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Review

Chrono-Nutrition in Human Health and Diseases

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ABSTRACT

Only in the last two decades have new genetic clues shed light on the mystery of biological time. The availability of molecular clock genes has allowed for an unprecedented level of understanding of the physiological mechanisms involved in the circadian rhythm. The experimental disassembly of the clock reveals an inseparable relationship between energetics and timing. There are several aspects of circadian clocks that remain a mystery, including:

1. *their relationship to metabolic homeostasis in the brain and peripheral tissues;*
2. *the energetics of sleep disruption and circadian rhythms;*
3. *the relationship between nutritional status and circadian homeostasis; and*
4. *the effects of circadian clock systems on human physiology.*

Ultimately, these studies will shed light on the connections between genetics, metabolic diseases, and behaviour. Eating healthily and keeping separate feeding and fasting cycles in line with metabolic processes controlled by the clock help keep behavioural and physiological circadian rhythms in check. The link between circadian disturbance and metabolic instability has received a lot of attention. Some studies have linked changes in clock genes to metabolic risk factors, obesity, type 2 diabetes, and calorie intake.

KEYWORDS: Chronobiology, Nutrigenetics, "Clock genes", Circadian desynchrony, Microbiome, Epigenome, Chrono-disruption, Non-communicable diseases

INTRODUCTION

The Circadian Rhythm

The human circadian clock has a roughly 24-hour period, and research on the effects of "chrono-disruption" has significantly increased. Modern lifestyle and environmental influences, such as artificial lighting, jet lag, shift work, and constant access to high-energy foods, can cause circadian system disturbances, which can have a negative impact on an individual's health. There is

mounting evidence that the circadian clock and metabolism have a complex reciprocal relationship in which changes in one system have an impact on the other. Genetic variations in clock genes can affect metabolic health and alter an individual's reaction to diet, according to nutritional genomics. Furthermore, it has been shown that the gut microbiota, epigenome, and circadian rhythm interact, and that the diet can alter this intricate relationship, indicating a remarkable degree of flexibility in the underlying mechanisms. According to this perspective, the investigation of the effects of eating timing by combining components of chrono-biology and nutritional research, or chrono-nutrition, may have important ramifications for customized nutrition in terms of lowering the burden and prevalence of chronic illnesses. An overview of the available data on the relationship between diet and the circadian system is given in this paper, with particular attention to how this relationship may affect the microbiome and epigenome. Additionally, potential dietary approaches to control feeding that is in sync with the circadian rhythm are proposed.

Numerous behavioural and physiological processes are regulated by the circadian rhythms (circa = around and dies = one day), which are triggered at both the central and local levels by clocks in various peripheral tissues[1,2]. These rhythms occur during the day/night cycle[2]. Furthermore, energy/nutrient input can alter the basic circadian clock machinery, indicating the critical involvement of energy metabolism[3,4]. The circadian clock system and metabolism have been found to be intricately and reciprocally interconnected in this setting; as a result, it is likely that changes in one system will have an impact on the other. A number of chrono disruptors, including shift work, stress, jet lag, and sleep disturbance, can cause circadian desynchrony, which is common in modern societies and can harm people's health by raising their risk of metabolic disorders. Since our clock mechanisms are synchronized by our diet, irregular meal schedules may cause ambient oscillators to separate from the central pacemaker, which could have detrimental effects.

According to nutrigenetics, chronobiology should be included in nutritional practice since a number of genetic variations in circadian-related genes might affect an individual's response to diet by interacting with dietary intakes and obesogenic behaviors[5,6]. However, the circadian rhythm is most suited for feeding during the light phase[7], therefore by synchronizing the central and peripheral clocks, dietary input enhances circadian activity.

Chrono-nutrition is a relatively young field of study that examines how an organism's health is affected by when it eats. Specifically, a tendency toward nutrition-related illnesses like obesity, type 2 diabetes (T2DM), and cardiovascular disease (CVD) has been linked to the alteration of the cycle between eating and fasting periods. An overview of the most recent research on the genetic and environmental variables causing disruptions in the molecular clock in relation to the start of non-communicable diseases (NCDs) is given in this article. It also looks at how nutrition and the circadian system interact, emphasizing how this relationship affects the microbiota and epigenome. Lastly, it makes recommendations for potential dietary approaches to control feeding that is in sync with the circadian rhythm[8].

The Molecular Clock

The clock circadian regulator (CLOCK), aryl hydrocarbon receptor nuclear translocator-like (BMAL1, also called ARNTL), period circadian regulators (PER1 and PER2), and cryptochrome circadian regulators (CRY1 and CRY2) are among the complex array of genes known as "clock genes" that produce circadian oscillations at the molecular level. These genes encode proteins that are essential for controlling circadian rhythmicity.

The transcriptional autoregulatory feedback loop that underpins the molecular clock is defined by the activation of BMAL1 and CLOCK, which at the start of the cycle positively regulate the expression of their target PER and CRY (***Fig. 1***). To inhibit BMAL1/CLOCK activity, the negative-feedback repressor complex PER/CRY moves into the nucleus[9,10].

This feedback loop, which is mostly coordinated with the environment through light, has a genetically fixed period length of roughly 24 hours. Additionally, CLOCK-BMAL1 regulates a dozen additional clock-controlled genes, which are downstream target genes. The circadian network is an intricately regulated system. SCF (Skp1-Cullin-F-box protein) E3 ubiquitin ligase complexes regulate the stability of the PER and CRY proteins. Furthermore, the kinases casein kinase 1ε/δ (CK1ε/δ) and AMP kinase (AMPK) cause the phosphorylation of the PER and CRY proteins, respectively. This leads to polyubiquitination by their respective E3 ubiquitin ligase complexes, which then activate the 26S proteasome complex to break down the PER and CRY proteins[11].

