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IN-DEPTH REVIEW

Time Matters: An Insight into the Relationship Between Chrononutrition and Diabetes

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ABSTRACT

Chrononutrition is a branch of chronobiology that evaluates nutrients and the pathways implicated in their regulation in accordance with circadian rhythms. Sleep deprivation and disturbances have been strongly associated with the progression of different metabolic alterations, and the time of food intake plays a fundamental role in maintaining metabolic homeostasis. It has been demonstrated that not only the components of food are important, but quantity and quality are also crucial elements of a healthy eating pattern. Chrononutrition is an emerging tool that could help improve dietary interventions beyond those derived from consuming an adequate amount of each nutrient. Diabetes is a complex endocrine pathology characterized by sustained hyperglycemia. Dietary changes are a key component in obtaining adequate control and preventing long-term complications. Recent studies emphasize the use of chrononutrition and its components as a novel dietary intervention that could improve metabolic control. The use of chrononutrition as a dietary intervention is faced with challenges such as the presence of gaps in the literature that limit its implementation. This emphasizes the imperative need for additional research that can lead to an evidence-based use of this intervention. (REV INVEST CLIN. 2024;76(2):80-90)

Keywords: Chronobiology disorders. Diabetes mellitus. Medical nutrition therapy. Circadian dysregulation.

INTRODUCTION

In the field of nutrition, the emerging concept of chrononutrition offers a fresh perspective by exploring the intricate relationship between dietary habits and the body's circadian rhythms. Defined as the investigation of how diet and nutrition interact with our internal biological clocks, chrononutrition sheds light on the crucial role of timing in nutrient metabolism. Beyond simply considering what we eat, it emphasizes when we eat, aligning our dietary patterns with the natural rhythms of the day.

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Notably, research suggests that meal timing may wield significant influence over metabolic parameters, questioning the importance of meal frequency and total calorie intake. This insight underscores the profound impact of the daily rhythm of fasting and feeding, intricately intertwined with our sleep–wake cycle, a fundamental adaptation to circadian rhythms. Disruptions to these cycles, whether through irregular eating patterns or sleep disturbances, have been implicated in the onset and exacerbation of various metabolic disorders. Within this context, the focus of this review is to dissect the literature surrounding chrononutrition and its implications for metabolic health, with a particular emphasis on its relevance to diabetes.

CIRCADIAN RHYTHM: HOW DOES IT WORK?

It is well known that the human body responds to its environment and day-and-night shifts according to an inner clock, rather than a passive response to environmental changes. This regulation is called the circadian rhythm, which plays a crucial role in controlling the body's sleep–wake cycle. Circadian rhythm can be affected due to multifactorial causes, one of them being the genetic expression. There are "clock genes" that direct the rhythmic behavior in humans, animals, and even insects[1]. The human body's inner clock is controlled by the suprachiasmatic nucleus (SCN), also known as the "master clock", and the main external regulators of the SCN are the day/night shift changes. Most of the peripheral organs have an independent, autonomous control of the circadian rhythm through the synthesis of target proteins; however, the liver, adipose tissue, adrenal glands, pancreas, thyroid, kidneys, heart, and skeletal muscle require direct regulation from the SCN[2] (Fig. 1).

As new information surges regarding hormones and their intricate relation with day-and-night cycles, the importance of the circadian rhythm for eating patterns is better understood. Along with homeostatic, hedonic, and social patterns, the circadian rhythm settles the eating pattern, consolidating the term chrononutrition, a branch that arises from chronobiology that studies the nutrients and how their use changes in the organism according to the hour of the day. The time of food intake is an important component that helps maintain metabolic homeostasis[2].

