

Lifestyle and Circadian Health: Where the Challenges Lie?

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ABSTRACT: Modern life is facilitated by extended light hours at night and longer hours of eating. Compromised sleep, sedentary life, and modern diet adversely affect human health. Studies emphasizing importance of evidence-driven longitudinal studies on daily rhythms of human eating and sleeping behaviour provide a baseline for adequate insight into causal factors for circadian misalignment. Molecular chronobiology studies in animal models debrief endogenous regulation of organismal circadian clock; their regulation by environmental cues and how they segregate incompatible processes. But effective utilization of the knowledge needs randomized chrono-therapeutic intervention trials in humans. However, nutrition, activity, and lifestyle being society specific, baseline longitudinal studies must precede intervention trials as primary method to decipher circadian disruption. Our pilot survey studies investigating current lifestyle trends responsible for circadian rhythm disruption revealed that accelerated urban life, more than 8 hours work operations and long commutes to work inflict a sleep loss in Indian working women living in metropolitan cities. This sleep loss is sufficient to adversely impact their wellness. Besides, daily work routines and fast-food popularity have contributed to circadian disruption in daily rhythms of eating and sleep, enhancing disease consequences.

KEYWORDS: Lifestyle, eating behaviour, sleep, circadian disruption

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Introduction

Circadian rhythms synchronize organismal functions to 24 hours per day, aligning physiological responses and improving metabolic fitness in a time-dependent manner. Although daily changes in light and food entrain the cellular clocks in most organisms, healthful eating is a human pursuit across the globe. Worldwide, one's daily light exposure and eating behaviour varies with the way of living, for example, artificial lighting has enabled indoor living, often leading to relatively dim days and bright nights.¹ The 'long lighted days' have empowered longer eating hours daily.² Lifestyle, therefore, is an integral consideration of human chrono-nutrition. It is of primary concern that in an era of digitalized information, effective communication and health awareness, lifestyle disorders are surmounting. Compromised sleep, sedentary life and improper eating behaviour(s) such as snacking at night, eating in front of TV screen, and skipping breakfast are few additions of technology in a real-life human scenario. Many studies in Western countries, have assigned food quality to increasing chronic diseases such as cardiovascular disorder, type-2 diabetes and so on, but the temporal aspects of food intake on health are addressed to a lesser extent³. This review highlights importance of evidence-driven longitudinal studies on daily rhythms of human physiology and behaviour (e.g. feeding-fasting and sleep-wake cycles) for adequate insight into causal factors for circadian misalignment. In essence, two important preparations ensure effective utilization of knowledge of circadian rhythms to mitigate circadian misalignment. One, studies on live animal models⁴ and cell-culture techniques⁵ have increased our basic understanding of cell cycle, genetic basis, and biochemical pathways mediating

regulation of organismal circadian clock. These cell-autonomous circadian clocks interact with key environmental cues to temporally sort out incompatible processes and manage energy use to optimize physiology. Notably, though, upkeep of metabolic homeostasis through clock-nutrition interplay in animals depends on nature's food availability; human feeding behaviour is nurtured by society, industry and culture. Another preparation to ensure benefit from circadian rhythm knowledge is by randomized chrono-therapeutic intervention trials in humans. However, nutrition, activity, and lifestyle being society specific, baseline longitudinal studies must precede intervention trials as primary method to decipher circadian disruption.

Biological insight into molecular clock nexus has come from studies on various animals including mammalian model organisms showing that large number of genes express diurnally and differentially to regulate daily physiology.⁶ Contemporary use of genome-wide tools detailing out global transcription in cell,⁷ has highlighted cyclic yet tissue-specific expression of genes that regulate functional processes as metabolic state, endocrine activity, and neural excitability.⁸ These timing mechanisms are regulated by transcription-translation feedback loops in cell-autonomous molecular circadian oscillator machinery. Briefly, two core clock genes, that is, the genes whose protein products are required to generate and regulate circadian rhythms within individual cells – CLOCK and BMAL1 bind noncovalently in the cytoplasm. The CLOCK/BMAL1 heterodimer translocate into the nucleus and binds to E-boxes on the promoter of other core clock genes such as PER1, PER2, PER3, CRY1, and CRY2. CLOCK/BMAL1 heterodimer also regulates BMAL1 transcription. CRY and



