Circadian Rhythm and Metabolic Diseases:

The Effects of Circadian Rhythm On Weight and Metabolic Diseases

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It is well established that the average person should get at least seven to nine hours of sleep each night, as sleep restored the body and brain, but the consequences of a disrupted circadian pattern are often overlooked. A disrupted circadian rhythm is often characterized by Sleep deprivation can be a major factor in developing depression, anxiety, heart disease and even in degeneration of memory.

The circadian rhythm is controlled by the suprachiasmatic nucleus (SCN) which makes its home in the brain's hypothalamus. The SCN sends timed messages, often according to light hitting the eye - which is why bright lights tend to keep humans awake - and its messages reach different locations in the brain, such as the pineal gland in order for the body to release melatonin.

FIRST STUDY

In Boer-Martins' (2011) study on the autonomic nervous system, they assessed its activity's correlation with various metabolic diseases using heart rate variability. Heart rate variability (HRV) is an accurate method of assessing the health of a patient's autonomic nervous system, as the parasympathetic and sympathetic nervous systems have a substantial amount of control over heart rate. HRV analyzes the amount of time between each heart beat in order to measure its pace more accurately rather than measuring the amount of heart beats per minute. Therefore, imbalances in the autonomic system are easier to detect using HRV.

Autonomic imbalance has been linked to increased insulin resistance, hypertension (HTN) and eventually type 2 diabetes (T2D). In order to understand exactly what triggers these diseases, they observed autonomic activity in the circadian rhythm and its connection to type 2 diabetes and also observed its connection to adiponectin levels. Adiponectin is a hormone that regulates glucose in the body and low levels are associated with type 2 diabetes.

They used a group of patients who had already been taking prescriptions for HTN (15 subjects) and another group with the same HTN prescriptions but with a comorbidity of T2D (10 subjects). Their blood pressure was measured using two methods: office blood pressure measurement and ambulatory blood pressure monitoring (ABPM). Office blood pressure measurement refers to an automated technique in recording multiple blood pressure measurements, whereas ABPM refers to one's blood pressure being monitored over a period of 24 hours. Other than blood pressure, the patients also went through laboratory analysis of complete blood count (CBC), fasting blood sugar levels, glycolized hemoglobin, and other important measures regarding blood sugar and pressure. Each patient also went through a transthoracic echocardiography, an ultrasound examining the heart, in order to further record heart health. The fourth and final procedure was a recording of HRV parameters using a 24-hour Holter monitor. The purpose of these recordings was to analyze the heart at different points in the patient's circadian rhythm - recording different statistics during daytime (DT), night time (NT), and transition periods: 1-5pm and 2-6am. Throughout these time periods, heart rate was recorded in time and frequency and then used to calculate standard deviations and errors and frequency domain.

The HRV results were conveyed as mean (μ), standard deviation (SD) and standard error of the mean (SEM). The p-value, or probability of a Type I error (a rejection of the null hypothesis when the null was in fact correct), was also recorded for each characteristic on the table. In the first table, each group's results were recorded as the mean (of characteristic) ±

standard deviation (SD) for general characteristics, such as age, body mass index (BMI), etc. The first three types of analysis (blood pressure, lab analysis and echocardiographic exam) were included in this table. Table 2 separately analyzed HRV variability in calculations of mean (M) ± standard error (SD). This is how data is recorded and analyzed in the following two studies as well.

The study resulted in multiple observations. First there was a higher autonomic imbalance in the patient group with RHTN and T2D than the group without T2D, but both groups showed a reversed pattern in autonomic tones. The parasympathetic nervous system is meant to be more active during the night and less active during the day, as most people require rest accordingly, but in this study both groups showed a more active parasympathetic system during the day and active sympathetic system during the night, pointing towards autonomic imbalance (AI).