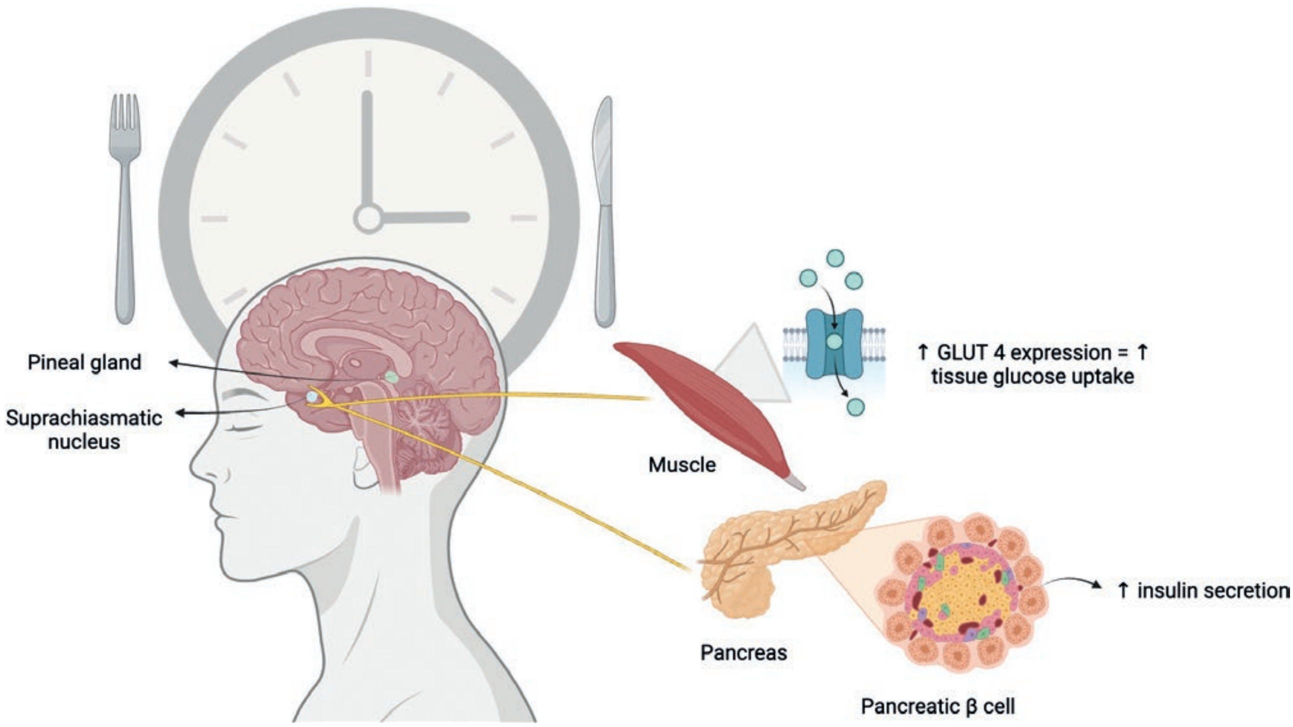
CHRONOTYPE

Within chrononutrition, the term known as chronotype refers to everyone's natural inclination to experience periods of high energy or rest depending on the time of day, and it varies from person to person. It encompasses biological, psychosocial, and genetic components that are associated with morning and evening traits[3]. There are different tools to define the chronotype[4] that investigate the time of getting up and going to bed and the time preferences of individuals for physical and mental activities, along with the subjective perception of the level of alertness. Some questionnaires classify these results into three typologies: morning types or "larks," night types or "owls," and neutral or undefined types. However, there are more refined methods that consider additional aspects to assign a chronotype, such as sleep latency, waking mechanism, and time required to get up. These methods classify subjects into six categories: 0 (extreme morning), 1 (moderate morning), 2 (light morning), 3 (neutral), 4 (light evening), 5 (moderate evening), and 6 (extreme evening)[4]. Regardless of the technique employed for its measurement, the chronotype represents the specific circadian phase of each person. This phase, in turn, influences various physiological and behavioral aspects, including physical functions, hormonal levels, cognitive abilities, and sleep and dietary patterns[4]. The evidence indicates that the chronotype undergoes modifications as age progresses, as has been documented in some investigations[3]. This phenomenon is attributed to the ability of the human organism to continuously adapt to both internal and external variations, which are intrinsically linked to the development and aging processes. A significant correlation has been observed between circadian preferences and age, with individuals tending to exhibit a morning-oriented inclination as they grow older[4].