An antiphase oscillation in the expression of the Bmal1 gene is caused by the supplementary feedback loop involving Rev-erbα, which suppresses the transcription of Bmal1[12]. As explained in the next paragraphs, circadian misalignment promotes risk-associated metabolic abnormalities and chronic disorders like obesity by causing a conflict between central and peripheral signals as a result of the feeding/fasting and light/dark cycles[13].

Peripheral Clock and Supra Chiasmatic Nucleus (SCN)

Up until the 1990s, it was thought that only certain pacemaker cells in the SCN were responsible for timekeeping. It is now widely acknowledged that all mammalian peripheral tissues contain the molecular machinery (Clock, Per) required for circadian oscillation, and independent clocks have been discovered in the majority of cells outside of the SCN in a

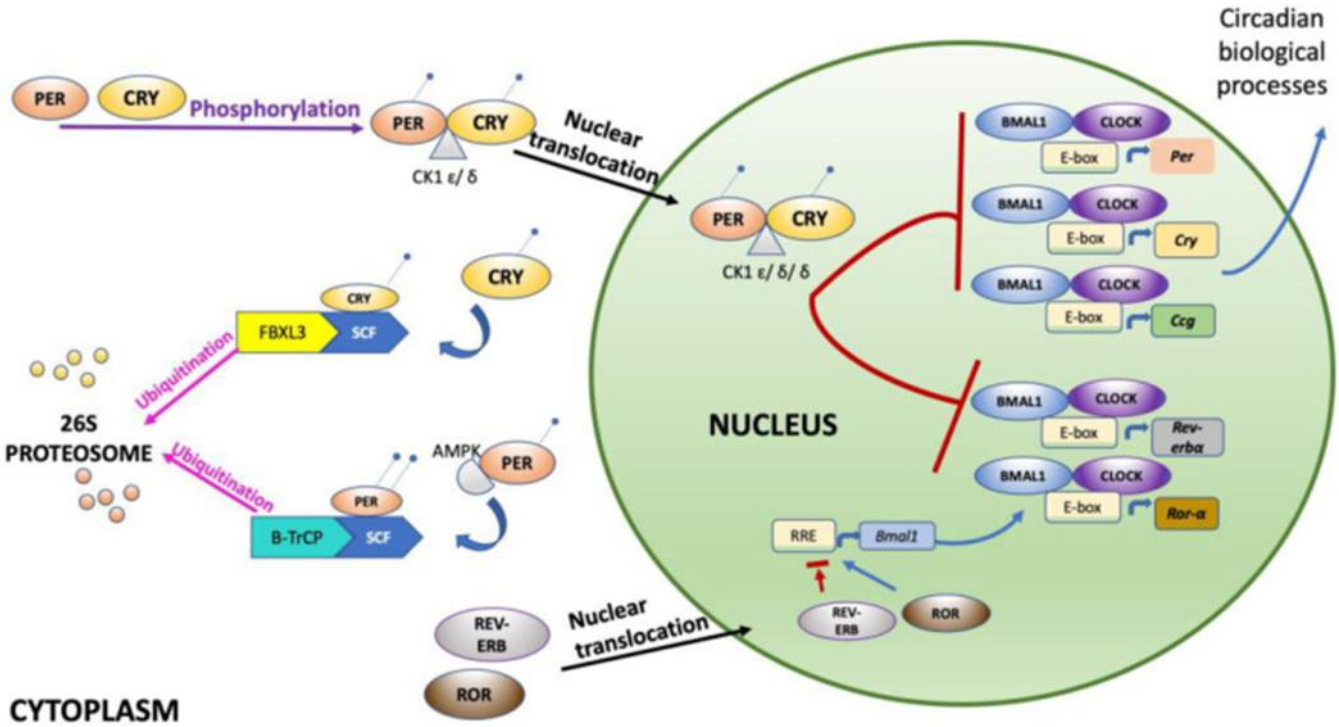

Figure 1: The Circadian Cycle
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number of species[14,15]. The SCN sends phase-resetting signals to these so-called peripheral oscillators, but a variety of other entraining events can also reset their phase, with the feeding/fasting cycle being one of the most significant, at least for certain tissues[16,17]. These elements have the capacity to activate signal transduction pathways that affect peripheral cells' molecular oscillator (reviewed in Reference 16). Through behavioural, neuroendocrine, and autonomic mechanisms, the SCN regulates peripheral clocks[18,19]. First, behaviour-facilitating (extra-)hypothalamic centres can be inhibited or activated by the SCN. Second, the neuroendocrine hypothalamic regions in charge of hormone secretion may be impacted by the SCN. Lastly, the SCN can alter panautonomic hypothalamic neurons that control the brain stem's and the spinal cord's parasympathetic and sympathetic autonomic centres [intermediolateral column of the spinal cord (IML)] and dorsal motor nucleus of the vagus (DMV), respectively[18].

The retina, olfactory bulb, and medio basal hypothalamus (MBH) are just a few of the brain nuclei that have peripheral clocks, often known as non-SCN brain clocks. Restricted feeding, for example, can decouple these non-SCN clocks from SCN control, even though they are in sync with the SCN (127). A key component of the brain that controls eating and energy metabolism is the medio basal hypothalamus, which is made up of the DMH, ventromedial hypothalamus (VMH), PVN, and arcuate nucleus. Therefore, it appears crucial that the brain's non-SCN clocks synchronize with the SCN for the best energy homeostasis [Figure 1].

The output of the suprachiasmatic nucleus (SCN) to peripheral and non-SCN brain clocks. The light-dark cycle corrects the approximate 24-hour rhythm produced by the SCN to an exact 24-hour rhythm. Through the Retinohypothalamic tract, SCN gets photic information. It then relays this information to other hypothalamic nuclei, primarily the paraventricular nucleus of the hypothalamus (PVN). Information is then converted into autonomic and hormonal signals that are sent to the peripheral organs. Endogenous clocks are also present in non-SCN brain regions and peripheral organs, and they are synchronized by the SCN in addition to outside cues like the feeding/fasting cycle[21].

