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Circadian Rhythm Disruption as a Convergence Point for Obesity and Diabetes Pathogenesis

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ABSTRACT

Circadian rhythms orchestrate 24-hour cycles in behavior and physiology that are fundamental to metabolic homeostasis. A central clock in the suprachiasmatic nucleus and peripheral clocks in liver, adipose tissue, skeletal muscle, pancreas, and gut coordinate sleep–wake timing, feeding–fasting cycles, hormone secretion, and substrate utilization. When these clocks are misaligned with environmental and behavioral cues through shift work, irregular sleep, late eating, or chronic jet lag, metabolic control deteriorates. Epidemiologic data show that circadian disruption is associated with a higher risk of obesity and type 2 diabetes (T2D), while mechanistic studies link clock gene perturbations to insulin resistance, β-cell dysfunction, and altered glucose and lipid metabolism. This review examines circadian rhythm disruption as a convergence point in the pathogenesis of obesity and T2D. We outline the architecture of the circadian system and its integration with metabolic pathways, summarize experimental evidence that disrupting the clock induces obesity and insulin resistance, and synthesize epidemiologic data on shift work and social jet lag as risk factors for T2D. We then discuss organ-specific mechanisms linking clock dysfunction in liver, adipose tissue, muscle, and pancreatic islets to disturbed glucose homeostasis, and explore chrononutrition as a behavioral interface between circadian timing and metabolism. Finally, we consider therapeutic approaches to restore circadian alignment, including sleep regularity, light exposure, meal timing, and pharmacologic clock modulators, and highlight emerging opportunities for circadian-informed precision prevention of obesity-related diabetes.

Keywords: circadian rhythms; clock genes; shift work; chrononutrition; type 2 diabetes

INTRODUCTION

Circadian Organization of Metabolism and Its Breakdown in Modern Life

In mammals, virtually every aspect of metabolism exhibits daily rhythms. Glucose tolerance, insulin secretion, hepatic gluconeogenesis, lipid absorption, adipose lipolysis, and muscle substrate oxidation fluctuate across the 24-hour day, anticipating changes in feeding and activity[1]. These rhythms are generated by a hierarchical circadian system. A central pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus is entrained primarily by the light–dark cycle via retinal photic input. The SCN synchronizes clocks in peripheral tissues through neural, endocrine, and behavioral outputs, particularly the timing of sleep–wake and feeding–fasting cycles[1].

At the cellular level, circadian timing is generated by transcription–translation feedback loops. The core clock proteins CLOCK and BMAL1 form a heterodimer that drives expression of Period (Per) and Cryptochrome (Cry) genes, whose protein products feedback to repress CLOCK: BMAL1 activity. Additional feedback arms involve nuclear receptors such as REV-ERBα/β and RORs that regulate Bmal1 transcription. This molecular clockwork is expressed in SCN neurons and in metabolic tissues, including liver, adipose tissue, muscle, and pancreatic islets[2]. Many metabolic genes are direct or indirect targets of clock-controlled transcription, producing rhythms in enzymes, transporters, and hormones[3]. Under conditions of good circadian alignment, regular light–dark cycles, consolidated nocturnal sleep, and daytime feeding, central and peripheral clocks are synchronized. Glucose tolerance is typically higher in the biological morning than evening; insulin sensitivity and β-cell responsiveness peak earlier in the day, while nocturnal fasting supports lipolysis, fatty acid oxidation, and autophagy[3, 4]. This temporal organization optimizes energy use, limits postprandial excursions, and minimizes conflict between anabolic and catabolic pathways.