CHRONODISRUPTION

In recent decades, the concept of chronodisruption has gained importance due to its potential impact on health. Aberrant exposure to zeitgebers, which are environmental cues that regulate circadian cycles, can disrupt circadian homeostasis and can have detrimental effects on human health. Chronodisruption is defined as an alteration in the functioning of the

Figure 1. Relationship between the inner clock, peripheral tissues, and insulin. Created with BioRender.



circadian system, specifically a disturbance in the critical timing of internal biological processes in response to external cues. An illustrative example of chronodisruption is found in night shift workers who are chronically exposed to such stimuli. It is well documented that chronic exposure to this chronodisruption factor can lead to adverse health outcomes[5]. Chronodisruptors are factors, both exogenous and endogenous, that are chronobiologically active and can disrupt the timing and order of physiological functions. Common chronodisruptors include the use of artificial light and screens, sleep deprivation, and nighttime meal consumption. These factors have been associated with a higher risk of developing metabolic pathologies such as obesity, alterations in glucose metabolism, diabetes, dyslipidemia, and other components of metabolic syndrome[5].

METABOLIC IMPLICATIONS OF CHRONONUTRITION

Diabetes is a complex metabolic disorder that is characterized by sustained hyperglycemia secondary to defects in insulin secretion or its action in peripheral tissues. In less than 50 years, this pathology has become one of the main public health concerns, with approximately 537 million affected adults worldwide. Type 2 diabetes (T2D) accounts for more than 90% of all diabetes cases globally and requires multifactorial strategies and ongoing medical care to reduce the risk of complications[6]. It is well described that lifestyle changes are fundamental in obtaining adequate metabolic control and preventing long-term complications in T2D. Dietary modifications are a pivotal lifestyle change, particularly when living in a social context where food is readily available. The effect of nutritional interventions in lowering glycated hemoglobin is approximately 0.3-2% while improving insulin sensitivity, blood pressure values, and lipid profiles[7]. Despite the favorable evidence surrounding nutritional interventions, there is a constant controversy regarding different macronutrient intake patterns (i.e., high-fat vs. low-carbohydrate) and metabolic control. This controversy stems from a variety of factors, including the complexity of human metabolism, the variability in individual responses to different diets, and the limitations of research methodologies. Therefore, it is crucial that meal planning and dietary interventions are carefully tailored according to individual needs. In addition, there is a growing need for evidence-based nutritional interventions that can aid in simplifying decision-making when prescribing a particular diet[8].

THE COMPLEX RELATIONSHIP BETWEEN CIRCADIAN BIOLOGY AND METABOLIC HEALTH

In humans, glucose metabolism exhibits a circadian rhythm, with insulin secretion and sensitivity peaking during daylight hours. In addition, a variety of hormones, which are also subject to circadian regulation, exert an influence on glucose metabolism, such as melatonin, often referred to as the “sleep hormone.” This hormone is responsible for altering insulin sensitivity and creating an insulin-resistance environment[2]. These adverse metabolic effects are further enhanced by unusual food intake timings. The complex relationship between melatonin and nocturnal food intake is believed to cause dysregulation in pancreatic β-cells[9]. This emphasizes the importance of the concept of food intake timing, which refers to the moment of the day when the food is consumed. In addition, the order of macronutrient intake plays a pivotal role in glucose metabolism; this is especially true for carbohydrate intake. The quantity, quality, and velocity of carbohydrate ingestion have a direct effect on post-prandial glucose levels and peripheral tissue insulin response[2]. It has been reported that consuming carbohydrates toward the end of a meal can have a positive impact on glucose levels, resulting in a reduced post-prandial spike at 180 min following meal consumption[9].