Effect of Glucose and Fat

Numerous studies have demonstrated the complex connections between the circadian clock system, energy metabolism, and food intake timing. Apart from the timing of food consumption, the food's content may also play a significant role in interfering with the regular clock output. In other words, the periodic availability of circulating macronutrients may be the cause of the feeding-dependent resetting of the peripheral and non-SCN brain circadian network. For example, in cultured fibroblasts,

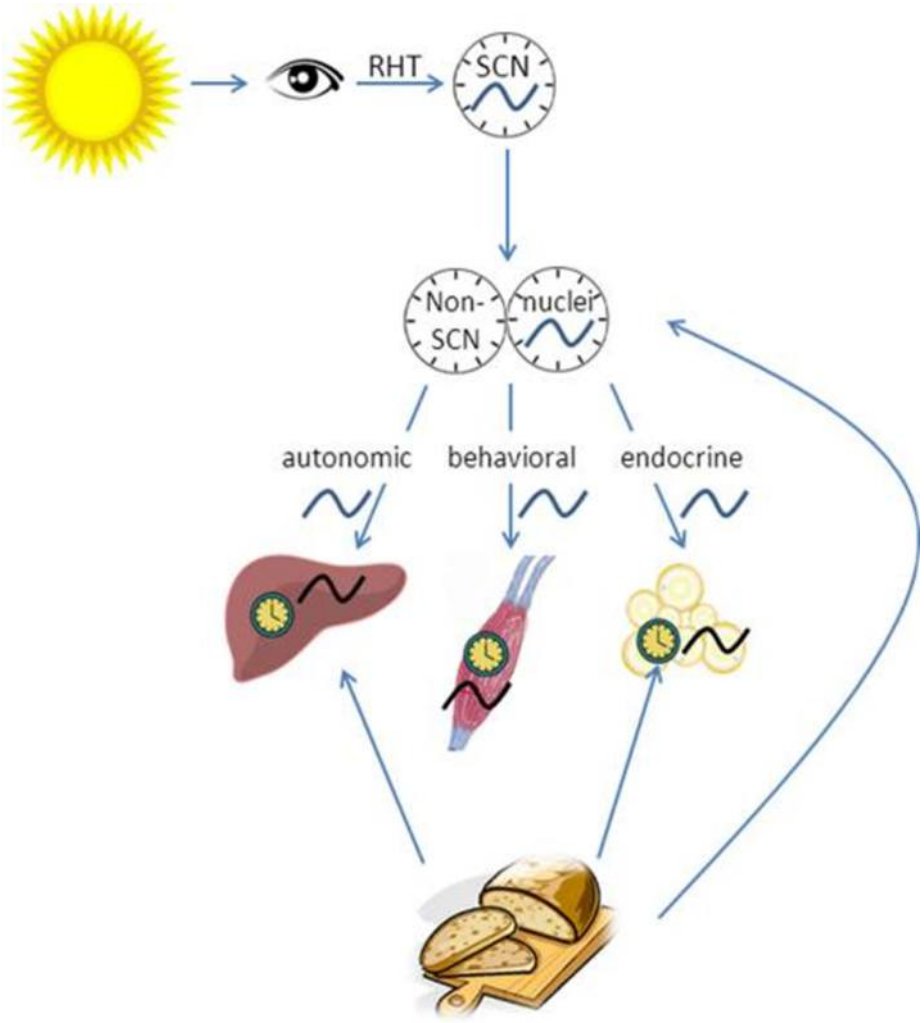

Figure 2: SCN and its output to non-SCN Areas
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glucose can trigger the circadian expression of Per1, Per2, albumin D site-binding protein (Dbp), and Bmal1[22]. This could imply that glucose plays a part in bringing the peripheral and possibly central clocks into sync. Clock gene expression may be disrupted, peripheral clocks may get desynchronized from SCN control, or clock genes and metabolic genes may become desynchronized as a result of changes in the temporal availability of glucose.

This review will concentrate on the effects of fat and sugar on metabolism and the molecular circadian clock, as well as how these factors interact, in light of the rising prevalence of obesity and obesity-related metabolic symptoms in Western society, which coincides with rising consumption of fat and sugar. Numerous components of the human diet, such as alcohol, caffeine, and amino acids, have been demonstrated to have direct or indirect effects on the clock; however, a detailed discussion of these components is outside the purview of this study and is explicitly provided in another recent review[23].

Given that Morris et al.[24] discovered that mice with restricted access to fructose only during the light period gained more body weight, displayed a greater increase in white adipose tissue, and had higher levels of insulin and leptin than mice with restricted access to fructose at night, the timing of glucose intake may be crucial for maintaining normal energy homeostasis. Rats given a high-fat diet with diurnal access to liquid sugar gained greater body weight than rats on an isocaloric diet with only nocturnal access to sugar. This suggests that timing of sugar intake is crucial for maintaining body weight homeostasis[25].

Since glucose provides the majority of the metabolic energy used by the brain, it is imperative that blood glucose levels stay above ~5 mM. This is made possible by the presence of glucose-sensing systems in the peripheral and central nervous systems, which regulate glucose homeostasis, food habits, and energy storage[26]. The regulation of glucose homeostasis depends on the central clock. The regulation of glucose

homeostasis is compromised by surgical ablation of the SCN, and plasma glucose levels exhibit diurnal oscillation that is unrelated to meal consumption[27]. Additionally, it is well acknowledged that there is diurnal fluctuation in glucose uptake [Figure 3; see References in 55, 64]. Given the brain's sensitivity to glucose and the role the SCN in the hypothalamus plays in maintaining glucose homeostasis, it is intriguing to determine whether changes in feeding-induced glucose levels can affect the molecular circadian clock peripherally, centrally in the SCN, or in non-SCN brain nuclei.