Autonomic imbalance is also connected to insulin resistance and together they increase the likelihood of obesity. The authors noted that a major factor in insulin resistance may be related to the ability to regulate blood glucose which is inhibited by angiotensin II - an oligopeptide that is part of the Renin-Angiotensin System, which regulates blood pressure and other bodily fluids. An increased angiotensin level would increase inhibition of the glucose carrier GLUT4, therefore increasing insulin resistance. Another symptom that often comes with insulin resistance is a reduced ability to diessapitate energy in the body. A steady increase in sympathetic activity - therefore autonomic hyperactivity, or, autonomic imbalance - can reduce the body's ability to use energy, therefore leaving it to be stored as weight. These connections prove that hyper-autonomic activity and the body's reduced ability to manage glucose levels -

also known as a condition called hypoadiponectinemia - are related and therefore the authors were able to find a correlation between their recorded HRV results and the inability to regulate glucose.

It is also highly likely that a regular disruption in circadian rhythm, characterized by disturbed sleep-wake cycles, autonomic imbalance - increased nervous activity while resting and low activity while awake - along with increased energy, or food, intake will lead to weight gain. Since disruption of circadian rhythm was found in both hypertensive study groups, the authors came to the conclusion that a disturbance in circadian rhythm is an essential link to metabolic disorders and diseases that increase one's risk of heart disease and T2D.

SECOND STUDY

Yuan et al. (2020) conducted another study analyzing the relationship between metabolic diseases and circadian rhythm disorder by examining lipid levels. Lipids are made of hydrocarbons - a binding of only hydrogen and carbon - which make up fossil fuels in the world and also the lipids in our bodies. Inside the body's cell, they serve many functions depending on the animal. They can store extra energy the body does not need right away in the form of fat, they can repel water in animals that need to stay dry (as they have hydrophobic properties), and most importantly keeping your brain healthy, by performing tasks such as sheathing and sustaining neurons. Essentially, lipids are the building blocks of our bodies and perform, or help perform, many of our body's functions.

Triglycerides (or TGs) are the most common type of lipid found in the body which originate from the fats one eats, such as butter and oil, and are often stored as extra fat. TGs are measured in milligrams per deciliter, or mg/dL, and a normal range for TGs is less than 150mg/dL. Anything higher puts the individual at risk for heart disease and other dangerous metabolic symptoms such as diabetes, insulin resistance and high blood pressure. This is why measuring triglycerides is one of the most important markers in assessing a person's health, especially in regards to cardiovascular diseases.

In this study, the researchers recognized beforehand that circadian rhythm are directly related to metabolic syndromes, such as hypertension, obesity and diabetes, as in the first study. But they point out that other studies have failed to separate circadian rhythms from meal patters and quality of sleep, as those are factors that also influence metabolism. The authors examined the influence of circadian rhythm on TGs, cholesterol (CHOL), high-density and low-density lipoproteins (HDL, LDL), all while factoring out activity, sleep and meals in healthy people.

The forced desynchrony (FD) protocol, which was used in this study, is a method of studying circadian rhythm that rules out other factors such as eating habits and amount of sleep. This is done by introducing a new sleep schedule which is noticeably different from the typical, 24-hour cycle subject are used to. For example, for this study, the researchers required all participants to keep a 28-hour cycle, staying in bed for 10 hours every night at least 3 weeks before the study was conducted and during the study. Fasting blood samples were taken in the morning and core body temperature was measured throughout the day.

The data that was assessed for the results were fasting lipid levels (from drawing blood in the morning) and circadian phase. They found that the younger participants' TG levels tended to fluctuate more significantly along with their circadian rhythm rather than in older, healthy adults, who's TG levels tended to stay around the same throughout the day. The fact that this pattern was found, independent of meal times, amount of sleep and other factors, means that TG levels may be related to the regulation of circadian rhythm by the suprachiasmatic nucleus (SCN), which regulates circadian rhythm.

As a result, the researchers in this study also expressed a concern with how TG levels are assessed in doctor's offices for checkups. Regardless of whether blood is drawn while the patient is fasting or not, the time of day, or point in the patient's circadian rhythm, may skew the results.

Source 3:

THIRD STUDY

Brambilla et al. (1987) also studied wight in regards to circadian rhythm, but instead analyzing weight as the cause to circadian fluctuations rather than the effect. Anorexia nervosa (AN) has been poorly studied at the time of this study (1987) although, it has been established is that a disordered circadian rhythm is linked with most common mental disorders, such as depression and alcoholism. But contradicting data has been shown for AN, confirming that there have not been enough studies performed on the connection between circadian rhythm and AN, and even the few tests that were done may have been incorrectly executed.

