

Review

What and When to Eat? Role of Chrono-Nutrition in Disease Prevention

S.K. Verma^{1*} and Riya Pareek²

¹Professor Emeritus, Department of Medicine,
Pacific Medical College and Hospital, Udaipur, Rajasthan, India

²Graduate Student in Public Health,
Schulich School of Medicine & Dentistry, University of Western Ontario

Corresponding Author Email: skvermaster@gmail.com

ABSTRACT

Human biology is extremely complex. It is in fact a real reflection of vast Cosmic Mind's creation. Every bodily system is running cyclically and orderly like a systemic bodily clock. This biological clock is the human circadian system which has a period of 24 hours. Recent studies on circadian rhythm and on the consequences of its disruption- "Chrono-disruption" have been expanded to a great extent. Modern life-style and environmental factors can disrupt the circadian system of the body and may lead to adverse effects on individual's health. Furthermore, complex reciprocal relationship between metabolism and the circadian system of the body have been demonstrated. Current research evidences also provide the impact of the interaction between the circadian system and nutrition and the way this link can influence the epigenome and microbiome. Based on this whole concept, it is possible to develop nutritional strategies to manage circadian-aligned feeding that is what and when to eat in order to reduce the prevalence and burden of chronic diseases.

KEYWORDS: Chrono-disruption; Epigenetic; Nutrigenetics; Nutrimicromics

INTRODUCTION

The term circadian rhythm has come from circa -around and dies -one day. These rhythms occur at central and local levels in several peripheral tissues and regulate many behavioral and biochemical processes through day/night cycle¹. In addition to these, the core circadian clock machinery can be modulated by energy/nutrient input, pointing towards the role of energy metabolism^{2,3}. In this regard, a reciprocal and complex interconnectivity between the circadian system and metabolism has been identified. Circadian desynchrony typical of modern living and triggered by several chronodisruptions such as night shift work, stress, sleep disruption, social jet lag etc. can have adverse effect on human health, resulting in an increased risk of metabolic diseases. It has also been demon-

strated that diet is one of the synchronizers of the human circadian clock mechanisms and therefore abnormal feeding times can lead to unhealthy consequences⁴.

Looking from the point of nutrigenetics, several genetic variants in circadian-related genes, interacting with dietary intakes and obesogenic behaviors, can influence the individual response to diet; stressing that chronobiology should be taken into consideration when thinking in nutritional practices⁵⁻⁷.

Epigenomes and gut microbiomas also show diurnal rhythms. Epigenome is the collection of all the epigenetic markers on the DNA in a single cell. The epigenetic mechanisms also play an important role in the regulation of the molecular clock machinery transcription, and clock -

controlled genes, gut microbiota and microbial metabolism are known to mediate the effects of disruptions of circadian rhythms on human health. New opportunities have risen from recent findings on a dynamic crosstalk among diet-biological rhythm-omics^{8,9}.

The effect of dietary components on human health outcomes has been widely explored. However, the complex relationship between meal timings and the circadian machinery is still undergoing investigations. Interestingly, chrono-nutrition has emerged as a new area of research which is involved in studying the impact of the timing of eating on the well-being of an organism. The modification of the cycle between periods of eating and fasting has been associated with predisposition to nutrition-related diseases including obesity, type 2 diabetes and cardiovascular disease⁴.

Circadian Rhythms

The circadian system is composed of a set of interconnected clock oscillators which are located in the suprachiasmatic nuclei (SCN) of the hypothalamus and in some metabolically active peripheral organs. This system regulates the physiological daily rhythms of sleep/wake, fasting/feeding and catabolic/anabolic cycles, body temperature and endocrine functions¹⁰.

Several factors are expressed and secreted following circadian stimuli such as glucose tolerance peaks during daylight and is lower the night, melatonin drops at 7.00 and rises at 20.00, cortisol rises at 8.00, sleep deepens at 1.00 and body temperature rises at 3.00¹¹.

Chronotype

Circadian system is entrained to an external light-dark cycle with a period of 24 hours, even then there are inter-individual circadian preferences influencing behavior patterns, defined as chronotypes. Chronotype is a biological characteristic leading to interindividual differences in the circadian phase relative to the light-dark cycle.

Categories of chronotypes¹²

- (i) "Morning" types.
- (ii) "Evening" types.
- (iii) "Intermediate" types.

Morning types prefer activities at the beginning of the day and evening types prefer main activities in the late afternoon or evening¹³. The intermediate chronotype occupies an intermediate position between the morning and evening types. Several studies have described the different features between extreme groups in circadian rhythmicity^{13,14}.

