Volume 3, December 2021, 978549

GUHES

Journal of Gazi University Health Sciences Institute

journal homepage: https://dergipark.org.tr/tr/pub/guhes

The Relationship Between Circadian Rhythm and Body Weight

Zeynep Gül Gündüz[1*], Nurhan Ünüsan[1]

[1] KTO Karatay University, Department of Nutrition and Dietetics, Konya, Turkey

Article info:

Received: 02.09.2021

Accepted: 21.12.2021

Keywords:

Circadian Rhythm, Hormones, Genes, Body Weight

Abstract

Physiological responses of living things take place in a rhythm that repeats every 24 hours. The Circadian rhythm is defined as the biological rhythm that repeats in 24 hours. Various physiological functions such as sleep/wake cycle, blood pressure, blood glucose level, secretion of hormones such as cortisol and melatonin, regulation of body temperature and adipose tissue activity exhibit 24-hour cycles. The circadian system consists of central and peripheral clocks. The suprachiasmatic nucleus in the hypothalamus regulates the central clock according to light and dark information. Peripheral clocks found in organs such as the liver and adipose tissue are regulated by environmental factors including nutrition and physical activity. While the central clock is regulated by the light-dark cycle and peripheral clocks work in harmony with the central clock. External factors (shift work, jetlag, sleep disturbances, sleeping and eating at inappropriate times, etc.) that disrupt the operation of the central and peripheral clocks negatively affect the normal functioning of the human body. In this review, the effect of distrupted circadian rhythm on body weight is examined in detail.

1. Introduction

Biological rhythms are physical, mental, and behavioral responses of many living things, from bacteria to humans, against cyclic factors and, are divided into subgroups according to cycle times, such as ultradian, circadian, infradian, and circannual. While ultradian rhythms have more than one cycle in a day and a cycle of the infradian rhythm can take weeks or months. Rhythms that complete their cycle in about a year are called circannual rhythms. Circadian rhythms (with a Latin equivalent of circa = approximate, dies = one day) are rhythms that take place within a day and need 24 hours to complete their cycle (Sözlü & Şanlıer, 2017). Synchronization of behavioral and physiological rhythms by the suprachiasmatic nucleus (SCN), the main circadian clock in the hypothalamus is expressed as circadian alignment. The main circadian clock performs a circadian alignment by binding to the peripheral tissues, including the molecular clock mechanism, which is required for rhythmic gene expression and regional circadian oscillation (Cagampang & Bruce, 2012).

Circadian rhythms primarily respond to the light-dark cycle of the organism. The majority of the cells in the hypothalamus adapt to the light-dark cycle with the information provided by the photoreceptive retinal ganglion cells. The stimulation created in these cells is transmitted primarily to the melanopsin-expressing retinal ganglion cells, in which the signals are transported to the SCN via the retinohypothalamic tract (Engin, 2017).

Crucial functions, such as sleeping at night and staying awake during the day with the effect of the sun in addition to the hormonal release, eating behaviors, digestion, and preservation of body temperature, are examples of rhythms that react to the light-dark cycle. In mammals, aside from rhythms regulated by light, some rhythms are dependent on food consumption and physical activity that synchronize meal times and activities after food intake (Laermans & Depoortere, 2016).

Peripheral clocks can be synchronized by rhythm regulators affected by food intake. Organs adapt to the fasting/feeding cycle at different times, for example, the adaptation of the liver is faster than the lung. Many central clocks in the brain can change phases according to food intake. On the contrary, if the light-dark cycle is present in the environment, it was observed that animals with food restriction rarely had a phase shift with food intake in the main circadian clock. Therefore, the central and peripheral clocks, which are affected by the restricted food intake and the food intake, deviate from the main circadian clock, causing internal synchronization to deteriorate (Damiola et al., 2000). As a result, the rhythm of the hormones affected by food intake or starvation can be profoundly affected by restricted food intake. Phase shifts in the hormones that stimulate gene expression, especially clock genes, can affect internal synchronization (Mistlberger, 2011).

2. Hormones and Circadian Rhythm

During the daily 24-hour cycle, nutrient intake, energy use in the body and energy storage patterns work depending on a neuro-endocrinological system. There are different circadian oscillations between

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

hormones that have similar metabolic functions and must occur simultaneously and other hormones, and the most well-known of these hormones are melatonin, cortisol, gonadal steroids, prolactin, thyroid hormone and Hrowth Hormone (GH). Hormones sensitive to nutrients such as insulin, leptin, ghrelin, and adiponectin are also released due to the circadian rhythm and their release is partially regulated by environmental stimuli such as feeding time and light-dark cycles (Westerterp-Plantenga, 2016; Gnocchi & Bruscalupi, 2017).