EATING WINDOW

Studies have demonstrated that having a prefixed meal consumption schedule involving shortening the daily duration over which food is consumed can play a favorable role in delaying metabolic disorders. The recommended eating window is typically 12 h/day, and it is hypothesized that this specific eating period is connected to changes in gene expression within peripheral tissues like the liver, pancreas, and adipose tissue. Nevertheless, it is worth noting that diverse studies have indicated that there is no advantage in shortening the eating window further, as doing so has been linked to elevated total cholesterol and triglyceride levels[10-13]. In contrast, available evidence indicates that every hour that dinner consumption is delayed leads to elevated blood glucose levels and a greater body fat percentage, attributed to changes in insulin sensitivity and elevated melatonin concentrations, leading to metabolic disorders such as T2D and obesity[10-13]. These changes can be observed between groups with the same macronutrient and calorie distribution, which further underscores the importance of tailoring an adequate eating window, especially in patients with incipient metabolic dysfunction[12]. The question that arises within this discussion is: What is the optimal period during which food intake should be restricted (i.e., daytime vs. nighttime)? Studies conducted by Farshchi et al.[14] in healthy women illustrate the impact of food intake restriction during the daytime. In this study, a late breakfast intake during a 2-week period was associated with an increase in total and low-density lipoprotein (LDL) cholesterol levels, as well as elevated insulin levels after glucose intake. Another study conducted on healthy participants observed a modest increase in glucose variability in individuals who fasted until 12:00 p.m. for 6 weeks as compared to individuals who consumed breakfast before 11:00 a.m.[15]. Conversely, a similar study conducted on individuals with obesity did not show any difference in lipid profile between both groups[16]. To address this question, there is a pressing need for additional evidence in populations with metabolic disorders. In addition, it is essential to conduct comparative studies between groups practicing morning or evening fasting with an extended follow-up period.

MACRONUTRIENT AND ENERGY DISTRIBUTION THROUGHOUT THE DAY

Circadian cycles are reprogrammed following complex metabolic pathways depending on macronutrient dietary content and intake schedule. Additionally, the significance of macronutrient distribution is equally as important as the total energy intake, as both elements are linked to the risk of diseases, morbidity, and potential complications[1,2]. There is growing evidence regarding macronutrient distribution, and studies have revealed enhanced insulin responses in individuals with T2D who primarily consume their daily-recommended carbohydrates during breakfast. This was observed in a randomized, open-label, crossover design study analyzing 18 individuals with T2D treated exclusively with metformin. In this study, there was a noticeable reduction in post-prandial glucose levels, with a 30% decrease in the area under the curve (AUC) in patients within the breakfast-focused group with a macronutrient distribution corresponding to 22% fats, 47% carbohydrates, and 31% proteins, compared to those who predominantly consumed carbohydrates during dinner with the same macronutrient distribution[17]. Despite the available evidence, there is still a lack of well-defined, evidence-based recommendations regarding calorie distribution throughout the day as well as the recommended quantity of carbohydrates to consume during daylight hours to optimize insulin response and sensitivity.

MEAL FREQUENCY

Adequate meal distribution throughout the day has a great impact on maintaining optimum energy and glucose levels; this can be obtained with the correct meal frequency. In addition, adhering to consistent meal timing can aid in improving physical performance and concentration during daily life activities. A cross-over study conducted in women with obesity has demonstrated that irregular meal patterns can lead to elevated serum lipid levels, in particular total cholesterol values, compared to individuals who consume meals at consistent intervals of time. In addition, a decreased energy intake was also noticed in this cohort[18]. Furthermore, studies evaluating meal frequency without a notable calorie restriction in 21 healthy, normal-weight, middle-aged adults have reported an 11.7% increase in total cholesterol values along with a 16.8% increase in LDL cholesterol among individuals who consume only one meal during the day[19]. When considering meal frequency, a lingering question emerges regarding whether there is an optimal number of meals an individual should have and that can be recommended for different metabolic states. Nonetheless, this aspect remains uncertain, which highlights the need for further research, ideally on a larger scale.

SEQUENCE OF FOOD CONSUMPTION

The sequence in which various food groups are ingested significantly affects the body's capability to process nutrients and impacts feelings of satiety and energy levels. This dietary sequence not only influences the efficiency of digestion but can also affect the blood sugar level response and the release of hormones associated with satiety. Therefore, understanding the role of the sequence of food consumption is fundamental in managing chronic metabolic diseases such as T2D. The current research has explored an ideal food consumption sequence, revealing insights into a specific order that can help reduce post-prandial glucose levels and insulin secretion. This sequence involves starting with protein consumption and concluding with the intake of carbohydrates[20,21]. One of the strongest hypotheses for ameliorating post-prandial blood sugar increase is the consumption of vegetables first during meals. A cross-over study done by Imai et al.[21] included 18 young, healthy women and analyzed changes in insulin concentration post-prandial blood glucose, free fatty acids, and triglyceride levels after having a 671-kcal breakfast divided into different groups. The study showed that there was a significant difference in post-prandial glucose when women ate vegetables first versus at the end of the meal, regardless of how long it took them to consume them. It was also demonstrated that glucose variability was less when vegetables were eaten first during a 2-h glucose curve; this outcome is pivotal for clinical practice management[21]. Similar outcomes were illustrated in a study done by Shukla et al., where they evaluated the order of food intake[20]. The population was divided into three groups: the first group ate carbohydrates at the beginning of the meal, the second started with protein, and the last group did not have any specific order to eat. In the results, there was a statistically significant change in the glucose and insulin AUC, with lower values in the second group. Both studies[20,21] highlighted the importance of having a sequence of food intake during meals for an adequate regulation in post-prandial glucose levels.