PER, after activation from CLOCK/BMAL1, heterodimerize in the cytoplasm and translocate to the nucleus, where these inhibit CLOCK/BMAL1 transcription activity thereby forming negative feedback loop. Two different nuclear hormone receptors REV-ERBa/b and RORa tend to compete near clock genes for the RAR-related orphan receptor (ROR) elements, thus, inhibiting and stimulating BMAL1 expression, respectively. A positive feedback loop results from CLOCK/BMAL1 regulating RORa expression which then feeds back to promote BMAL1. In addition to its role in timekeeping, CLOCK/BMAL1 heterodimer activates clock-controlled genes (CCGs). The CCGs do not directly function in timekeeping but contribute to the transcriptional output(s) of the circadian clock. The rhythmic regulation of production of CCGs generates daily rhythms in their own protein levels as well as thousands of other target genes regulating a variety of biochemical and physiological processes. These intra cellular processes orchestrate circadian secretion of metabolites. The metabolites and other signalling molecules transmit information at cellular, tissue, and organismal level. The role of a circadian pacemaker (Supra Chiasmatic Nucleus, SCN located in the brain hypothalamus in mammals), is to fine-tune these processes for all body components. Rhythms are evolutionarily hardwired in central and peripheral clocks with SCN acting as 'master clock'. Environmental light-dark cycle entrains the central SCN clock function, providing input to the core clock genes (CLOCK, BMAL, PER1, PER2, PER3, CRY1, and CRY2) in SCN cell populations. These temporal signals from SCN drive feeding-fasting and activity-rest rhythms, that in turn, synchronize clock genes in peripheral clocks,⁹ such as liver cells and other metabolic tissues like skeletal muscle, heart, and white fat. At the level of chromatin, circadian rhythms balance daily genomic transcription to coincide with the daily metabolic demands of the organism and to optimize the energy utilization of gene expression.¹⁰ Importantly, food intake entrains peripheral clocks including liver, not the SCN; such that food intake outside the designated 'temporal' window, leads to asynchrony between peripheral clocks and SCN.¹¹ Food intake has the capability to regulate tissue-specific gene expression of peripheral clocks although SCN, itself is protected from nutrient deregulation. Any aberration in light-dark cycle or feeding-fasting cycle accrues adverse effects on the body clocks leading to circadian disruption.

Lifestyle and Circadian Health

Lifestyle is a major determinant of circadian health and relates to people's psychosomatic factors, feeding-fasting, work (activity)-rest, sleep-wake routines. Technology growth provided a platform to lifestyle modifications. Its excess usage perturbs circadian health, leading to conditions like mental depression, cancers, cardiovascular disease, diabetes, and many other diseases. The daily optimal times for working, eating, or sleeping are frequently altered for multiple reasons; naming a

few – enhanced workload, shift work, travel, career stress etc. leading to continued irregularity of routine(s) such as untimely eating, diminished or no sleepiness. Moreover, these irregularities are subjective and society specific. Genome-wide associations of susceptibility to a disease are important, so are behavioural and physiological correlates. Self-reported questionnaire-based surveys of these correlates from sample of populations are often helpful in suggesting disease-enhancing putative factors. However, an in-depth preview of these factors is explicit through longitudinal collection of information. For example, in a study, in Pennsylvania, to assess consequences of prolonged sleep restriction (>5.6 h) for 3 weeks under control conditions, American subjects experienced decreased resting metabolic rate, and increased postprandial plasma glucose suggesting increased risk of obesity and diabetes. They took 9 days of recovery sleep to re-entrain and normalize.¹² In another study, a 3-year follow-up under natural conditions revealed that the risk of progression from impaired glucose fasting or tolerance to clinically classified diabetes became five-fold higher among night shift workers than day workers.¹³ Lack of evidence-driven longitudinal data depicting various factors, such as food, temperature, and activity rhythm, of circadian disruption in humans is because it needs pursuance, persistence, and precise technology. Knowledge of circadian rhythms is used to improve dys-metabolism through corrective life management such as optimizing schooling and work schedules to enable better eating and sleeping regimes.