Morning Chronotype verses Evening Chronotype

Morning chronotypes are characterized by a phase advance in the peak of body temperature and alertness in the sleep-wake cycle, and in the performance compared with evening types¹⁵.

Evening chronotype is associated with irregular eating and meal skipping especially breakfast skipping as well as being related to a lower intake of fruits and vegetables and a higher intake of energy drinks and fat, suggesting long-term consequences on cardio-metabolic health¹⁶. The evening chronotypes therefore have been correlated with the risk of a variety of conditions including metabolic dysfunction, diabetes, gastrointestinal disorders, psychiatric symptoms and some cardiovascular risk factors such as higher rate of smoking and obesity when compared with the morning chronotype^{13,17}.

Evening chronotypes have also been associated with poor glycemic control in type 2 diabetes patients¹⁸ as well as increased risk of all-cause mortality over 6.5 years¹⁷. These data suggest that chronotype may be predictive of disease outcomes, highlighting the role of circadian system in metabolic regulation. Eating schedule, in fact, is a key to reduce the risk of diabetes. A recent prospective cohort study published online in Diabetes Care has shown that consuming foods with a more glycemic load and having more calories in the late morning is associated with reduced risk of developing type 2 diabetes.

Circadian Misalignment in Adolescence

Circadian misalignment and metabolic disease in adolescence, which is considered a vulnerable period for obesity, have also been investigated. It has been reported that adolescents sleeping less than eight hours consumed a higher proportion of calories from fats compared to those with a nocturnal sleep of more than eight hours¹⁹. These young adolescents are at risk of increased BMI and poorer dietary behaviors with a higher frequency of consuming unhealthy snacks, night time caffeine consumption, and inadequate daily intake of fruits and vegetables²⁰.

Chrono-disruptions

Past few years have witnessed growing amount of attention on the role of circadian disruption in the susceptibility to non-communicable diseases. Chrono-disruption as defined by Erren et al. is a "disturbance of the circadian organization of physiology, endocrinology, metabolism, and behavior"²¹. Escalating chrono-disruption is resulting from the adaptation of modern life styles, especially including excessive energy consumption, irregular times of food consumption, sleep disturbances a night shift work⁴.

Researchers have reported that prolonged short sleep durations and/or poor sleep quality with circadian misalignment are correlated with metabolic dysfunctions, including obesity, type 2 diabetes and hypertension²²⁻²⁴ as well as with decreased leptin, increased appetite and insulin resistance^{24,25}.

Chrono-Nutrition

The concept of chrono-nutrition was developed by Alain Delabos in 1986²⁶.

It is in fact a nutritional regimen that follows our biological clock, which in turn is marked by changes in metabolism that occur throughout the day. Late meal timings and irregular eating are the factors which are not in line with biological clock and therefore associated with increased adiposity, T2DM and cardio-metabolic risk factors^{27,28}. The concept of chrono-nutrition is based on three different dimensions of eating behavior including timing, frequency and regularity²⁹⁻³¹.

Analysis of modern lifestyle habits reveal that this is characterized by being more often in a postprandial state with exposure to unhealthy diets, prolonged sitting times (sedentary habitus), irregular eating, skipping meals, chronic psychological stress, emotional eating and food consumption late at night^{32,33}. This triggers a vicious cycle where obesity - causing unhealthy lifestyle results in disrupted circadian rhythms, which in turn leads to obesity.

Several studies have shown a beneficial effect of dietary regimens which are based on an availability of food only at discrete windows of time within the daily cycle¹¹. These strategies can delay and often reverse the symptoms associated with metabolic disorders, reducing insulin resistance and increasing glucose tolerance³⁴⁻³⁷.

Clock Genes Variants

The effect of chronotype combined with the genotypes of several clock genes through eating time has also been investigated. Several single nucleotide polymorphisms (SNPs) in circadian-related genes have been associated with the susceptibility to obesity, cardiovascular disease and metabolic syndrome, as well as gene-diet interactions being described for some of these genetic variants³⁸⁻⁴⁰.

Nutrigenetics

Nutrigenetic, a branch of nutritional genomics, focuses on the role of genetic susceptibility to diseases as well as on the link between genetic variants and response to diet⁴¹. It is noteworthy that by changing our eating habits it is possible to reduce or even eliminate the deleterious effect induced by a specific allele risk. The interplay between gene variants in circadian machinery and diet may help to design effective, personalized nutritional strategies based on the identification of specific allele carriers⁴.