At the forefront of nutritional research, the search for novel strategies has become crucial to effectively address the intricacies of health and well-being. One of the most promising emerging areas is chrononutrition, which focuses on the timing of food consumption and its synchronization with the body's natural rhythms. This innovative perspective considers not only what we eat but also when we do so, acknowledging that our biological systems follow cyclic patterns throughout the day. In the context of chronic metabolic conditions like T2D, implementing chrononutrition as part of treatment strategies could hold significant potential due to its crucial role in glucose metabolism. However, the evidence remains quite diverse in terms of the number of participants, studied outcomes, follow-up periods, studied populations, and research focused on individual chrononutrition components rather than a holistic approach. Deeper and more varied research is needed to establish robust conclusions and provide clear, evidence-based recommendations for the application of these strategies in the treatment of T2D and other health conditions. The consideration of multiple variables is essential to build a strong knowledge foundation, to develop genuinely effective and personalized nutritional approaches.

PREGNANCY, GLUCOSE METABOLISM, AND CHRONONUTRITION

Hyperglycemia can affect a significant number of women during pregnancy, with an estimated prevalence of 16.7% worldwide, 80.3% of women with gestational diabetes, 9.1% with other types of diabetes detected during pregnancy, and 10.6% of women who had diabetes prior to their pregnancy[6]. Insulin resistance is classically associated with pregnancy, especially during the second and third trimesters, since there is an alternate metabolic and hormonal balance to ensure an adequate supply of nutrients and glucose for the fetus's growth. In addition, there are physiological changes described in late pregnancy, such as alterations in the rhythm of growth hormones as well as a significant increase in the concentration of cortisol and glucagon. These hormones have antagonistic effects on insulin and increase blood glucose concentration[22]. Different studies have shown that an improvement in glycemic control and insulin sensitivity during pregnancy can be achieved with certain measures. These include adequate meal timing, ensuring breakfast consumption and increasing the period of overnight fasting. Furthermore, it is also important to consider the sequence of consumption of the macronutrients during the day, such as consuming carbohydrates, mainly in the morning[22]. A cross-sectional study performed in 1061 Asian women in their late second trimester of pregnancy demonstrated that an increase in the number of meals per day (4 vs. 5-10 times) was associated with a higher 2-h post-prandial glucose concentration, a higher daily energy intake, and a reduction in the protein consumption. In addition, this study demonstrated that pregnant women with a night fasting window of 11-12 h versus < 11 h had a lower fasting glucose concentration[23]. A randomized cross-over trial in 12 women in the third trimester of pregnancy showed that a higher intake of carbohydrates and energy in the morning vs. at night (50% of total carbohydrates and 40-50% of energy distributed in the breakfast and morning snack vs. in the dinner and nighttime snack) during a 4-day period reduced the fasting glucose, mean glucose, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). However, a higher consumption of carbohydrates in the morning also produced an increase in the mean amplitude of glucose excursions and in the coefficient of variation[24]. Similar outcomes were illustrated in a study that agreed that a higher consumption of energy and carbohydrates at dinner is associated with higher fasting glucose concentrations[25]. In addition, Peterson and Jovanovic-Peterson[26] concluded that the intake of carbohydrates led to a higher post-prandial glucose variability at dinner. Furthermore, a randomized cross-over trial in 30 pregnant women in the third trimester of pregnancy reported that the consumption of mixed meals with the same energy content, but with 51% carbohydrates in breakfast and 44% in dinner, caused a higher post-prandial glucose response in the night despite its lower carbohydrate proportion[27]. Since the ideal amount of carbohydrates and energy to consume in the morning during pregnancy is unclear, the recommendation is to consume a higher proportion during breakfast.