It has been demonstrated that a high-fat diet and continuous light exposure can both independently and additively affect body weight gain by upsetting the circadian rhythm. This suggests that a hypercaloric diet and a disturbance in the molecular circadian clock are more harmful to body weight balance than any of these factors by themselves[28]. When it comes to how a high-fat diet affects energy homeostasis, timing is crucial. In contrast to mice fed a similar high-fat diet at the start of the active time, Bray et al.[29] observed that giving mice a high-fat meal near the conclusion of the active period led to increased adiposity. This was probably caused by a disruption in the temporal control of β-oxidation[29].

In conclusion, a high-fat diet may affect both the central and peripheral clocks because, as previously mentioned, it may cause abnormalities in the circadian patterns of behaviour and lipid and glucose metabolism in mice. It's possible that eating fat can help the molecular clock synchronize. Fatty acids' effects on the molecular circadian clock, which will be discussed below, have been the subject of very few investigations.

Chrono Nutrition (Precision Nutrition): The Research Gap

The science of nutrition and how it is applied to enhance public health are constantly evolving. From the early identification of critical micronutrients to the measurement of needs to prevent deficiency disorders, to the recommendation and fortification of adequate intakes, and, most recently, to a comprehensive focus on dietary patterns that lower the risk of chronic diseases, nutrition has advanced. Since diet is one of the most promising modifiable elements to improve human health, it is imperative to create evidence-based, scientifically supported public health initiatives to lower the high prevalence of chronic diseases linked to nutrition. With the aim of enhancing population health through dietary advice, governments and associated

Figure 3: Plasma Glucose and Glucose Disappearance
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organizations offer comprehensive dietary and nutrition assistance. A broad-based public health nutrition strategy is reflected in nutrient- and food-based guidelines, which promote the consumption of nutrients, food components, foods, and dietary patterns at prescribed intake levels. These recommendations have shown successful in treating diseases caused by nutritional deficiencies[30]. If all members of the population or a small number of population subgroups react similarly to food and nutrient exposures, the majority of the time, authoritative nutritional guidelines have used this population-based approach. This method has been effective in treating dietary deficiencies, but it becomes more complex when considering how nutrition affects chronic illnesses.

Efforts to expand the objective or end point of nutrient- and food-based guidelines and policies to include chronic disease reduction have been spurred by the unprecedented rise in the incidence of diet-related chronic diseases over the past three decades, as well as the resulting impact on healthcare costs[30]. There is a need for more precision in achieving health through diet, which must be largely reflected in more nuanced dietary guidance, practice, and food policy. This is made evident by the multifactorial Etiology of chronic diseases, the complexity of food composition and the multitude of interactions of foods with physiological systems, nutrition behaviours, the aging process, and individual knowledge of human biological variation.

Recommendations for reducing chronic disease must take into account both the causal relationship or relationships between diet and disease, as well as the role that diet plays in the overall risk of chronic disease in comparison to other lifestyle interventions. This is in contrast to nutrient- and food-based recommendations that aim to prevent nutrient deficiencies. In order to determine the most effective behavioural changes at the community and individual levels to reduce chronic disease, it is imperative that all individual lifestyle risk variables be subject to similar evidential criteria. Therefore, our dietary recommendations should be more sensitive to the specific nutritional needs of different population subgroups with known differences in responses or with similar risk levels or behavioural patterns and their relative impact compared with other lifestyle modifications in order to minimize the risk of disease and/or to maximize human health.

Strong diet-disease relationships with adjudicated end points or validated surrogate indicators of disease risk that may be linked to dietary changes are necessary for the establishment of Dietary Reference Intake (DRIs) for the reduction of the risk of chronic diseases[31]. Therefore, with the development of the Chronic Disease Risk Reduction (CDRR), a novel aspect of the DRI for sodium is the first change from preventing possible excess and deficiency to determining the ideal dietary intakes for decreased risk of chronic disease. When there is at least a reasonable level of causal evidence linking a food intake level to a health outcome, the CDRR can be established. Based on a reasonable level of evidence for hypertension and cardiovascular illness combined with strong evidence for salt and blood pressure management, the CDRR is currently only defined for sodium[32].

In order to gain public trust and encourage adoption of the recommendations, it is imperative that the urgency of addressing the rising rates of chronic disease through the development of public food and nutrition guidelines be balanced with an open and honest communication of the quality of the scientific evidence underlying the recommendations for reducing chronic disease. Currently, the dietary guidelines are not followed by the majority of Americans[33]. Public confidence in nutrition research and population-based dietary recommendations has to be significantly strengthened because significant changes in recommendations over time have damaged public trust[34]. The aspirational objective of attaining public health through precision nutrition depends on the public's acceptance of food and nutrition guidelines.

Personality and Nutrition

There is mounting evidence that personality and individual differences in thought, behaviour, and emotion may potentially contribute to the risk of obesity, in addition to hereditary, environmental, and social factors[35]. The Five Factor Model (FFM), sometimes known as the Big Five, is a well-known, popular, valid, and reliable measure of personality that captures personality in the dimensions of neuroticism, extraversion, conscientiousness, agreeableness, and openness to experience[36]. Individuals are described by these five general, reproducible aspects of personality in terms of common thought, emotion, and behaviour patterns[36]. The FFM is widely used in research and, when compared to other personality measures, has independent dimensions with support for external validity[36]. Active, upbeat, and assertiveness are traits of neuroticism; enthusiasm and action-orientedness are traits of extraversion; curiosity, imagination, and open-mindedness are traits of openness; self-discipline, order, and strength of will are traits of conscientiousness; and compliance and empathy are traits of agreeableness[37]. While certain researches have consistently demonstrated that a high level of conscientiousness is related with a lower risk of obesity[38], other studies imply that personality qualities including neuroticism, extraversion, openness, and agreeableness are associated with BMI[38].

The relationship between personality and dietary consumption is of relevance since the fundamental personality qualities that people are born with remain constant and stable across time[39]. Consistent behaviours, such eating at comparable times of the day and adhering to healthy habits, are linked to certain personality traits, such as conscientiousness[39]. The idea of "chrono-nutrition," which emphasizes not only what we eat but also when we consume[40], is the eating habit of interest in this review and may have an indirect relationship to personality.