Whether or not any hormonal changes in the circadian rhythm of anorexic patients is caused by a change in brain chemistry is still an open question, as starvation can also cause several hormonal changes in the body.

It has also been reported that primary affective disorders (PAD), or disorders that alter the patient's senses and mood, and AN are similar in the way they affect activity in the central nervous system (CNS). PAD alters the circadian rhythm which and subsequently alters beta-receptor activity, which have a huge effect on the sympathetic system.

This study examined the 24-hour circadian cycles in anorexic and morbidly obese patients, along with a control group of normal weight patients. They studied their weights and feeding habits in order to find whether or not they influenced specifically the circadian cycle of secretion of melatonin.

Twelve female, anorexic patients were examined as well as thirteen obese women. Any patient with PAD or metabolic diseases were excluded from the study. The control group consisted of nine healthy women within their ideal weights. None of their diets were controlled as the data recorded was mostly observational. Although their diets were not controlled, all patients ate at the same time, three times per day, and slept from 2100h to 0600h.

Blood was drawn seven times every day in a scheduled format and were examined for melatonin levels using radioimmunoassay (RIA) kits.

AN patients showed higher melatonin levels than patients in both the obese and control group. The AN patients' levels were similar to the other groups' during the day, but showed a significant increase in secretion of melatonin during the night, increasing the chances of arousal during sleep and fatigue during the day. Although obese patients did not have a significant increase in melatonin levels, many patients showed disruption in circadian rhythms, such as abnormal - advanced or delayed - nocturnal peaks and rises, as well as abnormal diurnal peaks.

Neither body mass index, age nor duration of obesity or AN seemed to have any correlation with melatonin secretion during circadian rhythm.

Melatonin is inhibited and stimulated through the alpha-adrenergic and bet-adrenergic receptors respectively, which are triggered by the neurotransmitter noradrenaline, which is common in the sympathetic nervous system in order to trigger the “fight or flight” response. Since this neurotransmitter is affected by diet, it may be the cause for the increased melatonin levels in AN patients and the change in circadian rhythm in obese patients, but there is not enough evidence to support a concise conclusion.

CONCLUDING ANALYSIS

According to the above studies there is a wide range of effects of the circadian rhythm from TG levels to melatonin and weight. The first study (Boer-Martins et al., 2011) showed a causal correlation between a disrupted of circadian rhythm and autonomic imbalance, or unusual arousal during sleep and inactivity during wake times. Autonomic imbalance is also connected to weight gain or loss, as along with a disruption in sleep, a person will likely experience a disordered eating pattern and trouble staying active throughout the day. The second study (Yuan et al., 2020) showed a direct connection between circadian rhythm the patterns and fluctuations of triglycerides, of which high levels can put a person at risk for weight gain and various metabolic diseases. Although the sample tested was small and may not be applied as universally as other studies, there was a difference in triglyceride levels in people of difference ages and different circadian patterns. Younger participants tended to have larger fluctuations in TGs, indicating the importance of having a regular sleep pattern in order to keep TG levels on the lower side. This study also indicated that when having their blood drawn for TG levels, time of circadian rhythm is a better gauge of TG peaks and lows than fasting before drawing blood. The third study (Brambilla et al., 1987) focused on the relationship between obese and anorexic patients and their different circadian patterns by analyzing melatonin levels. They found that anorexic patients secreted high levels of melatonin, often reversing the effect hormone and leading to arousal during the night, while obese patients did not experience high levels of melatonin but a disruption in rhythm altogether, encountering delayed nocturnal and diurnal peaks throughout the 24-hour period.

These studies provide an answer to inquiries about the relationship between disruption of circadian rhythm and weight, while also pointing to metabolic diseases as a marker of a disordered sleep schedule. Weight is indirectly affected by a change in circadian rhythm, largely through an increased risk of metabolic diseases caused by an autonomic imbalance and high levels of triglycerides. An indicator and cause of disrupted circadian rhythm is possibly anorexia and obesity. This information can contribute towards prevention of metabolic disease and, as mentioned by the authors of the second study (Yuan et al., 2020), can serve as evidence against fasting before drawing blood, as the patient’s circadian rhythm - such as when they last slept - can be a better predictor for levels of lipids.

References

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