Consumption of more than 25% of the daily calories after dinner is considered evening hyperphagia. Due to the modern lifestyle and the symptoms associated with pregnancy, night eating becomes very frequent during pregnancy, and it is present in 15-45% of pregnancies[28]. A cross-sectional study conducted in 148 pregnant women in the third trimester demonstrated that participants with night eating syndrome had an increase in fasting insulin, HOMA-IR, and breakfast skipping[28]. This behavior could lead to sleep and mood disturbances. A prospective cohort study that included 100 pregnant women found that women with an evening chronotype were younger, ate breakfast later, consumed more calories and carbohydrates at dinner, and showed greater weight gain in the third trimester[29]. On the other hand, it has been reported that pregnant women with a morning chronotype have a higher quality of diet in general and have significantly higher consumption of dairy products, fruits, and whole grains, and lower consumption of saturated fats[30]. It is important to mention that the requirement of carbohydrates in pregnancy is higher, at 175 g/day; therefore, diets with carbohydrate restrictions should be avoided[7]. Registered dietitians should adjust the nutritional therapy to find a balance between an adequate quantity and quality of carbohydrates, ensuring a correct intake of protein, fiber, water, and micronutrients, and taking into consideration the chrononutrition strategies previously described. Finally, a period of fasting longer than 12 h is not recommended since it could increase the concentration of ketone bodies, which can affect the neurological development of the fetus[31].

THE ROLE OF SLEEP HYGIENE AND MELATONIN IN METABOLIC CONTROL

Sleep is a crucial factor for human health as it is involved in the regulation of circadian rhythm and multiple neurobiological processes in the body. The sleeping cycle is composed of two main phases: rapid eye movement (REM) and non-REM (NREM)[32]. The REM phase is related to the activation of the sympathetic nervous system, whereas NREM sleep is associated with a parasympathetic response and contributes to the control of metabolic regulation and memory consolidation. Having a good sleep quality is influenced by sleeping time, which should be around 7-9 h in adults, as recommended by the U.S. National Sleep Foundation. Sleep is also influenced by the quality and amount of physical activity, diet, genetics, and environmental factors[32]. Sleep deprivation and disturbances have been strongly associated with the progression of different diseases, such as metabolic imbalance, depression, cardiovascular disease, and even neoplasms. This has been mainly studied in employees who work night shifts; multiple epidemiological sources provide clear evidence that these individuals are more likely to experience chronic conditions including obesity, T2D, cardiometabolic issues, and sleep disorders[32]. One of the main hormones involved in the sleeping cycle is melatonin, a pineal hormone with antioxidative and anti-inflammatory properties. Melatonin is mainly secreted when there is absence of light, and its secretion diminishes with aging[2]. Studies have shown that having poor sleep hygiene has been linked with hormonal changes, including the release of leptin, ghrelin, and melatonin[33]. Recently, melatonin properties related to glucose control have been uncovered; showing that the release of endogenous melatonin directly stimulates insulin secretion[32]. However, a meta-analysis by Lauritzen et al. showed that exogenous consumption of melatonin at daytime increases insulin resistance[34]. These studies demonstrate the importance of having a well-regulated sleep, where hormones can be secreted at an adequate time and metabolic disturbances can be avoided.

ABNORMAL LIGHT EXPOSURE AND METABOLIC IMBALANCE

Exposure to long-wavelength light during prolonged hours and at night is related with reduced melatonin concentrations in the blood. Previous studies have demonstrated that employees who are exposed to artificial light during night shifts have alterations in their circadian rhythm, including impaired cortisol secretion, body temperature, and oxidative stress, which increase the risk of developing insulin resistance[35]. A preclinical study performed by Park et al.[36] demonstrated that feeding mice late at night was related to an increase in oxidative stress species and reactive oxygen species levels, mainly when they were exposed to artificial light. Disturbances related to abnormal light exposure have been described. The International Agency for Research in Cancer categorized night shifts as a possible carcinogenic agent for humans[33]. On the other hand, it has been described that reducing exposure to artificial light, such as the use of smartphones, TV, and computers, reduces the latency of sleep by more than 7 min. This backs up the idea that long-wavelength light reduces the production of melatonin, causing poor sleep hygiene and impaired metabolic control[32,33]. It is estimated that over one-third of adults in America, Europe, and Asia sleep less than 7 h per night. This can cause circadian misalignment, which occurs when the fasting and feeding times are not synchronized[35]. Night-shift patterns are related to altered eating patterns and eating through the 24 h; furthermore, it has been demonstrated that people tend to eat more carbohydrates and fats during the night[37]. Evidence suggests that nighttime light exposure not only affects the circadian rhythm and hormonal control but also affects the cravings that individuals have. This increases the susceptibility to gaining weight and, consequently, having a higher risk of developing metabolic diseases such as insulin resistance, diabetes, and metabolic syndrome.