The sense of time in any society is subjective and location-specific. A 'temporal' perspective for a biologist is in perceiving clocks as innate substrates, while, a social view of biological rhythms underlies aberrant conditions such as jet lag or shift work. Longitudinal studies involving observations of daily feeding patterns are important from either perspective. For example, studies on daily eating pattern in Indian and American workforce cohorts revealed that these subjects consumed larger portion of their total daily calories in the evening/night,^{14,15} irrespective of chronotype or daily activity-rest rhythm. From circadian health point of view, large night mixed-meals have negative consequences in all human beings.¹⁶ Obese subjects with reduced dinner intake have a relative advantage in the management of obesity and metabolic syndrome.^{17,18}

Eating Behaviour Varies in Different Countries

Pandemic generalization about daily feeding behaviours across the globe is difficult. In developed countries like America, traditional eating schedule ranges from early morning 6.00 to 7.00 a.m. to dinner up to 8.00 p.m. Most dinner gatherings end by 9.00 p.m., but night snacking being very popular, chances of night bingeing, increase. The traditional Japanese diet has more quantity of vegetables, allowing more essential nutrients and phytochemicals and last meal of day lasts 7.00 p.m. In India, the eating routines are diverse and largely affected by status,

social strata, and networking. For example, metropolitan cities in Indian subcontinent have an accelerated urban life and longer commutes to work than countryside counterparts. Introduction of active sharing of hi-tech advances among Indian masses has escalated the need for additional material resources but diminished the physical activity levels. There are a few survey-based studies in India reporting up to 40% expansion of India's fast-food industry year by year. Modern India has larger variety of food ranging from home-cooked, home-delivered, carry-out eating places, and restaurants because of changing social criteria like great taste, quick preparation, and conveniently ending meal. Increasing attraction of adolescents to fast food has also been related to current obesity epidemic in younger generation.^{19,20} Despite the alarm raised, changing food choices continues to grow.²¹ Studies delineating relative contribution of time of food intake and extent of fast-food intake through a survey and a longitudinal observation of eating habits in young adults are not available. In Indian big cities, fast-growing popularity of 'eating away from home' or 'outside home food' is viewed as conglomeration of American and European cultures influence. Along this line, there is visible difference in body mass index (BMI) of urban and rural age-matched cohorts.²² Notably, in some countries, like Japan, Asian culture accommodate health-promoting practices, such as intermittent fasting. These have been suggested as measures to combat obesity, for example, food-focused Mediterranean dietary regime is a noted dietary pattern to mitigate obesity.^{23,24}

Diminished Sleep Availability to Indian Workforce Especially Working Women in Metropolitan Cities

Modernization has inflicted the financial burden of 'once upon a time' agrarian Indian society from men folk, to an equal share holding by women, in metro cities. Inadvertently though, the pace of social change like house chores sharing in recognition of social responsibility is much slower and accrued additional burden of workplace to home responsibilities, implicating less sleep availability to working women on a daily basis. Our pilot survey on corporate working women living in Delhi-NCR revealed that more than 10-hour work-routine away from home inflicted a sleep loss in women (our unpublished data). Such a sleep-deficit is sufficient to adversely impact well-being^{25,26} of women in developing countries.

Erratic Eating Patterns in Indian Adults

Medium-income group professionals living in big cities of India have intense work regime or nonavailability of 8 hours for sleep, leading to difficulty in coping with a truly circadian routine. Indian IT industry, a low-cost hub to worldwide business has multifold shiftwork creating 'light at night' (LAN) cities. Notably, LAN is viewed as a cause of circadian disruption; there are other unseen factors as well. For example, few cultures across the globe have practices promoting night eating such as

Ramadan, Indian weddings, and festivals. This way, the factors contributing to unmindful eating, exclusive to India are – festivity meal transitions and weddings; but our survey revealed that ignorance or lack of awareness was associated with erratic eating. As per the self-reported information, before the outreach, most people wrongly conceived the idea that they traditionally ate three times a day.¹⁵ Although many people agreed that coping with natural day-night cycles improves physiological and psychological function thus streamlining short- and long-term health, most people spent 14 to 20 (median: 15.53) waking hours having untimely caloric intake. The extended duration of eating withheld the metabolic system from rejuvenation. Dinner was the biggest caloric meal; 32.2% of their daily intake was consumed between 7.00 p.m. and 11.00 p.m. Indian eating behaviour was comparable to people in the United States,¹⁴ where most people ate frequently and erratically in their waking hours and fasted only during a shorter-than-optimal sleep duration.

Although lifestyle is a sum whole of daily activities, dietary habits, exercise, sleep and so on, circadian rhythms temporally align organismal physiology to improve metabolic fitness. Within a human body, all cells, tissues, and organs have their own daily rhythms which are streamlined by noninvasive interventions such as 'eating at right time' and/or 'sleeping in night for 6 to 8 hours'. These circadian routines improve digestion, metabolism, and cognition. However, knowledge of lifestyle traits is a prerequisite to their optimization. A circadian health initiative needs elaborate knowledge of individual lifestyle through society-specific cohort-based longitudinal studies on various lifestyle aspects providing evidence-driven baseline to these health interventions.

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