Epigenetic Alterations

DNA methylation, micro-RNAs and histone modifications are the epigenetic mechanisms, that can regulate gene expression and control many physiological processes⁴¹⁻⁴³. These epigenetic alterations are considered as potential contributors to the

development of health and disease⁴⁴. Different dietary patterns, lifestyle alterations, and environmental insults have potential to modulate the DNA methylation and can influence circadian rhythm⁴⁵.

It has been suggested that for future research, nutrimiomics, the science that studies the influence of the diet on the modification of gene expression due to micro RNAs and chronobiology should be merged to evaluate the circadian-related micro RNAs and their modulation by dietary compounds in order to understand if this relationship may affect the risk of chronic diseases⁴.

Gut Microbiome and Circadian Rhythm

Gut microbiome (GM) is a complex and dynamic population of microorganisms living in the human gut. It is considered as an auxiliary metabolic organ^{46,47}. The GM plays a crucial role in the preservation of mucosal integrity of the intestinal epithelial barrier and in the digestion, metabolism as well as in regulation of many hormones levels⁴⁸. The main bacterial phyla in healthy individuals are Bacteroidetes and Firmicutes⁴⁹. They have symbiotic relationship with the host. The bacterial rhythms also have a period of 24 hours with variation of bacteria during light and dark periods regulated by melatonin and temperature^{50,51}.

There are many factors such as dietary regimen, food additives, pre and probiotic supplements, food processing and cooking methods that can contribute to shaping the GM^{52,53}. High-fat diet affects the composition of the GM. Interestingly, it has also been observed that the establishment of a persons GM, which are essential for metabolic processes and immune function is influenced not only by the factors described above but also on the mode of delivery⁵⁴. Infants born via cesarian section, do not pass through the birth canal and are, therefore, not exposed to maternal microbiota. As a result, their initial GM composition may differ from those born vaginally. GM plays an important role in immune system development and overall health⁵⁵. Data are emerging that demonstrate that the disruption of the circadian system from the host can influence the composition of GM. Not only this, the gut microbial community can regulate host circadian and metabolic homeostasis and also exhibit diurnal oscillations^{56,57}.

It is obvious that nutrients and bioactive compounds of food can modify gut-microbial composition and functions. Several recent strategies based on manipulation of GM may at least partially consolidate host circadian rhythms. Plant-food-derived fiber and poly-phenols can generate bioactive short chain fatty acids, vitamins, bioamines might help in re-synchronization of circadian rhythms, mitigating some of the modern-life style associated metabolic change⁵⁸⁻⁶⁰.