2.1. Glucocorticoids

The Hypothalamus-Pituitary-Adrenal axis (HPA axis), which is an important component of the human neuroendocrine system, is vital for all mammals, including humans. The physiological function of the HPA axis is important for maintaining homeostasis, adapting to environmental changes, and regulating human behavior, emotions, and cognitive functions. The main end product of the HPA axis is cortisol derived from cholesterol (Huang, Xu, He, Huang & Wu, 2020). The main glucocorticoid is cortisol in humans and hamsters, whereas it is corticosterone in mice. Glucocorticoids are released ultradian and more often circadian (Challet, 2015). The circadian release of glucocorticoids begins to increase with sunrise in diurnal species and sunset in nocturnal species. Cortisol production in humans generally increases at night and peaks around 07:00 - 08:00 in the morning. In this way, it adjusts the endocrine system balance for metabolic functions associated with waking (Dickmeis, 2009). The circadian rhythm of glucocorticoids is regulated by the changes that occur during the release of corticotropin by the anterior pituitary gland which is controlled by the corticotropin-releasing hormone secreted from the paraventricular nucleus of the hypothalamus. The sensitivity of adrenal steroidogenesis is provided sympathetically by both the adrenal clock and the light dependent SCN (Challet, 2015).

Glucocorticoid rhythm plays an important role in daily oscillations of genes involved in both liver and white adipose tissue metabolic function, as shown in adrenalectomized animals. The rhythm of clock genes in the pituitary and salivary glands is not affected by the glucocorticoid rhythm, but the cornea, pineal, lung and kidneys are highly sensitive to glucocorticoid stimuli and absence (Pezük, Mohawk, Wang & Menaker, 2012).

The glucocorticoid rhythm can also affect other hormonal rhythms. In a study wherein adrenalectomized animals were administered with corticosterone, a 4-hour phase progression was observed in the plasma leptin rhythm. In other words, leptin started to be secreted 4 hours before normal secretion time. Considering these findings, it can be concluded that the glucocorticoid rhythm is important but not necessary in the regulation of peripheral clocks (Kalsbeek et al., 2001).

2.2. Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is an amphiphilic neurohormone synthesized mainly by the pineal gland during the dark phase of the circadian rhythm in both diurnal and nocturnal animals and secreted immediately after its synthesis, as it is not stored in pinealocytes (Reiter, 1991). Night synthesis of melatonin is activated by sympathetic stimuli sent to the pineal gland under SCN control (Pevet & Challet, 2011). Therefore, the

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

rhythm of melatonin in humans can be used as an indicator of synchronization provided by the SCN.

The best-known feature of melatonin is that it decreases according to the seasons and regulates the seasonal physiology according to the increasing day length. Since most of the circulating melatonin is synthesized from the pineal gland, it is found in trace amounts in the blood of pinealectomized animals. Moreover, the daily plasma melatonin rhythm is resistant to sleep disturbances and irregular nutritional conditions (except for the energy restriction that causes phase shifts in the SCN and melatonin rhythm) (Mendoza, Graff, Dardente, Pevet & Challet, 2005).

Based on the results of the studies, it has been found that melatonin functions through three types of receptors on the cell membrane: MT1 (high affinity) receptor, MT (low affinity) receptor, and MT3 receptor (from the guanine reductase family), which is the most recently discovered receptor. In mice whose MT1 and MT2 melatonin receptors were suppressed, it was observed that gene expressions in the liver and pancreas changed (Mühlbauer, Gross, Labucay, Wolgast & Peschke, 2009). It was also found that GLP-1 activation decreased, and insulin secretion was suppressed when melatonin treatment was applied to β-cells in the pancreas (Peschke, Bahr & Mühlbauer, 2013). In pinealectomized hamsters, the rhythm of leptin release disappeared, and phase shifts occurred in the cortisol rhythm (Chakir et al., 2015).

Melatonin is the key mediator molecule between the rhythmic cycle required for a healthy metabolism and the circadian distribution of physiological and behavioral processes necessary for energy balance and body weight regulation. Melatonin is involved in the regulation of GLUT4 expression and acts by increasing central and peripheral insulin sensitivity or triggering insulin signaling. Melatonin is a powerful chronobiotic agent that synchronizes the daily rhythms of metabolic processes with the cycle of physical activity-nutrition/rest-hunger (Cipolla-Neto, Amaral, Afeche, Tan & Reiter, 2014).

Numerous experimental observations show that melatonin is associated with the amelioration of obesity and the reduction of increased body weight and adiposity either by promoting weight loss by stimulating thermogenesis or by stimulating brown adipose tissue formation in small mammals (Tan, Manchester, Fuentes-Broto, Paredes & Reiter, 2011).

In one study, wild type and obese (ob/ob) leptin deficit mice received intraperitoneal injections of melatonin at a daily dose of 500 μg/kg body weight for 4 weeks. Although food consumption in obese mice receiving melatonin increased by 26% compared to mice not receiving melatonin, it was observed that body weight gain did not occur. Based on this, it can be said that melatonin administration improves cellular energy homeostasis and provides a more efficient food combustion and energy expenditure in the absence of leptin in the body (de Luxán-Delgado et al., 2016).