SLEEP DURATION AND RISK OF T2D

In modern societies, sleep deprivation has become a prevalent disorder due to multiple factors, such as a markedly fast-paced lifestyle and constant accessibility to technology and social media. This phenomenon has a significant negative impact on public health through a range of pathological changes[38]. One of the pathological changes observed in sleep deprivation is a decline in glucose tolerance and insulin sensitivity. This has been evidenced by studies demonstrating an increase in hepatic glucose production and a reduction in peripheral glucose clearance[38-40]. In addition, recent research suggests that sleep deprivation might induce insulin resistance in human adipocytes by reducing AKT phosphorylation. This underscores the crucial role of sleep as a regulator of energy metabolism in peripheral tissues[41]. Furthermore, insufficient sleep duration has been associated with increases in inflammatory markers[39] such as C-reactive protein and interleukin-6, indicating the presence of low-grade persistent systemic inflammation. These alterations play a significant role in the pathogenesis of metabolic diseases, including T2D[38]. The study conducted by Shan et al.38 revealed that a reduction of an hour of sleep below the standard 7-h recommendation per day could increase the risk of developing T2D by 9%. However, an increase of an hour of sleep beyond 7 h per day was also associated with an increased risk of developing T2D by 14%. Both insufficient and excessive sleeps were linked to a higher risk of T2D as compared to people adhering to the recommended 7-h time frame.

NIGHT EATERS

Bedtime snacking is defined as the tendency to consume a substantial amount of food during the night or wake up during the night to consume food. In the study conducted by Morse et al., involving 714 patients at a tertiary care facility caring for patients with both T1 and T2 diabetes, it was determined that individuals who consumed more than 25% of their daily food intake during the night had higher glucose levels and demonstrated lower adherence to diet and exercise regimens. These observations were attributed to various dysregulations in the hormonal axes. In contrast, patients who did not engage in nocturnal eating had a reduced risk of developing additional metabolic disorders like obesity[42]. A large longitudinal cohort study in night shift and day shift health workers conducted by Viklund et al. in Sweden between 2013 and 2017, demonstrated an increased risk for T2D development in the 1st year following night shift work in comparison to those health employees who consistently worked day shifts[43]. This increased risk of T2D development in night shift workers can be attributed to various mechanisms, such as circadian rhythm disturbances that can lead to hormonal changes, including increased cortisol and pro-inflammatory cytokine release, both of which can favor an aberrant glucose metabolism and an insulin resistance environment. Moreover, the adoption of stress coping mechanisms and behavioral alterations can play an additive role in hormonal dysregulation, further enhancing glucose metabolism alterations. The studies featured in this section serve as illustrative examples of the importance of adequate meal intake timings both in healthy patients and patients with underlying metabolic morbidities. Bedtime or nocturnal food consumption, influenced by various factors, can trigger a range of disruptions in circadian rhythms and hormones, ultimately elevating the risk of developing T2D and impairing metabolic control.