REFERENCES

1. Bass J and Takahashi JS. "Circadian Integration of Metabolism and Energetics". *Science* 330 (2010): 1349-1354.
2. Bailey SM, Udoh US and E Young M. "Circadian regulation of metabolism". *J. Endocrinol* 222 (2014): R75-R96.
3. Oosterman JE., et al. "Impact of nutrients on circadian rhythmicity". *Am. J. Physiol. Integr. Comp. Physiol* 308 (2015): R337-R350.
4. Franzago M., et al. "Chrono-nutrition: Circadian Rhythm and Personalized Nutrition". *Int.J.Mol.Sci* 24 (2023): 2571-2587.
5. Corbalán-Tutau M., et al. "Toward a chronobiological characterization of obesity and metabolic syndrome in clinical practice". *Clin. Nutr* 34 (2015): 477-483.
6. Micó V, Díez-Ricote L and Daimiel L. "Nutrigenetics and Nutrimomics of the Circadian System: The Time for Human Health". *Int. J. Mol. Sci* 17 (2016): 299.
7. Hawley JA, Sassone-Corsi P and Zierath JR. "Chrono-nutrition for the prevention and treatment of obesity and type 2 diabetes: From mice to men". *Diabetologia* 63 (2020): 2253-2259.
8. Bishehsari F, Voigt RM and Keshavarzian A. "Circadian rhythms and the gut microbiota: From the metabolic syndrome to cancer". *Nat. Rev. Endocrinol* 16 (2020): 731-739.
9. Oh ES and Petronis A. "Origins of human disease: The chrono-epigenetic perspective". *Nat. Rev. Genet* 22 (2021): 533-546.
10. Mohawk JA, Green CB and Takahashi JS. "Central and peripheral circadian clocks in mammals". *Annu. Rev. Neurosci* 35 (2012): 445-462.
11. Asher G and Sassone-Corsi P. "Time for Food: The Intimate Interplay between Nutrition, Metabolism, and the Circadian Clock". *Cell* 161 (2015): 84-92.
12. Horne JA and Ostberg O. "A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms". *Int. J. Chronobiol* 4 (1976): 97-110.
13. Yu JH., et al. "Evening Chronotype Is Associated With Metabolic Disorders and Body Composition in Middle-Aged Adults". *J. Clin. Endocrinol. Metab* 100 (2015): 1494-1502.
14. Montaruli A., et al. "Biological Rhythm and Chronotype: New Perspectives in Health". *Biomolecules* 11 (2021): 487.
15. Natale V., et al. "Morningness-eveningness preference and eating dis-orders". *Personal. Individ. Differ* 45 (2008): 549-553.
16. Almoosawi S., et al. "Chronotype: Implications for Epidemiologic Studies on Chrono-Nutrition and Cardiometabolic Health". *Adv. Nutr. Int. Rev. J* 10 (2018): 30-42.
17. Knutson KL and von Schantz M. "Associations between chronotype, morbidity and mortality in the UK Biobank cohort". *Chronobiol. Int* 35 (2018): 1045-1053.
18. Reutrakul S., et al. "The Relationship Between Breakfast Skipping, Chronotype, and Glycemic Control in Type 2 Diabetes". *Chronobiol. Int* 31 (2013): 64-71.
19. Weiss A., et al. "The association of sleep duration with ado-lescents' fat and carbohydrate consumption". *Sleep* 33 (2010): 1201-1209.
20. Arora T and Taheri S. "Associations among late chronotype, body mass index and dietary behaviors in young adolescents". *Int. J.Obes* 39 (2014): 39-44.
21. Erren TC, Reiter RJ and Piekarski C. "Light, timing of biological rhythms, and chronodisruption in man". *Sci. Nat* 90 (2003): 485-494.
22. Chaput JP and Tremblay A. "Does short sleep duration favor abdominal adiposity in children?". *Int. J. Pediatr. Obes* 2 (2007): 188-191.
23. Chaput JP., et al. "Sleep duration and health in adults: An overview of systematic reviews". *Appl. Physiol. Nutr. Metab* 45 (2020): S218-S231.
24. Gangwisch JE. "Epidemiological evidence for the links between sleep, circadian rhythms and metabolism". *Obes. Rev. Off. J. Int. Assoc. Study Obes* 10 (2009): 37-45.
25. Chaput J-P., et al. "Association of sleep duration with type 2 diabetes and impaired glucose tolerance". *Diabetologia* 50 (2007): 2298-2304.
26. Delabos A and Rapin JR. "Mincir sur Mesure: Grâce à la Chrono-Nutrition". Éditions Albin Michel; Paris, France (2005).
27. Tarquini R and Mazzocchi G. "Clock Genes, Metabolism, and Cardiovascular Risk". *Heart Fail. Clin* 13 (2017): 645-655.
28. Dashti HS., et al. "Late eating is associated with cardiometabolic risk traits, obesogenic behaviors, and impaired weight loss". *Am. J. Clin. Nutr* 113 (2020): 154-161.
29. Crispim CA and Mota MC. "New perspectives on chrononutrition". *Biol. Rhythm. Res* 50 (2018): 63-77.

