CHRONOBIOLOGY: UNDERSTANDING THE ROLE OF THE RHYTHM THAT SUSTAINS US

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Chronobiology is a field of biology that examines periodic (cyclic) phenomena in living organisms and their adaptation to solarand lunar-related rhythms. These cycles are known as biological rhythms. Chronobiology comes from the ancient Greek chrónos, meaning "time", and biology, which pertains to the study, or science, of life. The related terms chronomics and chronome have been used in some cases to describe either the molecular mechanisms involved in chronobiological phenomena or the more quantitative aspects of chronobiology, particularly where comparison of cycles between organisms is required.

The most important rhythm in chronobiology is the circadian rhythm, a roughly 24-hour cycle shown by physiological processes in all these organisms. The term circadian comes from the Latin circa, meaning "around" and dies, "day", meaning "approximately a day." It is regulated by circadian clocks and can further be broken down into routine cycles during the 24-hour day:

- **Diurnal**, which describes organisms active during daytime
- **Nocturnal**, which describes organisms active in the night
- **Crepuscular**, which describes animals primarily active during the dawn and dusk hours (ex: white-tailed deer, some bats)

While circadian rhythms are defined as endogenously regulated, other biological cycles may be regulated by exogenous signals.

- **Infradian rhythms**, which are cycles longer than a day. Examples include circannual or annual cycles that govern migration or reproduction cycles in many plants and animals, or the human menstrual cycle.
- **Ultradian rhythms**, which are cycles shorter than 24 hours, such as the 90-minute rapid eye movement(REM) cycle, the 4-hour nasal cycle, or the 3-hour cycle of growth hormone production.
- **Tidal rhythms**, commonly observed in marine life, which follow the roughly 12.4-hour transition from high to low tide and back.
- **Lunar rhythms**, which follow the lunar month (29.5 days). They are relevant e.g. for marine life, as the level of the tides is modulated across the lunar cycle.
- **Gene oscillations** – some genes are expressed more during certain hours of the day than during other hours. Within each cycle, the time period during which the process is more active is called the **acrophase**.When the process is less active, the cycle is in its **bathyphase or trough phase.**

Applying concepts of Chronobiology to patients of diabetes and hypertension

Dietary composition and calorie level are key factors affecting aging and age-related diseases. Dietary restriction (DR) promotes metabolic and cellular changes that affect oxidative damage and inflammation, optimize energy metabolism, and enhance cellular protection. Fasting, the most extreme form of DR, which entails the abstinence from all food, but not water, can be applied in a chronic manner as intermittent fasting (IF) or periodically as cycles of prolonged fasting (PF) lasting 2 or more days. In rodents, IF promotes protection against diabetes, cancer, heart disease, and neuro-degeneration. In humans, IF and less-severe regimens (e.g., consumption of approximately 500 kcal/day for 2 days a week) have beneficial effects on insulin, glucose, C-reactive protein, and blood pressure.Intermittent fasting is not a diet but rather a pattern of eating. It involves periods of eating and fasting. Two of the most popular types of intermittent fast are the 5:2 fast and time restricted feeding fast.The 5:2 fast or 5:2 Diet/The Fast Diet, calls for eating normally five days a week and restricting calories—500 calories per day for women and 600 calories per day for men—on the other two days. Time-restricted feeding involves eating food within a narrow window of time, typically a six to eight-hour window. Then fasting the remaining 16 to 18 hours a day.Research shows this type of fast is more manageable because most of the fasting period is overnight and into the morning.

Does Intermittent Fasting Work?

There is an emerging body of evidence that shows the benefits of intermittent fasting for type 2 diabetes and obesity are similar to those of a calorie restricted diet, but easier to follow. Research shows intermittent fasting is beneficial in reducing inflammation, lowering blood pressure, lowering heart rate, lowering cholesterol, and reducing insulin resistance.A recently published study in February 2017 highlights the benefits of intermittent fasting. People in the study were separated into two groups. One group ate a regular diet. The second group followed a fasting-mimicking diet (FMD) consisting of 750 to 1,100 calories per day, for five consecutive days each month for three months. The FMD group was able to decrease body mass index, glucose, triglycerides, cholesterol, and C-reactive protein (a marker of inflammation). Moreover, those who were at risk of diabetes benefited more from the fast than participants who were not at risk.Intermittent fasting is not recommended for pregnant women, women who are breastfeeding, the elderly, individuals under the age of 20, people who are underweight and anyone with an eating disorder.