Coordinating food consumption with the circadian body rhythm, or the internal biological clock, is known as chrono-nutrition[41]. It addresses the following three areas:

1) Food intake irregularity (changing energy intake levels during the day and at different times from day to day),

2) Food intake frequency (number of meals per day)

3) Food intake timing (time of day)[42,43]

A physiological adaptation to sleeping and eating at irregular circadian times may be the reason of the correlation between meal timings and patterns and weight that is suggested by current views on the subject[40]. The circadian body rhythm, which includes numerous physiological and metabolic processes like glycolysis, glycogenesis, and lipid metabolism, may be impacted by irregular meal consumption[40]. Moreover, it has been demonstrated that circadian misalignment alters the levels of circulating satiety hormones including ghrelin and leptin, which in turn affects calorie intake and expenditure[44]. It's also critical to take into account the thermic effect of food (TEF), which is the rise in energy expenditure following meal ingestion. It has been demonstrated that consuming a snack in the morning as opposed to at night considerably increases the TEF[45]. Additionally, nocturnal insulin resistance may be associated with this decreased evening thermic response[45], indicating a connection between meal timing and TEF.

Epigenomic Basis

In order to distinguish between the phenotypic expression of cell groups with the same genome background, epigenomics describes a collection of reactions and processes that control changes (activation or suppression) in the functions of genes without changing the sequences of the nitrogen bases (adenine, guanine, cytosine, and thymine) of the DNA (deoxyribonucleic acid) molecule[46,47,48].

Compounds that bind to DNA during the demethylation/methylation reaction, to histone proteins during the acetylation process, or to other radicals are the primary agents responsible for epigenetic control[47]. Enzymes that promote or undermine these links, including DNA methyltransferase, histone acetyltransferase, and histone deacetylase, mediate these processes. These linkages result in either a looser chromatin (euchromatin), which promotes transcription factor binding and cellular pathway regulation, or a more compact chromatin (heterochromatin), which hinders DNA transcription[49].

Taking into account the effects of biological cycles, gut microbiome dynamics, and chrono-nutrition further complicates epigenetic modulation. In fact, new data indicates that the circadian clock-influenced timing of food and nutrient intake may alter epigenetic processes[50]. Furthermore, the gut microbiota is essential for the metabolism of nutrients and the production of bioactive substances that might affect epigenetic homeostasis, and it is intimately associated with circadian rhythms[51,52]. As these complex components come together, a thorough investigation of potential relationships will reveal new information about how lifestyle choices shape the epigenome and, in turn, affect general health and metabolic balance.

Regulation & Interaction

One of the environmental factors that has emerged as a significant modulator of CR in several systems is the combination of light/dark cycle exposure and nutrition, which is influenced by the meal's timing primarily but also by the diet's content[53]. The involuntary and unconscious biological processes that organisms use to digest, absorb, metabolize, and use nutrients for survival are referred to as nutrition[54]. The same is true for biological clocks, which are controlled by a series of 24-hour cyclical physiological and metabolic factors that interact with meal timing, frequency, and composition to define the circadian distribution of food intake [Figure 4] and give rise to the concept of chrono-nutrition[55,56].

Chrono-nutrition and circadian rhythm modulation in diet. Biological rhythms related to food intake (hormonal regulation of hunger-satiety; regulation of the digestive and absorptive process; metabolism and use of nutrients and their serum concentrations) are regulated by the central circadian regulator (SCN) and peripheral circadian regulators (white adipose tissue, liver, intestine, and pancreas) in response to environmental cues such as light, meal composition, and/or time variation between the first and last meal of the day[57].

Gut Flora and their Role

The intestinal lumen is the final and primary layer of contact between the gastrointestinal system and nutrients in their absorptive form, regardless of when meals are consumed[58]. Enterocytes, which are absorptive cells found along the epithelium, goblet cells, which produce mucins, which are proteins that can provide both a protective barrier and molecular exchange between the intestinal epithelium and the environment, and Paneth cells, which secrete antimicrobial products when the epithelium detects external microbial fragments, are among the various cell types that make up the small intestine. These cells are important for metabolic homeostasis and defence functions[58,59].

Given this, the gut contains 70–80% of immune cells and is a significant lymphoid tissue that is rich in Peyer's patches, which release dendritic cells, macrophages, plasma cells (which produce immunoglobulin A), and CD4/CD8 T lymphocytes. The M cells that carry out endocytosis, mesenteric lymph nodes, and a large surface covered in diffuse lymphocytes are located above Peyer's patches. This represents the interaction between the immune system and the gut and is crucial for the daily defence against pathogens and for mediating the low-grade chronic inflammatory process[60].