Modern lifestyles increasingly challenge this temporal architecture. Artificial lighting extends wakefulness into the night, exposure to screens at night shifts melatonin onset, and irregular work schedules fracture sleep. Many people eat a large fraction of daily calories in the late evening or night, often with prolonged eating windows that span 14–16 hours. Rotating shift work and permanent night shifts impose extreme misalignment, forcing wakefulness, activity, and feeding at times when the SCN and peripheral clocks anticipate rest and fasting[5, 6].
Epidemiologic studies consistently link such circadian disruption with metabolic disease. Cross-sectional and cohort analyses show that short sleep, irregular sleep timing, and social jet lag associate with higher BMI, central adiposity, and components of the metabolic syndrome[7–9]. Meta-analyses of night shift workers reveal an elevated risk of T2D, with some dose–response data indicating that longer duration and more frequent night shifts confer greater risk. A recent cohort-based meta-analysis reported that night shift work significantly increases T2D incidence, with sex and obesity potentially modulating the effect[10]. These relationships persist after adjustment for traditional risk factors, suggesting that circadian misalignment is an independent contributor. Experimental work provides mechanistic support. In rodents, chronic shifting of the light–dark cycle, forced activity during the rest phase, or feeding during the usual sleep phase rapidly induces weight gain, hepatic steatosis, and insulin resistance, even without increased caloric intake[11]. Genetic disruption of core clock components such as Clock or Bmal1 perturbs daily cycles of glucose tolerance and insulin action; whole-body or tissue-specific Bmal1 deletion can cause hyperglycemia, impaired glucose-stimulated insulin secretion, or exaggerated diet-induced obesity depending on the tissue targeted[12].
These findings support the concept that circadian rhythms are not epiphenomena of behavior but active regulators of metabolic pathways. When clocks are misaligned with behaviour such as eating at the "wrong" biological time, metabolic processes optimized for fasting are forced to handle nutrient loads. Hepatic gluconeogenesis and lipid output may remain elevated when insulin sensitivity is low; nocturnal eating occurs when muscle glucose uptake is less efficient and pancreatic β-cells are less responsive. Over time, repeated mismatches may contribute to chronic hyperglycemia, dyslipidemia, and weight gain[13]. Circadian disruption can also act through hormonal axes. The hypothalamic–pituitary–adrenal (HPA) axis exhibits strong circadian rhythmicity in glucocorticoid secretion, which is controlled by SCN outputs and local adrenal clocks. Flattening or phase-shifting of cortisol rhythms, as seen with irregular sleep or chronic stress, can promote central adiposity, hepatic insulin resistance, and impaired glucose tolerance[13]. Rhythms in growth hormone, incretins, leptin, ghrelin, and adiponectin are likewise sensitive to the timing of sleep and meals.
Thus, circadian rhythm disruption emerges as a convergence point where environmental, behavioral, and molecular factors intersect to produce metabolic dysfunction. It integrates light exposure, sleep patterns, work schedules, and meal timing with the intrinsic clock machinery of metabolic tissues. In the subsequent sections, we move from this systems-level perspective to more granular mechanisms, examining how organ-specific clocks and their disruption contribute to obesity and T2D, and how aligning lifestyle behaviors with circadian biology might mitigate risk.

2. Molecular Clockwork and Metabolic Gene Networks in Metabolic Tissues

The same molecular clock that operates in the SCN is echoed in metabolic tissues, where it directly interfaces with nutrient and hormone signaling pathways. In hepatocytes, CLOCK: BMAL1 drives rhythmic expression of genes involved in gluconeogenesis, de novo lipogenesis, bile acid synthesis, and VLDL secretion. REV-ERBα and RORs integrate clock output with lipid-sensing nuclear receptors, linking circadian timing to hepatic fat handling[14].
In adipose tissue, clock genes regulate lipolysis, adipogenesis, and adipokine secretion. Rhythms in lipoprotein lipase, hormone-sensitive lipase, and perilipins coordinate diurnal cycles of fat storage and mobilization, while circadian variation in leptin and adiponectin secretion feeds back on appetite and systemic insulin sensitivity[15]. Clock gene perturbations in adipocytes can shift the balance toward daytime lipolysis and nocturnal storage, disrupting coupling between feeding and lipid flux and promoting ectopic fat deposition[16].
Skeletal muscle clocks influence insulin-stimulated glucose uptake, mitochondrial biogenesis, and substrate preference. BMAL1-deficient muscle exhibits altered glycolytic flux and reduced glucose utilization, leading to impaired systemic glucose tolerance. Recent work suggests that BMAL1 interacts with hypoxia-inducible factor pathways to adapt muscle metabolism to nutrient stress, and that restoring this axis can reverse diet-induced glucose intolerance in mice[17].
Pancreatic islets also harbor autonomous clocks. Clock and Bmal1 regulate genes involved in insulin synthesis, processing, and exocytosis, and coordinate β-cell responsiveness with anticipated feeding times. Disruption of islet clocks in animal models impairs the coupling between glucose stimulus and insulin response, flattening daily rhythms in insulin secretion and contributing to glucose intolerance[18]. Clinical studies report blunted circadian amplitude of insulin and C-peptide rhythms in T2D patients[18]. Importantly, these tissue clocks are influenced not only by light-driven SCN signals but also by feeding schedules, nutrient composition, and hormonal cues. Asynchronous feeding, e.g., night eating in humans or daytime feeding in nocturnal rodents, can uncouple peripheral clocks from the central pacemaker. In such states, hepatic and adipose clocks may align more with feeding time, while muscle or islet clocks remain tied to SCN-driven cues, creating internal misalignment among organs that normally act in concert[19].