Preventing obesity with time- restricted feeding (TRF; 8–9 hr food access in the active phase) is promising. TRF in mice under diverse nutritional challenges shows that TRF attenuated metabolic diseases arising from a variety of obesogenic diets, and that benefits were proportional to the fasting duration. Furthermore, protective effects were maintained even when TRF was temporarily interrupted by ad libitum access to food during weekends, a regimen particularly relevant to human lifestyle. TRF stabilized and reversed progression of metabolic diseases in mice with pre-existing obesity and type II diabetes. The circadian clock intimately interacts with nutrient-sensing pathways. This fed and fasting state physiology is made use of in time restricted meal intake.

A randomized trial, was conducted at Department of Physiology, KGMU, Lucknow among 400 patients with Type 2 diabetes. The patients were randomly divided based on whether they gave consent for early dinner TRM(time restricted meal) group or not (control group). Follow up was done at 6 months and 12 months for anthropometric measurement, height, weight, waist hip ratio, neck size , fasting, post prandial blood sugar and HbA1c. The follow up after 12 months revealed that 65% of TRM group and 40% (non-TRM) had normal HbA1c after 12 months. HbA1c in TRM Group had a significant p-value of 0.017. A p-value of <0.0001 was observed on comparing the values of blood sugar (fasting) in TRM Group from the first visit and second follow-up. In brief, time-restricted meal intake in diabetes patients shows promise and its effects are worth exploring further. Time-Restricted Meal intake in type 2 diabetics has significant effect in controlling and maintaining HbA1c as the reduction in HbA1c value was very significant in the TRM group versus the control group. Similar, highly significant results were obtained in the case of fasting and post-prandial values of blood sugar in TRM group, when compared to the control group.Waist and neck size were not significantly different after 12 months of early and late night meal intake but BMI, Hip size, systolic blood pressure were significantly different.

1.	Time restricted meal intake works well with normal North Indian diets comprising of pulses, vegetables, chap rice and curd.
2.	Time restricted meal intake can be used as a therapeutic intervention against metabolic diseases.
3.	Time restricted meal intake is effective as a method for weight loss and significant changes were observed in size and waist size in Type 2 diabetes patients
4.	Time restricted meal intake ameliorates metabolic fitness and counters hypercholesterolemia.

Effects of Chronobiology

Medicine dosage is very much dependent on the time during which the drug has been consumed, it has been proved by studies that non-steroidal anti-inflammatory drugs (NSAIDs) may be less dangerous to the stomach lining when taken at night rather than day. In one study of individuals with osteoarthritis the incidence of adverse effects was cut in half when NSAIDs were taken at night instead of in the morning and there is some evidence that morning pain can also be

controlled by taking NSAIDs at night. Profound cardiac rhythms can be observed in frequency and intensity of symptoms in arthritic diseases such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gout. People suffering from rheumatoid arthritis have reported higher severity of joint pain swelling and stiffness during mornings while those with osteoarthritis reported higher pain during night. Heartburn and ulcers get worse at night during 10 PM to 2 AM, this can be related to secretion of stomach acid which is 2–3 times higher than during the day.These night-time rises are the result of a circadian rhythm of stomach acid production so if the medicine is given at same time it is more effective. Synchronization with the circadian rhythms is found to be far more advantageous when compared to other treatments for cardiovascular diseases or certain diseases such as asthma etc.

The Future

Correct knowledge of these temporal patterns not only helps guide patient care but research of their underlying endogenous mechanisms, i.e., circadian and others, and external triggers. At the same time it gives information regarding development and application of effective chrono-preventive and chronotherapeutic strategies. These strategies could be customized according to the specifics of each and every patient leading to accurate, long lasting and suitable treatments. Chronobiology will open new vistas which will lead to better outcomes for the patients, chronomedicine is still a nascent field and the possibilities for patient welfare are vast.

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