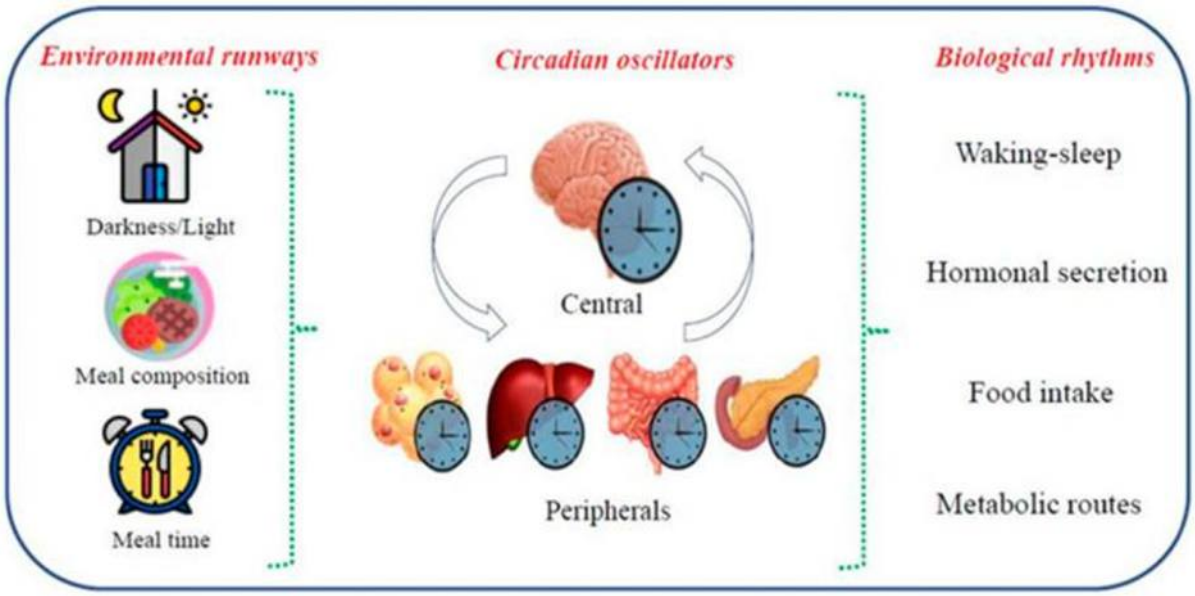

Figure 4: Regulation and Modulation
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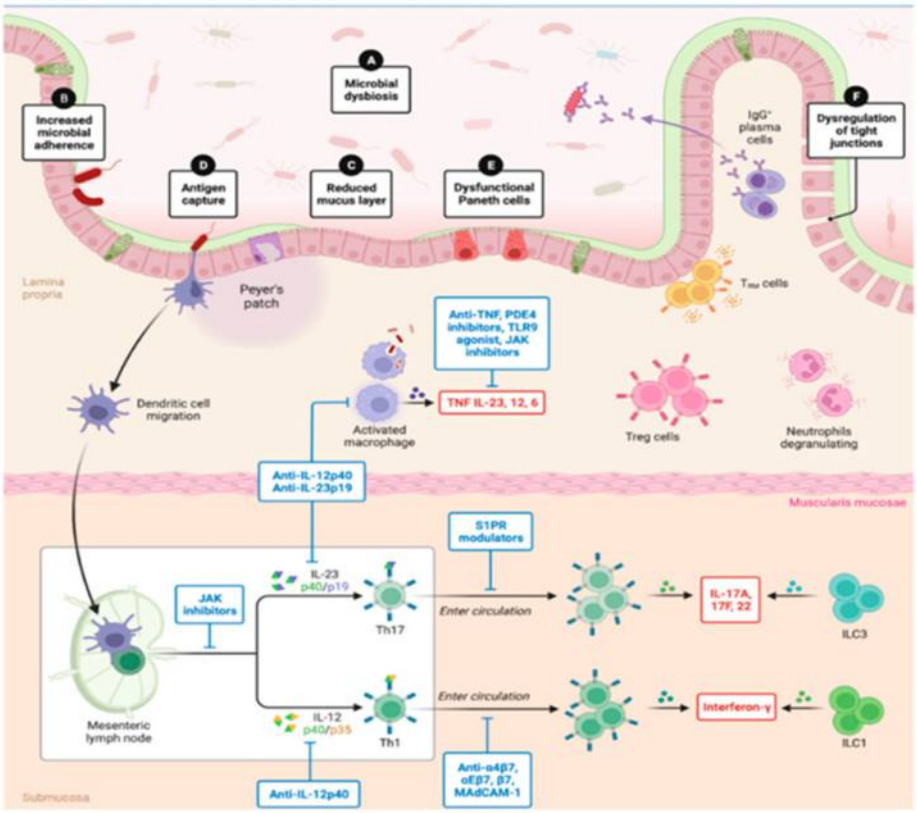

Figure 5: Inflammatory Cascade
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Intestinal homeostasis is a crucial factor in the control of the state of organic stress, even if the inflammatory process linked to poor diet and obesity happens systemically[61]. Toxins, dietary antigens, and intestinal microorganisms are prevented from entering the lumen by the gut's epithelial layer[62]. Yet, vulnerability to both internal and external factors (e.g., genetic predisposition, dietary pattern, antibiotic use, or disruption of the circadian rhythm) can cause specific components, like lipopolysaccharide, to migrate to the lamina propria, triggering the initiation of pro- and anti-inflammatory processes linked to the pathophysiology of the chronic inflammatory state[63] as stated in Figure 5.

The daily synchronization of clock-gene-regulated physiological processes throughout the body, particularly in the gastrointestinal tract and related systems like gut flora, is influenced by the meal schedule and daily metabolic activity throughout a 24-hour period. By modifying the inflammatory state and other regulatory pathways, the interactions between intestinal microorganisms and their host have daily nutritional, immunological, and metabolic effects linked to maintaining health and establishing and/or controlling chronic non-communicable diseases. This emphasizes the significance of multidirectional interactions between nutrients, the circadian system, and gut flora interfaces.

This interaction (nutrient and mealtime/biological rhythm/GM) is multidirectional and modulated by epigenetic mechanisms that occur concurrently at different cellular levels and organic systems. This is an emerging and complex area for renewed scientific research for precision nutrition, according to heterochromatin and multi-omics studies concerning the identification of changes in the DNA configuration, the genetic sequencing of gut flora, and the expression of clock genes in different tissues.

Future perspectives should encourage an aim to elucidate mechanistic pathways and networks involving epigenetic interactions, not only in the gut microbiota-host relationship but also within the microbial community itself, even though numerous studies in humans and experimental models provide data on circadian synchronization/desynchronization, gut microbial composition, epigenetic pathways, and the associated repercussions on the health-disease process. Additionally, based on epigenetic signatures and modulation for precision health maintenance, potential therapeutic targets that can be influenced by the synchronization of circadian rhythms and gut microbiota will include purported lifestyle modifications, especially those pertaining to daytime meals and the adoption of healthy eating patterns[57].