In a study conducted on female fruit bats, the effects of melatonin on leptin production from white adipose tissue were investigated. White adipose tissue treated in vitro with melatonin or insulin alone showed a significant increase in leptin synthesis compared to control adipose tissue. It was observed that leptin synthesis increased significantly in white adipose

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

tissue treated with melatonin with insulin compared to white adipose tissue treated with either melatonin or insulin alone (Banerjee, Udin & Krishna, 2011).

Melatonin is mainly responsible for establishing energy balance by regulating the flow of energy entering and leaving its stores and directly regulating energy expenditure through activation of brown adipose tissue. Additionally, melatonin helps regulate body weight by turning white adipose tissue into brown adipose tissue. Decreasing or ending melatonin production due to aging, working in shifts or being in a constantly illuminated environment during the nighttime may lead to insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian disturbance and causes a vicious cycle that disrupts the general health status and leading to obesity (Cipolla-Neto et al., 2014).

In the light of these studies, although it can be said that melatonin has a weight-reducing effect in the absence of leptin and that melatonin increases leptin synthesis from adipose tissue, the direct effect of melatonin on body weight and the proliferation of adipocytes is not fully understood.

2.3. Leptin

Internal leptin is the first adipokine identified and plays a key role in appetite and body weight regulation. Synthesized by white adipose tissue, leptin is a hormone that acts on the mediobasal hypothalamus to prevent overfeeding and also plays a role in the metabolism of glucose and lipids. The plasma level of this adipokine begins to increase after increased hepatic sugar level due to food consumption (Patton & Mistlberger, 2013). Leptin levels also exhibit sexual dimorphism, meaning there is a difference between different sexes plasma leptin levels. Women have higher leptin levels than men because leptin synthesis is stimulated by estrogen and inhibited by testosterone. Leptin is secreted in a pulsating manner and its release exhibits a circadian rhythm. Leptin rhythm is controlled by the SCN and adiposity clocks (Park & Ahima, 2015; Otway, Frost & Johnston, 2009).

Levels of leptin in plasma are highly correlated with BMI and adiposity level. In obese subjects, plasma leptin is usually found at high levels. In nocturnal rodents fed ad libitum, the circulating leptin hormone reaches its peak level at night. The role of leptin in regulating peripheral clocks was first demonstrated by disruptions in the expression of clock genes in the liver and white adipose tissue of ob/ob mice that could not synthesize sufficient leptin. The role of leptin in regulating peripheral clocks was first demonstrated by disruptions in the expression of clock genes in the liver and white adipose tissue of ob/ob mice that could not synthesize sufficient leptin (Ando et al., 2011). Disrupted leptin signaling in ob/ob and db/db (mutated leptin receptors) mice did not affect blood lipid rhythm but disrupted blood glucose rhythm and high blood lipid levels were observed in mice (Grosbellet et al., 2015). Based on the increase in meal anticipation of such mice, it can be said that leptin has an effect on reducing meal anticipation (Patton & Mistlberger, 2013).

Similar to rodents, leptin levels in humans reach a peak at night. In humans, high-fat diets reduce blood leptin levels, while increased fat mass and obesity cause hyperleptinemia. In summary, the leptin rhythm is closely related to glucose and lipid

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

metabolism and contributes to the regulation of the circadian rhythm (Gnocchi & Bruscalupi, 2017).

2.4. Ghrelin

Ghrelin is secreted from the stomach's parietal cells (delomorphous or oxyntic cells in which stomach acid is secreted). Ghrelin is an orexigenic hormone since it activates the arcuate nucleus, which enables the synthesis of neuropeptide-Y and agouti-related peptide (Patton & Mistlberger, 2013). The orexigenic properties of ghrelin was shown by LeSauter et al.,who found that ghrelin administration increased free fatty acid and food intake and the free fatty acid intake decreased in mice lacking the ghrelin receptor (LeSauter, Hoque, Weintraub, Pfaff, Silver, 2009).

When the effects of ghrelin on the SCN were examined, it was observed that the in vitro administration of ghrelin resets the main clock. The phase shift in locomotor activity seen in fasted animals after ghrelin injection did not occur in well-fed animals. An increase in ghrelin release before meals was observed as a result of the feeding of nocturnal animals only during the day (Ando et al., 2011). In rodents with suppressed ghrelin receptors, decreased meal anticipation was observed, whereas, in rodents in which ghrelin synthesis was suppressed, this effect was observed to be negligible (Gunapala, Gallardo, Hsu & Steele, 2011). Considering this, it can be suggested that ghrelin has an important but not mandatory role in the expectation of food intake.

2.5. Insulin

Synthesized by small fluctuations from β-cells in the pancreas, insulin is highly affected by food intake (Patton & Mistlberger, 2013). Changes in daily insulin rhythm are inversely related to cortisol rhythm. Insulin secretion increases during night sleep, but serum insulin level does not increase with its secretion due to increased clearance at night. Depending on the levels of growth hormone, glucose levels increase during night sleep, (Van Cauter et al., 1991) this effect is called the dawn phenomenon and highlights the effect of circadian control on glucose metabolism (Bolli et al., 1984).