Thus, the molecular clockwork is woven intimately into metabolic gene networks. Circadian disruption can arise from gene variants and mutations, but more commonly from environmental behaviors that desynchronize central and peripheral clocks, creating temporal disarray across hepatic, adipose, muscular, and islet metabolic programs.

3. Circadian Disruption, Obesity, and Insulin Resistance

Circadian disruption promotes obesity through both increased energy intake and reduced energy expenditure, but also by altering how nutrients are processed across the day. Human laboratory studies show that eating identical meals at night, compared with daytime, leads to higher postprandial glucose and insulin excursions, lower diet-induced thermogenesis, and altered lipid handling, even when sleep duration is controlled[20].

Shift workers, who often eat and work at biological night, are a natural experiment. Cohort studies and meta-analyses have found that rotating and night shift work are associated with increased risk of weight gain, central obesity, and T2D, with some evidence of a dose–response relationship based on years of exposure and frequency of nights worked[21]. The increased risk persists even after adjusting for traditional factors such as smoking and physical activity, indicating that circadian misalignment per se contributes to metabolic deterioration. Mechanistically, misalignment disrupts daily rhythms of insulin sensitivity. Rodent studies demonstrate a robust circadian rhythm in insulin action; experimental misalignment of light and feeding cycles reduces the amplitude of this rhythm and leads to global insulin resistance and increased adiposity[21]. In humans, controlled simulated shift-work protocols induce impaired glucose tolerance and decreased insulin sensitivity within days.

Adipose tissue is particularly sensitive to timing. Eating late at night or extending the daily eating window increases the overlap between postprandial insulin exposure and the biological night, when adipose clocks favor lipolysis and fasting metabolism. This conflict may promote adipocyte hypertrophy, inflammation, and altered adipokine secretion, contributing to systemic insulin resistance and ectopic fat deposition[22, 23]. Chronotype and social jet lag further modulate risk. Evening-type individuals often eat later and sleep later, but social and occupational demands may force early wake times, producing chronic misalignment between internal and external clocks[24]. Observational studies link greater social jet lag to higher BMI, worse glycemic control, and features of the metabolic syndrome, especially when combined with irregular meal timing[25].

Together, these data support a model in which circadian disruption interacts with caloric excess and sedentary behavior to produce obesity and insulin resistance. Beyond total energy intake, the phase at which calories are consumed relative to internal time influences metabolic fate, tipping the balance between storage and oxidation.

4. Clock Dysfunction and Glucose Homeostasis: From β-Cell Rhythms to HPA Axis Crosstalk

Glucose homeostasis depends on the precise coordination of insulin secretion, hepatic glucose output, and peripheral uptake across the day–night cycle. Circadian disruption impairs each node[26]. In pancreatic islets, core clock components regulate the timing and magnitude of insulin secretion. Mouse models with β-cell–specific Clock or Bmal1 deletion show impaired glucose-stimulated insulin secretion, disrupted phase relationships between glucose and insulin rhythms, and progressive hyperglycemia[27]. The islet clock influences expression of genes involved in insulin synthesis, ion channels, and exocytotic machinery, thereby coupling β-cell responsiveness to anticipated feeding times. When feeding is shifted or fragmented, islet clocks may become misaligned with actual nutrient availability, leading to mismatches between insulin demand and supply. The liver, as the primary source of endogenous glucose production, exhibits rhythmic gluconeogenesis and glycogenolysis under clock control. Disrupting hepatic clocks alters the timing of glucose output, blunting fasting–postprandial transitions and contributing to elevated nocturnal or early-morning glucose levels, a phenomenon relevant to dawn hyperglycemia in T2D[27]. The HPA axis forms an important link between circadian rhythms and glucose regulation. Cortisol secretion peaks in the early morning and declines through the day, a pattern that supports waking, mobilizes energy substrates, and counterbalances insulin. Circadian clocks in the SCN and adrenal glands regulate this rhythm. Chronic circadian disruption can flatten or shift cortisol rhythms, leading to inappropriate nocturnal glucocorticoid exposure, central fat accumulation, and hepatic insulin resistance. Recent reviews highlight HPA dysregulation as a key pathway by which circadian disruption accelerates T2D progression[28]. Peripheral insulin-sensitive tissues also depend on local clocks to match glucose uptake capacity to expected demand. Muscle clocks regulate GLUT4 translocation and mitochondrial oxidative function; adipose clocks coordinate insulin-mediated suppression of lipolysis with feeding times. Misalignment reduces the synchrony between insulin peaks and peripheral responsiveness, exacerbating hyperglycemia[29].