Chrono Nutrition and Lifestyle Disorders

Time Restriction

The ability of nutritional components, such as macro- and micronutrients and naturally occurring bioactive chemicals, to directly or indirectly control central and peripheral clocks has gained widespread recognition in recent decades. For instance, the daily distribution of macronutrients and high-fat diets seem to function as disruptors, negatively affecting a number of metabolic health parameters[65]. Additionally, it's critical to align meal time, frequency, and energy consumption patterns with the day/night cycle[65]. Glycogenesis and lipogenesis-related genes are active during the day, whereas growth, repair, glycogenolysis, and lipolysis-related genes are activated at night[66]. Surprisingly, any issues within these time frames may be linked to energy metabolism impairment[67].

The prevalence of diabetes, obesity, atherosclerosis, and non-alcoholic fatty liver disease has grown to be a significant public health issue and a financial strain on healthcare systems worldwide[68]. Due of their pandemic dimensions, new and efficient management strategies are desperately needed on a global scale. Chronic chrono-disruption, or misalignment of circadian rhythms, has been linked in this regard to a higher risk of metabolic disorders as a result of industrialization, prolonged exposure to artificial light, increased shift work, sedentarism, jet lag, and premature and frequent snacking[69,70]. There is currently no easy way to deal with the rising risk of chronic diseases, especially in light of the aforementioned factors.

In order to ascertain whole-body physiology, the time-restricted eating (TRE) or time-restricted feeding (TRF) idea encourages regular periods of food and fasting[71]. Research has shown that TRE, a subtype of intermittent fasting (IF) regimen that specifies a certain window of time for eating and fasting every 24 hours, is an effective strategy for the prevention and co-treatment of metabolic disorders and obesity[72]. With no deliberate adjustments to calorie intake, the window of opportunity for eating spans from 4 to 12 hours[15,16]. Alternate-day fasting (ADF), which entails eating one day and fasting the next, is an illustration of such a change. One meal, generally lunch, that does not exceed 25% of the daily calorie intake is often ingested on the day of the fast. Adding one or two days of fasting every week (5:2 days) is another example of IF modification. On the fasting day, meals must be completely avoided or calories must be reduced to a minimum[71]. However, a slight calorie deficit is typical because of the short feeding period. However, TRF does more than merely limit calories; it also aligns meal times with the active/awake period, when the body is most capable of metabolizing food[66,73].

The time of meals seems to have an impact on the development of non-communicable diseases. Therefore, IF appears to be a potential strategy for their efficient administration. It would be important to note that following the most recent recommendations for diet composition and quality—which include reducing ultra-processed foods, consuming whole grains, plant-based diets, and controlling portion sizes—is essential while using TRE procedures. Metabolic diseases may be significantly improved by chrono nutrition practices like

TRE or TRF. Nonetheless, there are still very few, contradictory, and ambiguous results from the international scientific bibliography data[75]. In this regard, the current review's objective is to analyse and critically assess the preliminary research interest in TRE as a beneficial dietary intervention for people that may help regulate circadian rhythm, enhance metabolism, and promote general metabolic health in the areas of managing and preventing metabolic disorders.

A literature review[74] concluded that Clinical research assessing the possible positive impacts of particular chrono nutrition practices, like TRE or TRF, have been steadily growing in the past few years. With a focus on metabolic problems, these researches aim to prevent or co-treat a variety of chronic diseases. They specifically look at lowering blood sugar, insulin, triglycerides, body weight, body composition, and excessive body weight in people with metabolic illnesses linked to body weight. The chrono nutrition concept showed encouraging positive effects on metabolic diseases and promoted metabolic health in a number of clinical studies. Some of them, nevertheless, have significant drawbacks. To draw more accurate results in this area, it is strongly advised that future clinical studies be well-designed and have a sufficient period of nutritional intervention. Further research should also consider the long-term consequences of the COVID-19 pandemic and their possible influence on chrono nutrition practices.

A cross sectional study by Lujan et al.[76] focused on role of chrono type and chrono nutrition observed that a lower prevalence of Type 2 Diabetes is linked to a larger diet of carbohydrates (CHO) and a lower intake of lipids at breakfast. Furthermore, there seems to be a connection between a higher prevalence of T2DM and poor sleep quality. It is important to remember, though, that in order to develop a more solid and definitive knowledge of these linkages, these findings need to be confirmed by prospective research including bigger and more diverse populations.

Recommended Reading

In order to gain public trust and encourage adoption of the recommendations, it is imperative that the urgency of addressing the rising rates of chronic disease through the development of public food and nutrition guidelines be balanced with an open and honest communication of the quality of the scientific evidence underlying the recommendations for reducing chronic disease. Public confidence in nutrition research and population-based dietary recommendations has to be significantly strengthened because significant changes in recommendations over time have damaged public trust[43,46]. The aspirational objective of attaining public health through precision nutrition depends on the public's acceptance of food and nutrition guidelines.

1) Impact of nutrients on circadian rhythmicity[4]
2) Chrono-Nutrition: Circadian Rhythm and Personalized Nutrition[8]
3) Chrono-nutrition in the Prevention and Management of Metabolic Disorders: A Literature Review[74]