Loss of this circadian oscillatory rhythm is associated with obesity in humans (Rácz, Dušková, Stárka, Hainer & Kunešová 2018).

As a result of in vitro insulin administration to the SCN cells, it was observed that the working speed of clock neurons slowed down, and it can be suggested that endogenous insulin has a regulatory effect on the central clock. As expected in rodents whose food intake is restricted, insulin synthesis increases in the postprandial period. Feeding-induced insulin synthesis stimulates the upregulation of Per2 gene mRNA expression in the liver and downregulation in the REV-ERBα gene nRNA expression, causing acute changes in clock genes (Tahara, Otsuka, Fuse, Hirao & Shibata, 2011). Although insulin does not synchronize clock genes in the liver alone, postprandial insulin increase plays an important role in the synchronization of peripheral clocks (Challet, 2015).

As a result, if food intake occurs outside the rhythm that is regulated by light, metabolic processes associated with digestion, absorption, and use of nutrients are separated from the SCN, which is regulated by light, and cause phase shifts in energy availability, substrate oxidation, and storage

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

(National Institute of General Medical Sciences, 2020).

3. Circadian Rhythm and Body Weight

Circadian rhythms differ among individuals. According to their biological time, individuals can be classified based on their chronotypes: definite evening type or definite morning type (Horne & Östberg, 1976). Some social factors (working hours, jet lag, etc.) can prepare the ground for the chronotypes of individuals to shift to the evening type. This shift that develops between biological and social times is called social jet lag and may cause damage to the general well-being and increase the risk of obesity with increased adiposity. Many epidemiological studies have revealed that behaviors that adversely affect health (smoking, irregular/decreased physical activity, decreased/increased sleep times, unhealthy food consumption, etc.) are more common in evening-type individuals than in morning type individuals. However, the relationship of chronotypes with obesity is not yet clear. For example, based on the data from the DILGOM (Dietary Lifestyle and Genetic Determinants of Obesity and Metabolic Syndrome) study conducted in 2007, Maukonen et al. stated that a healthy Scandinavian diet was associated with decreased abdominal obesity as a result of the Baltic Sea Diet Score (BSDS) assessment. In the DILCOM study, the blood samples of the participants were collected, and specific questionnaires related to obesity, food consumption, and sleep behavior (food consumption frequency questionnaire containing 131 foods showing 12 months of food consumption and shortened 6-item version of the original 19-item Morningness–Eveningness Questionnaire (MEQ)) were used (Maukonen et al., 2016).

Measuring the compliance with a healthy Scandinavian diet, BSDS consists of nine variables and its results varying between 0 and 25 points are directly proportional to the compliance with the diet. In the study, it was found that the BSDS score of the evening-type individuals was low, although the energy intake was not significantly different from the other groups, the grain consumption was lower, and the alcohol consumption was higher. As a result of the statistical analysis, it was indicated that the chronotype did not directly affect the relationship between diet and obesity, but the compliance of the evening-type individuals to a healthy diet was less. It can be suggested that the percentage of obesity between the groups was not different due to the low average age of the evening-type individuals and the energy intakes were not different from the other groups. Moreover, the BSDS and MEQ data may be different from the results due to the inability of the individuals to remember based on their statements and behaviors, such as missing or false information, especially in women and obese individuals (Maukonen et al., 2016).

Kim et al. investigated the relationship between obesity and impaired circadian rhythm based on the data they obtained from the KNHANES VI study conducted between 2013 and 2015. 3658 male individuals aged between 18 and 60 participated in the study. Information about sleep times, breakfast habits, daily working hours and hours spent at workplaces, and sociodemographic and anthropometric features were obtained from the participants, and physical activity levels in terms of

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

metabolic equivalent (MET) were determined as a result of the International Physical Activity Questionnaire. Factors that disrupt the circadian rhythm were determined as less than 7–9 hours of sleep time, irregular breakfast patterns, and night shifts, and the participants were divided into groups according to the presence of these factors (0, 1, and ≥2) (Kim et al., 2019).

Considering these results, having an irregular breakfast pattern, and working in night shifts rather than in day or evening shifts are risk factors of general obesity, whereas sleeping for less than 7 hours a day increases the risk of abdominal and general obesity. It is stated that as the number of factors disrupting the circadian rhythm increases, the risk of developing obesity in the individual increases. Not skipping breakfast can play an important role in weight loss by reducing dietary fat intake and minimizing snack consumption during the day. At the molecular level, it is known that individuals with shifted circadian rhythms have an impaired expression of the CLOCK gene, which regulates the release of insulin. In this way, impaired circadian rhythm can cause insulin resistance, diabetes, and an increase in uncontrollable body weight. Considering the limitations of the study, it is not known whether the BMI and waist circumference of individuals have changed as a result of circadian rhythm disturbance since cross-sectional data are used and follow-up is not performed (Kim et al., 2019).