Clinical data support these mechanistic insights. Patients with T2D show reduced amplitude and altered phase of circadian rhythms in glucose, insulin, and free fatty acids. Polymorphisms in CLOCK and BMAL1 genes associate with increased T2D risk and insulin resistance independent of BMI[30]. Collectively, these findings indicate that clock dysfunction is not merely correlated with, but mechanistically involved in, the breakdown of glucose homeostasis.

5. Chrononutrition: Meal Timing, Time-Restricted Eating, and Metabolic Alignment

Chrononutrition, the study of how meal timing interacts with circadian rhythms, provides a practical interface between circadian biology and obesity/T2D prevention. Emerging evidence suggests that "when" we eat can significantly affect weight and glycemic control, independent of "what" and "how much" we eat[31].

Observational studies show that greater energy intake in the evening and night, skipping breakfast, and irregular meal timing are associated with higher BMI, worse insulin sensitivity, and increased T2D prevalence. Experimental trials in which calorie intake is redistributed earlier in the day, such as front-loading calories at breakfast and lunch, often demonstrate improved weight loss, lower postprandial glucose, and better insulin sensitivity compared with evening-heavy patterns, even at similar total calories[32]. Time-restricted eating (TRE), in which daily caloric intake is confined to a consistent 8–12 hour window aligned with the active phase, attempts to realign feeding–fasting cycles with circadian rhythms. Early TRE protocols, with eating windows occurring earlier in the day, have shown improvements in insulin sensitivity, blood pressure, and oxidative stress markers in individuals with obesity and prediabetes, sometimes with minimal weight loss[33]. By imposing a prolonged nightly fast and reducing late-night eating, TRE may restore the normal sequence of nocturnal catabolism and daytime anabolism.

Mechanistically, aligning meals with circadian phases may optimize β-cell responsiveness, enhance postprandial thermogenesis, and reduce conflict between dietary cues and fasting-programmed peripheral clocks. Earlier eating windows may also support better glycemic control because glucose tolerance is naturally higher in the biological morning than in the evening[34, 35]. However, not all TRE regimens are equivalent. Very late eating windows or highly variable day-to-day timing can reinforce rather than correct misalignment. Studies also differ in control of confounders such as sleep timing, caloric intake, and diet quality, emphasizing the need for carefully designed trials in T2D populations[36].

Overall, chrononutrition highlights that circadian alignment is a modifiable dimension of lifestyle, alongside diet composition and physical activity. For individuals at risk of T2D or with established disease, counseling that emphasizes regular meal timing, earlier main meals, and shortened eating windows aligned to the day's active phase may complement pharmacologic and behavioral interventions.

6. Therapeutic and Preventive Strategies to Restore Circadian–Metabolic Alignment

Recognizing circadian disruption as a convergence point for obesity and T2D opens multiple avenues for intervention. Behavioral strategies address upstream zeitgebers, while pharmacologic approaches target the clock machinery and downstream pathways[36]. Sleep regularity is fundamental. Interventions that increase sleep duration toward recommended levels, stabilize bed and wake times, and reduce social jet lag have shown modest improvements in insulin sensitivity and appetite regulation in short-term trials. Combining sleep extension with caloric restriction may yield additive benefits for weight loss and glycemic control[36].

Light is the primary entraining signal for the SCN. Morning bright-light exposure strengthens circadian phase and may support earlier sleep and meal timing, whereas evening light, particularly blue-enriched light from screens, delays circadian phase and suppresses melatonin. Practical recommendations include increasing daytime outdoor light exposure and minimizing bright light in the hour or two before bedtime, particularly for individuals with T2D and evening chronotypes[37, 38].