30. Flanagan A., et al. "Chrono-nutrition: From molecular and neuronal mechanisms to human epidemiology and timed feeding patterns". *J. Neurochem* 157 (2020): 53-72.
31. Pot GK. "Chrono-nutrition—An emerging, modifiable risk factor for chronic disease?". *Nutr. Bull* 46 (2021): 114-119.
32. Shapira N. "The Metabolic Concept of Meal Sequence vs. Satiety: Glycemic and Oxidative Responses with Reference to Inflammation Risk, Protective Principles and Mediterranean Diet". *Nutrients* 11 (2019): 2373.
33. Papakonstantinou E., et al. "Effects of Diet, Lifestyle, Chrononutrition and Alternative Dietary Interventions on Postprandial Glycemia and Insulin Resistance". *Nutrients* 14 (2022): 823.
34. Hatori M., et al. "Time-Restricted Feeding without Reducing Caloric Intake Prevents Metabolic Diseases in Mice Fed a High-Fat Diet". *Cell Metab* 15 (2012): 848-860.
35. Sherman H., et al. "Timed high-fat diet resets circadian metabolism and prevents obesity". *FASEB J* 26 (2012): 3493-3502.
36. Chaix A., et al. "Time-Restricted Feeding Is a Preventative and Therapeutic Intervention against Diverse Nutritional Challenges". *Cell Metab* 20 (2014): 991-1005.
37. Adamovich Y., et al. "Circadian Clocks and Feeding Time Regulate the Oscillations and Levels of Hepatic Triglycerides". *Cell Metab* 19 (2014): 319-330.
38. Lyssenko V., et al. "Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion". *Nat. Genet* 41 (2009): 82-88.
39. Dupuis J., et al. "New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk". *Nat. Genet* 42 (2010): 105-116.
40. Bonnefond A., et al. "Rare MTNR1B variants impairing melatonin receptor 1B function contribute to type 2 diabetes". *Nat. Genet* 44 (2012): 297-301.
41. Franzago M., et al. "Genes and Diet in the Prevention of Chronic Diseases in Future Generations". *Int. J. Mol. Sci* 21 (2020): 2633.
42. Franzago M., et al. "Nutrigenetic variants and response to diet/lifestyle intervention in obese subjects: A pilot study". *Acta Diabetol* 59 (2022): 69-81.
43. Franzago M., et al. "The epigenetic aging, obesity, and lifestyle". *Front. Cell Dev. Biol* 10 (2022): 985274.
44. Wadhwa P., et al. "Developmental Origins of Health and Disease: Brief History of the Approach and Current Focus on Epigenetic Mechanisms". *Semin. Reprod. Med* 27 (2009): 358-368.
45. Rigamonti AE., et al. "Changes in DNA Methylation of Clock Genes in Obese Adolescents after a Short-Term Body Weight Reduction Program: A Possible Metabolic and Endocrine Chrono-Resynchronization". *Int. J. Environ. Res. Public Health* 19 (2022): 15492.
46. Sonnenburg JL and Sonnenburg ED. "Vulnerability of the industrialized microbiota". *Science* 366 (2019): eaaw9255.
47. Bishehsari F and Keshavarzian A. "Microbes help to track time". *Science* 365 (2019): 1379-1380.
48. Shen J, Obin MS and Zhao L. "The gut microbiota, obesity and insulin resistance". *Mol. Asp. Med* 34 (2013): 39-58.
49. Moreno-Indias I., et al. "Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus". *Front. Microbiol* 5 (2014): 190.
50. Paulose JK., et al. "Human gut bacteria are sensitive to melatonin and express endogenous circadian rhythmicity". *PLoS ONE* 11 (2016): e0146643.
51. Paulose J., et al. "Entrainment of the Circadian Clock of the Enteric Bacterium *Klebsiella aerogenes* by Temperature Cycles". *Iscience* 19 (2019): 1202-1213.
52. Vitacolonna E., et al. "Inositols, Probiotics, and Gestational Diabetes: Clinical and Epigenetic Aspects". *Nutrients* 14 (2022): 1543.
53. Nova E, Gómez-Martínez S and González-Soltero R. "The Influence of Dietary Factors on the Gut Microbiota". *Microorganisms* 10 (2022): 1368.
54. Zhang C., et al. "The effects of delivery mode on the gut microbiota and health: state of art". *Front. Microbiol* 12 (2021): 724449.
55. Francavilla R., et al. "Intervention for dysbiosis in children born by C-section". *Ann. Nutr. Metab* 73. Suppl.3 (2018).
56. Zarrinpar A., et al. "Diet and Feeding Pattern Affect the Diurnal Dynamics of the Gut Microbiome". *Cell Metab* 20 (2014): 1006-1017.
57. Thaiss CA., et al. "Transkingdom Control of Microbiota Diurnal Oscillations Promotes Metabolic Homeostasis". *Cell* 159 (2014): 514-529.

58. Parkar SG, Kalsbeek A and Cheeseman JF. "Potential Role for the Gut Microbiota in Modulating Host Circadian Rhythms and Metabolic Health". *Microorganisms* 7 (2019): 41.
59. Tuohy KM., et al. "Up-regulating the Human Intestinal Microbiome Using Whole Plant Foods, Polyphenols, and/or Fiber". *J. Agric. Food Chem* 60 (2012): 8776-8782.
60. Erdmann K, Cheung BW and Schröder H. "The possible roles of food-derived bioactive peptides in reducing the risk of cardiovascular disease". *J. Nutr. Biochem* 19 (2008): 643-654.

[Reproduced with permission from *Medicon Medical Sciences* 2024; 7(3): 29-35]