4. CLOCK Genes and Body Weight

In animal experiments, mice with an impaired CLOCK gene were found to have an increased susceptibility to obesity (Turek et al., 2005) and impaired glucose tolerance (Rudic et al., 2004). It has been reported that C57BL/6J strain ClockΔ19 mice (the 19th exon of the CLOCK gene has been removed) are hyperphagic and obese and these mice develop hyperleptinemia, hyperlipidemia, fatty liver, hyperglycemia, and metabolic syndrome, as well as a decrease in diurnal feeding rhythms (Turek et al., 2005). Moreover, it has been reported that gluconeogenesis is impaired with changes in the conversion of pyruvate to glucose, changes in hepatic phosphoenolpyruvate carboxykinase enzyme activity, and hypoglycemia developing as a result of insulin injection which is more severe than unmodified mice (Rudic et al., 2004). In contrast to the C57BL/6J strain, the Jcl:ClockR19 mice of the ICR strain did not develop obesity, hyperglycemia, hyperlipidemia, or hyperleptinemia (Oishi et al., 2006).

Recent studies have focused on the role of disruptions, single nucleotide polymorphisms (SNP), and gene suppression in human obesity, such as the CLOCK gene, which regulates the circadian rhythm. For example, in a study conducted by Garaulet et al. in Spain on 454 obese individuals (BMI > 25 kg/m2, BMI < 40 kg/m2) aged between 20 and 65, the participants underwent therapies lasting 60 minutes every week for 4 months. In the therapies organized by the dietitian, the energy and macronutrients to be taken with diet were determined as 1200–1800 kcal/day for women and 1500–2000 kcal/day for men, and the participants created their own menus. Nutrition education was given to the groups, and the participants were informed about healthy eating behaviors that are planned to last a lifetime. Before the study, 75% of the participants were sedentary (less than 1 hour of physical activity per week), and their average sleep time was 7 hours a day. Based on the 24-hour food consumption of the participants, it

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

was observed that their carbohydrate consumption was less compared to both protein and fat consumptions than the amount that should be taken daily (Garaulet et al., 2010).

Based on the findings of the study, although an average of 8.85 kg of body weight loss occurred in all participants regardless of the CLOCK gene, it was proven that body weight regulation was adversely affected by SNPs in the CLOCK gene in some participants. In particular, the rs3749474, rs4864548, rs1464490, and rs1801260 genotypes have been reported to increase susceptibility to obesity, and the rs1801260 genotype reduces compliance to the therapy. Obesity and abdominal obesity were found to be higher in individuals with T allele (minor allele is a less common allele than the major allele) in the rs3749474 genotype (Garaulet et al., 2010).

5. Nutrigenetics, Epigenetics and Circadian Rhythm

Nutrigenetics is a branch of science that enables the development of a genetically dependent nutrition program based on the same effect of the same nutrient in different individuals with and without polymorphism in its genetic structure. It can be considered as a section of nutrigenomics that explores the interactions between foods and the genome, including not only genetics but also gene expression changes and epigenetics (Bordoni & Gabbianelli, 2019). In recent nutrigenetic studies, polymorphisms in circadian rhythm regulators were found to be associated with obesity.

When the relationship between the CLOCK SNP rs4580704 genotype and monounsaturated fatty acid (MUFA) intake was examined, it was found that when the MUFA intake was above 13.2%, the minor allele could have a positive effect on insulin sensitivity. In a study investigating the relationship of the CLOCK 3111T> C genotype with saturated fatty acid (SFA) intake, it was observed that the negative effect of the C genotype on waist circumference occurred when SFA intake was above 11.8%. In a study conducted in North America, with the increase of carbohydrate intake, it was found that only people with homozygous minor C allele in the CRY1 rs2287161 genotype had increased HOMA-IR and fasting insulin levels and decreased quantitative insulin sensitivity control index (QUICKI) results (Garaulet et al., 2010).

Epigenetics is the science branch that studies the changes in gene expression and gene suppression, not changes in DNA sequencing. In other words, epigenetics is the discipline of heritable changes in gene expression (active versus inactive genes) that does not involve changes to the underlying DNA sequence. Gene suppression takes place in three ways: DNA methylation, chromatin modifications, and post-transcriptional gene suppression. Methylation is the addition of a methyl group between the cytosine (C) and guanine (G) nucleotides in the gene, the C and G nucleotides combine with phosphate and form the CpG dinucleotide. As the level of CpG methylation increases, gene suppression increases. In the studies conducted, the methylation in the genes involved in the regulation of the circadian rhythm was associated with obesity and metabolic disorders (Lopez-Minguez, Gómez-Abellán & Garaulet, 2016).

In a study by Samblas et al., 61 overweight / obese (BMI mean 28.6 ± 3.4 kg/m^2) women were included

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

to determine the effect of body weight loss intervention based on the Mediterranean diet and the relationship between weight loss; methylation levels in the BMAL1, CLOCK, and NR1D1 genes; and serum lipid profile. Before the study, women who consumed a diet high in calories and carbohydrates were found to have higher CpG methylation levels in the BMAL1 gene. The women engaged in 40 minutes of group therapy per week for 4 months as recommended by a dietitian. While the average energy intake before the study was 2079 kcal/day, the amount of energy to be taken with the diet was kept between 1200-1800 kcal during the study to ensure the loss of 0.5-1 kg body weight per week (Samblas, Milagro, Gómez-Abellán, Martínez & Garaulet, 2016).