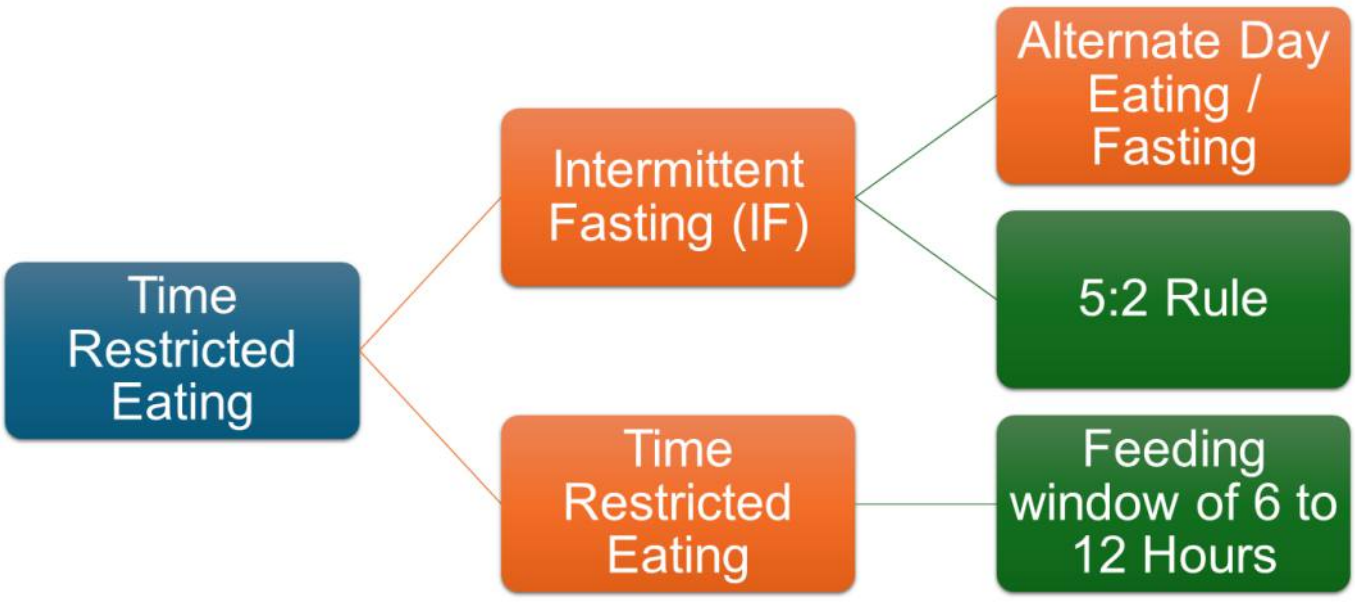

Figure 6: Methods of Time Restricted Eating
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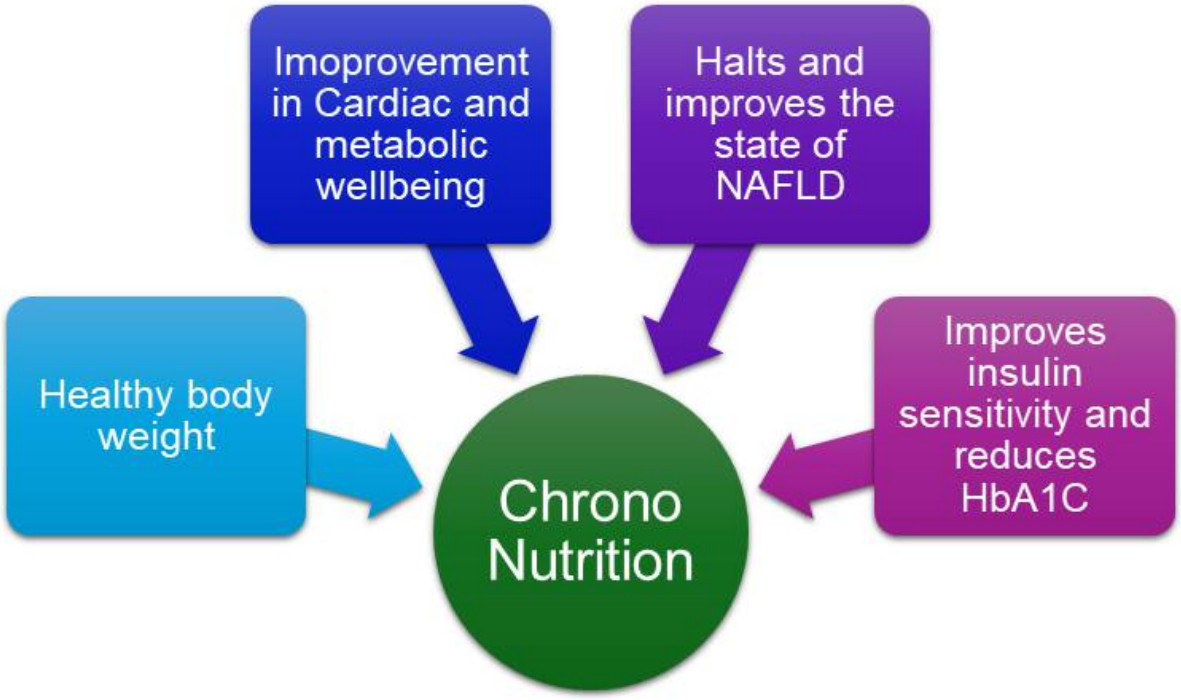

Figure 7: Chrono Nutrition as a Whole
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4) Precision Nutrition: The Hype Is Exceeding the Science and Evidentiary Standards Needed to Inform Public Health Recommendations for Prevention of Chronic Disease[77]

Concluding Remarks

Genetic discoveries have changed the enigma of biological timing in the last 20 years alone. The availability of molecular clock genes has thus made it possible to comprehend the circadian system's physiological processes in previously unheard-of detail. Timing and energetics appear to be inextricably linked when we experimentally disassemble the clock. We still don't fully understand

1) how brain and peripheral tissue clocks relate to metabolic homeostasis,
2) how sleep disruption and circadian rhythms interact in energetics,
3) how nutrient state and circadian homeostasis are related, and
4) how circadian clock systems affect human physiology.

In the end, these investigations will provide more understanding of the relationships among behaviour, genes, and metabolic disorders. Maintaining circadian rhythms in behaviour and physiology is facilitated by balanced diet and the synchronization of distinct feeding/fasting cycles with clock-regulated metabolic processes. Much emphasis has been paid to the connection between metabolic instability and circadian disruption. It has been shown that caloric intake, obesity, type 2 diabetes, and factors associated to metabolic risk are correlated with genetic variations in certain clock genes[78,79].

The man of 2024 is eating more and moving less, more food is available when it was not before and less labour is needed when more was required before, hence the need of the hour is to assess the lifestyle first, decide the food later.

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