y Tecnología, Mexico. Dr. Lino Palacios Cruz has served as an exhibitor for Novartis, Janssen, Eli Lilly and Shire, he was on the board of Novartis and Janssen; he has received income, per diem and support for continuing education and/or research from Laboratorios Shire/Takeda, Eli Lilly, Janssen, Novartis, and the Miguel Alemán Foundation. "The rest of the authors declare they have no conflicts of interest."

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