At the end of the diet therapy, a significant decrease was observed in the body weight, BMI and HOMA-IR values of the participants. Besides, at the end of the study, in the BMAL1 gene CpG5, CpG6.7 and CpG9 methylation increased significantly and CpG10.11 and CpG18 methylation decreased. As a result of the intervention, BMAL1 CpG5-CpG9 methylation decreased, and blood cholesterol and LDL levels decreased significantly. Although there was no significant change in CLOCK gene methylation at the end of the intervention, it was found that CLOCK gene CpG1 and CpG5.6 methylations were associated with BMI, body fat, waist circumference and weight loss percentage (Samblas et al., 2016).

It was found that BMAL1 methylation level correlated positively with the MEQ score and evening-type women had higher methylation levels in the CLOCK gene than morning-type individuals. At the end of the intervention, it was found that the decrease in BMAL1 methylation level of evening-type women was significantly higher than morning-type women. This study shows the importance of the BMAL1 gene in improving the blood lipid profile and in the treatment of obesity and metabolic syndrome (Samblas et al., 2016).

6. Conclusion

As a result of this review conducted on the studies investigating the effects of circadian rhythm, the release and action mechanism of hormones, chronotype, epigenetics, and nutrigenetics on body weight, it was seen that there was no consensus about the relationship of circadian rhythm with body weight change and obesity development. Also, human subject studies have been conducted on the effect of hormone release rhythms and the action mechanisms of the genome on body weight are especially limited, and it can be said that more research is needed on this subject.

Conflicts of interest

The authors declare no conflicts of interest.

References

Ando, H., Kumazaki, M., Motosugi, Y., Ushijima, K., Maekawa, T., Ishikawa, E., & Fujimura, A. (2011). Impairment of peripheral circadian clocks precedes metabolic abnormalities in ob/ob mice. *Endocrinology*, *152*(4), 1347–1354. https://doi.org/10.1210/en.2010-1068.

Banerjee, A., Udin, S., & Krishna, A. (2011). Regulation of leptin synthesis in white adipose tissue of the female fruit bat, Cynopterus sphinx: role of melatonin with or without insulin. *Experimental physiology*, *96*(2), 216–225. https://doi.org/10.1113/expphysiol.2010.055129.

Bolli, G. B., De Feo, P., De Cosmo, S., Perriello, G., Ventura, M. M., Calcinaro, F., Lolli, C., Campbell, P., Brunetti, P., & Gerich, J. E. (1984). Demonstration of a dawn phenomenon in normal human volunteers. *Diabetes*, *33(12)*, 1150–1153.

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

https://doi.org/10.2337/diab.33.12.1150.

Bordoni, L., & Gabbianelli, R. (2019). Primers on nutrigenetics and nutri(epi)genomics: Origins and development of precision nutrition. *Biochimie*, *160*, 156–171. https://doi.org/10.1016/j.biochi.2019.03.006.

Cagampang, F. R., & Bruce, K. D. (2012). The role of the circadian clock system in nutrition and metabolism. *The British journal of nutrition*, *108*(3), 381–392. https://doi.org/10.1017/S0007114512002139.

Chakir, I., Dumont, S., Pévet, P., Ouarour, A., Challet, E., & Vuillez, P. (2015). Pineal melatonin is a circadian time-giver for leptin rhythm in Syrian hamsters. *Frontiers in neuroscience*, *9*, 190. https://doi.org/10.3389/fnins.2015.00190.

Challet E. (2015). Keeping circadian time with hormones. *Diabetes, obesity & metabolism*, *17 Suppl 1*, 76–83. https://doi.org/10.1111/dom.12516.

Cipolla-Neto, J., Amaral, F. G., Afeche, S. C., Tan, D. X., & Reiter, R. J. (2014). Melatonin, energy metabolism, and obesity: a review. *Journal of pineal research*, *56*(4), 371–381. https://doi.org/10.1111/jpi.12137.

Damiola, F., Le Minh, N., Preitner, N., Kornmann, B., Fleury-Olela, F., & Schibler, U. (2000). Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes & development*, *14*(23), 2950–2961. https://doi.org/10.1101/gad.183500.

de Luxán-Delgado, B., Potes, Y., Rubio-González, A., Caballero, B., Solano, J. J., Fernández-Fernández, M., Bermúdez, M., Rodrigues Moreira Guimarães, M., Vega-Naredo, I., Boga, J. A., & Coto-Montes, A. (2016). Melatonin reduces endoplasmic reticulum stress and autophagy in liver of leptin-deficient mice. *Journal of pineal research*, *61*(1), 108–123. https://doi.org/10.1111/jpi.12333.