EXERCISE AND CHRONONUTRITION

It is well known that exercise has benefits for various metabolic parameters, such as blood pressure and glucose levels; the outcomes depend on different exercise factors, such as frequency, intensity, duration, and type of exercise [44,45]. A key component in achieving adequate metabolic control is adhering to exercise recommendations, the most studied being engaging in 150 min of moderate exercise per week, according to the American Heart Association[45]. However, the impact of the timing of when exercise should be done is still unknown. Recently, it has been suggested that the outcomes of exercise not only depend on its duration and intensity but also on the time of day when it is performed. Studies conducted in the past decade have shown that mealtime and the timing of physical activity serve as temporal cues to modify the phases of the biological clock mechanism in various peripheral tissues. These changes occur in an independent manner from the changes induced by the central clock[46]. The time of the day when exercise is performed has different metabolic changes in the body. For example, the impact on muscle strength is greater when exercise is performed in the afternoon, whereas physical activity carried out in the evening improves oxidative capacity[46]. A study conducted by Savikj et al. reported that a high-intensity interval exercise regime performed by individuals with T2D for 2 weeks improved glycemic control and led to greater body fat loss when the physical activity was performed in the afternoon as opposed to the morning[47]. In another study, Savikj et al. recently examined the effect of exercise on the metabolomics and proteomics of various tissues and muscles in patients with diabetes. They observed that lipid circulation increases, and the changes in adipose tissue composition are similar in both high-intensity morning and afternoon exercise. However, high-intensity afternoon exercise leads to an increase in lipids in muscle tissue and mitochondrial content. According to their conclusions, further research is still needed to determine the clinical implications of these findings[48].

HOW CAN WE APPLY CHRONONUTRITION IN CLINICAL PRACTICE?

According to the evidence reviewed regarding chrononutrition and its effect on metabolic alterations, the following recommendations can be considered in clinical practice[2,38,49,51-54]:

– An adequate diet structure is fundamental, having a greater proportion of the energy requirements during the morning, including approximately 40-50% of the recommended Kcal during breakfast, for maintaining a healthy weight. In addition, a reduced carbohydrate intake during the afternoon is recommended.

– Establish regular eating hours, having at least three main mealtimes, avoiding skipping breakfast and having a nighttime fasting window of at least 12 h.

– Implement an appropriate macronutrient intake order, if possible, at each meal consumed. This order should start with fiber-rich foods like vegetables, followed by a source of protein such as lean meat, which can be complemented with unsaturated fats, and ending a meal with carbohydrate-rich items such as whole grains and legumes.

– Meal composition is as important as other chrononutrition components; therefore, it is advisable to combine the three macronutrients in each meal. Regarding carbohydrates, there should be a focus on consuming those with a low glycemic index.

– It is worth mentioning that the glycemic index of a food can be modified using diverse culinary techniques, such as starch retrogradation in the case of pasta, rice bread, and potatoes; avoiding the ingestion of overripened fruit; and lowering the pH of the food using vinegar or lemon juice to delay gastric emptying.

– Whenever possible, nighttime eating and frequent snacking during the day should be avoided.

– Maintaining regularity in meal schedule, structure, frequency, and composition is a pivotal point to observe the benefits of the different components of chrononutrition.

– Sleep hygiene and ensuring an adequate number of hours of sleep per night are key in lowering the risk of developing metabolic diseases such as diabetes and obesity.

CONCLUSION

Both quantity and quality are crucial components of a healthy eating pattern. However, it is important to note that chrononutrition emerges as a tool that can enhance the beneficial effects attributed to a dietary intervention beyond those derived from consuming an adequate amount of each nutrient. Synchronizing food consumption with dietary quality of the diet and the circadian rhythm aids in achieving an optimum metabolism of nutrients and, therefore, promotes health at a cardiometabolic level, which represents an effective strategy for the control of chronic non-transmissible diseases such as diabetes. It is imperative for healthcare professionals to understand that consuming the same foods at different times of the day can yield varying impacts on nutrient metabolism. In this context, the commonly known saying *"Eat breakfast like a king, lunch like a prince, and dinner like a pauper"* seems to align appropriately with the current scientific literature regarding chrononutrition. A common theme in discussions within the health sciences, including chrononutrition, is the presence of gaps in evidence and knowledge; however, these gaps can be minimized by conducting clinical trials with adequate methodological quality. Therefore, novel and increasing evidence regarding chrononutrition is essential to uncover the true long-term impact of chrononutrition interventions both in healthy and metabolically affected cohorts. We believe that the future of chrononutrition will be centered on implementing individualized interventions tailored to a person's chronotype. This will allow health workers to focus on improving the temporal pattern of energy and macronutrient intake, the frequency and number of mealtimes, and in addition to promoting proper sleep hygiene and reducing the prevalence of nighttime eating syndrome.

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