At the level of behavior, structured shift-work scheduling that minimizes rapid rotations, limits consecutive night shifts, and provides adequate recovery time can reduce circadian strain. Scheduled naps, appropriately timed meals, and strategic light exposure may partially mitigate metabolic risk in unavoidable night work, though evidence is still evolving[39]. On the pharmacologic front, experimental clock-modulating agents such as REV-ERB agonists, ROR modulators, and small molecules targeting casein kinase 1δ/ε have shown the ability to shift circadian phase, enhance amplitude, or reprogram clock-controlled metabolic genes in preclinical models. Some improve glucose tolerance and protect against diet-induced obesity, though safety and off-target effects remain major concerns for chronic use in humans[40].

Conventional metabolic drugs may also interact with circadian pathways. Metformin influences clock gene expression in the liver and possibly in the SCN; GLP-1 receptor agonists have diurnal variation in efficacy and may align better with morning administration in some contexts; SGLT2 inhibitors modify nocturnal glucose and natriuretic rhythms. Optimizing dosing time, or chronopharmacology, is an emerging concept that could increase efficacy or reduce side effects by synchronizing drug action with target rhythms[41].

Taken together, these approaches suggest that restoring circadian–metabolic alignment will likely require multimodal strategies: regular sleep–wake schedules, light hygiene, chrononutrition, and potentially time-optimized medications. Such interventions may be especially impactful in high-risk groups such as shift workers, individuals with strong evening chronotypes, and patients with early T2D and marked glucose variability.

7. Circadian-Informed Precision Medicine for Obesity-Related Diabetes: Opportunities and Challenges

As awareness of circadian contributions to metabolic disease grows, the question becomes how to integrate this dimension into precision prevention and treatment of obesity-related T2D. One opportunity lies in circadian phenotyping. Wearable devices and smartphone apps can capture rest–activity rhythms, light exposure, and even eating timing, providing objective markers of circadian health[42]. Combined with questionnaires on chronotype and shift-work history, these data could identify individuals with significant misalignment who might benefit most from circadian-focused interventions. Recent statements by cardiovascular and metabolic societies underscore circadian health as a key yet underutilized determinant of cardiometabolic risk[42].

Another opportunity is biomarker development. Rhythms in glucose, insulin, cortisol, melatonin, and clock gene expression in blood cells may help detect circadian disruption and monitor response to interventions. Genetic variants in CLOCK, BMAL1, and other clock genes, which have been linked to T2D risk and insulin resistance,

might inform individualized recommendations on meal timing or shift-work tolerance, though robust clinical algorithms remain to be developed[43].

Chronotherapeutic strategies offer a third pillar. Adjusting the timing of existing treatments, such as administering insulin, GLP-1 receptor agonists, or antihypertensives at times that align with endogenous rhythms, may enhance efficacy and safety, particularly in patients with marked diurnal variability in glucose or blood pressure. However, rigorous trials are needed to define optimal schedules in diverse patient populations[44]. Significant challenges remain. Circadian interventions are inherently behavioral and must be adapted to social, occupational, and cultural contexts; shift work, caregiving, and socioeconomic constraints often limit the ability to maintain ideal schedules. Inter-individual variability in chronotype means that "one-size-fits-all" timing prescriptions may be suboptimal. Moreover, disentangling the independent effects of circadian disruption from confounding factors such as sleep deprivation, diet quality, and stress requires sophisticated study designs[44].

Despite these challenges, the convergence of obesity and diabetes pathogenesis on circadian disruption suggests that ignoring this dimension leaves a substantial modifiable risk factor unaddressed. Circadian-informed care does not replace established lifestyle and pharmacologic therapies but can enhance them by ensuring they act in temporal harmony with the body's intrinsic rhythms.

CONCLUSION

In summary, circadian rhythm disruption is a mechanistic bridge linking modern behaviors to obesity and T2D. Through misalignment of central and peripheral clocks, altered hormonal rhythms, and maladaptive timing of sleep and meals, circadian dysregulation undermines glucose homeostasis and promotes weight gain. Recognizing and correcting this misalignment via sleep and light hygiene, chrononutrition, shift-work optimization, and potentially clock-directed pharmacology represents a promising frontier in the prevention and management of obesity-related diabetes.

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