Dickmeis T. (2009). Glucocorticoids and the circadian clock. *The Journal of endocrinology*, *200*(1), 3–22. https://doi.org/10.1677/JOE-08-0415.

Engin A. (2017). Circadian Rhythms in Diet-Induced Obesity. *Advances in experimental medicine and biology*, *960*, 19–52. https://doi.org/10.1007/978-3-319-48382-5_2.

Garaulet, M., Corbalán, M. D., Madrid, J. A., Morales, E., Baraza, J. C., Lee, Y. C., & Ordovas, J. M. (2010). CLOCK gene is implicated in weight reduction in obese patients participating in a dietary programme based on the Mediterranean diet. *International journal of obesity (2005)*, *34*(3), 516–523. https://doi.org/10.1038/ijo.2009.255.

Gnocchi, D., & Bruscalupi, G. (2017). Circadian Rhythms and Hormonal Homeostasis: Pathophysiological Implications. *Biology*, *6*(1), 10. https://doi.org/10.3390/biology6010010.

Grosbellet, E., Dumont, S., Schuster-Klein, C., Guardiola-Lemaitre, B., Pevet, P., Criscuolo, F., & Challet, E. (2015). Leptin modulates the daily rhythmicity of blood glucose. *Chronobiology international*, *32*(5), 637–649. https://doi.org/10.3109/07420528.2015.1035440.

Gunapala, K. M., Gallardo, C. M., Hsu, C. T., & Steele, A. D. (2011). Single gene deletions of orexin, leptin, neuropeptide Y, and ghrelin do not appreciably alter food anticipatory activity in mice. *PloS one*, *6*(3), e18377. https://doi.org/10.1371/journal.pone.0018377.

Horne, J. A., & Ostberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International journal of chronobiology*, *4*(2), 97–110.

Huang, Y., Xu, C., He, M., Huang, W., & Wu, K. (2020). Saliva cortisol, melatonin levels and circadian rhythm alterations in Chinese primary school children with dyslexia. *Medicine*, *99*(6), e19098. https://doi.org/10.1097/MD.0000000000019098.

Kalsbeek, A., Fliers, E., Romijn, J. A., La Fleur, S. E., Wortel, J., Bakker, O., Endert, E., & Buijs, R. M. (2001). The suprachiasmatic nucleus generates the diurnal changes in plasma leptin levels. *Endocrinology*, *142*(6), 2677–2685. https://doi.org/10.1210/endo.142.6.8197.

Kim, H. J., Choi, S., Kim, K., Park, H., Kim, K. H., & Park, S. M. (2020). Association between misalignment of circadian rhythm and obesity in Korean men: Sixth Korea National Health and Nutrition Examination Survey. *Chronobiology international*, *37*(2), 272–280. https://doi.org/10.1080/07420528.2019.1671439.

Laermans, J., & Depoortere, I. (2016). Chronobesity: role of the circadian system in the obesity epidemic. *Obesity reviews : an official journal of the International Association for the Study of Obesity*, *17*(2), 108–125. https://doi.org/10.1111/obr.12351.

LeSauter, J., Hoque, N., Weintraub, M., Pfaff, D. W., & Silver, R. (2009). Stomach ghrelin-secreting cells as food-entrainable circadian clocks. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(32), 13582–13587. https://doi.org/10.1073/pnas.0906426106.

Lopez-Minguez, J., Gómez-Abellán, P., & Garaulet, M. (2016). Circadian rhythms, food timing and obesity. *The Proceedings of the Nutrition Society*, *75*(4), 501–511. https://doi.org/10.1017/S0029665116000628.

Maukonen, M., Kanerva, N., Partonen, T., Kronholm, E., Konttinen, H., Wennman, H., & Männistö, S. (2016). The associations between chronotype, a healthy diet and obesity. *Chronobiology international*, *33*(8), 972–981. https://doi.org/10.1080/07420528.2016.1183022.

Mendoza, J., Graff, C., Dardente, H., Pevet, P., & Challet, E. (2005). Feeding cues alter clock gene oscillations and photic responses in the suprachiasmatic nuclei of mice exposed to a light/dark cycle. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *25*(6), 1514–1522. https://doi.org/10.1523/JNEUROSCI.4397-04.2005.

Mistlberger R. E. (2011). Neurobiology of food anticipatory circadian rhythms. *Physiology & behavior*, *104*(4), 535–545. https://doi.org/10.1016/j.physbeh.2011.04.015.

Mühlbauer, E., Gross, E., Labucay, K., Wolgast, S., & Peschke, E. (2009). Loss of melatonin signalling and its impact on circadian rhythms in mouse organs

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr

regulating blood glucose. *European journal of pharmacology, 606*(1-3), 61–71. https://doi.org/10.1016/j.ejphar.2009.01.029.

National Institute of General Medical Sciences (2020) *Circadian Rhythms*. Retrieved from ://www.nigms.nih.gov/education/pages/factsheet_circadianrhythms.aspx

Oishi, K., Atsumi, G., Sugiyama, S., Kodomari, I., Kasamatsu, M., Machida, K., & Ishida, N. (2006). Disrupted fat absorption attenuates obesity induced by a high-fat diet in Clock mutant mice. *FEBS letters, 580*(1),127–130. https://doi.org/10.1016/j.febslet.2005.11.063.

Otway, D. T., Frost, G., & Johnston, J. D. (2009). Circadian rhythmicity in murine pre-adipocyte and adipocyte cells. *Chronobiology international, 26*(7), 1340–1354. https://doi.org/10.3109/07420520903412368.

Park, H. K., & Ahima, R. S. (2015). Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. *Metabolism: clinical and experimental, 64*(1),24–34. https://doi.org/10.1016/j.metabol.2014.08.004.

Patton, D. F., & Mistlberger, R. E. (2013). Circadian adaptations to meal timing: neuroendocrine mechanisms. *Frontiers in neuroscience, 7*, 185. https://doi.org/10.3389/fnins.2013.00185.

Peschke, E., Bähr, I., & Mühlbauer, E. (2013). Melatonin and pancreatic islets: interrelationships between melatonin, insulin and glucagon. *International journal of molecular sciences, 14*(4), 6981–7015. https://doi.org/10.3390/ijms14046981.

Pevet, P., & Challet, E. (2011). Melatonin: both master clock output and internal time-giver in the circadian clocks network. *Journal of physiology, Paris, 105*(4-6), 170–182. https://doi.org/10.1016/j.jphysparis.2011.07.001.

Pezük, P., Mohawk, J. A., Wang, L. A., & Menaker, M. (2012). Glucocorticoids as entraining signals for peripheral circadian oscillators. *Endocrinology, 153*(10), 4775–4783. https://doi.org/10.1210/en.2012-1486.

Rácz, B., Dušková, M., Stárka, L., Hainer, V., & Kunešová, M. (2018). Links between the circadian rhythm, obesity and the microbiome. *Physiological research, 67*(Suppl 3), S409–S420. https://doi.org/10.33549/physiolres.934020.

Reiter R. J. (1991). Melatonin: the chemical expression of darkness. *Molecular and cellular endocrinology, 79*(1-3), C153–C158. https://doi.org/10.1016/0303-7207(91)90087-9.

Rudic, R. D., McNamara, P., Curtis, A. M., Boston, R. C., Panda, S., Hogenesch, J. B., & Fitzgerald, G. A. (2004). BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. *PLoS biology, 2*(11), e377. https://doi.org/10.1371/journal.pbio.0020377.

Samblas, M., Milagro, F. I., Gómez-Abellán, P., Martínez, J. A., & Garaulet, M. (2016). Methylation on the Circadian Gene BMAL1 Is Associated with the Effects of a Weight Loss Intervention on Serum Lipid Levels. *Journal of biological rhythms, 31*(3), 308–317. https://doi.org/10.1177/0748730416629247.

Sözlü S. & Şanlıer N. (2017). Sirkadiyen Ritim, Sağlık ve Beslenme İlişkisi. *Türkiye Klinikleri Sağlık Bilimleri Dergisi, 2*(2), 100-109. https://doi.org/10.5336/healthsci.2015-48902.

Tahara, Y., Otsuka, M., Fuse, Y., Hirao, A., & Shibata, S. (2011). Refeeding after fasting elicits insulin-dependent regulation of Per2 and Rev-erbα with shifts in the liver clock. *Journal of biological rhythms, 26*(3), 230–240. https://doi.org/10.1177/0748730411405958.

Tan, D. X., Manchester, L. C., Fuentes-Broto, L., Paredes, S. D., & Reiter, R. J. (2011). Significance and application of melatonin in the regulation of brown adipose tissue metabolism: relation to human obesity. *Obesity reviews : an official journal of the International Association for the Study of Obesity, 12*(3), 167–188. https://doi.org/10.1111/j.1467-789X.2010.00756.x.

Turek, F. W., Joshu, C., Kohsaka, A., Lin, E., Ivanova, G., McDearmon, E., Laposky, A., Losee-Olson, S., Easton, A., Jensen, D. R., Eckel, R. H., Takahashi, J. S., & Bass, J. (2005). Obesity and metabolic syndrome in circadian Clock mutant mice. *Science (New York, N.Y.),308*(5724),1043–1045. https://doi.org/10.1126/science.1108750.

Van Cauter, E., Blackman, J. D., Roland, D., Spire, J. P., Refetoff, S., & Polonsky, K. S. (1991). Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. *The Journal of clinical investigation,88*(3),934–942. https://doi.org/10.1172/JCI115396.

Westerterp-Plantenga M. S. (2016). Sleep, circadian rhythm and body weight: parallel developments. *The Proceedings of the Nutrition Society, 75*(4), 431–439. https://doi.org/10.1017/S0029665116000227.

***Corresponding author:** Zeynep Gül Gündüz
e-mail address: zeynep.gul.gunduz@karatay.edu.tr