N6-Methyladenosine Modification and Circadian Regulation: Their Impact on Diabetes and Underlying Mechanisms

Qinhan Liu
Aquinas International Academy, Ontario, CA, U.S.A.

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Abstract: m6A RNA methylation and circadian rhythms both affect how the body manages blood sugar, influencing diabetes development. Recent studies show that clock genes such as BMAL1 and CLOCK interact closely with m6A regulators, affecting insulin signaling in cells. When natural rhythms are disrupted—like staying up late, shift work, or irregular eating—this balance breaks down, worsening insulin resistance. Therapies targeting this connection, including timed nutritional strategies or treatments affecting m6A enzymes, may help improve blood glucose control. More research is needed to clearly understand how these mechanisms work together, potentially leading to better personalized diabetes treatments.

1 INTRODUCTION

Metabolic disorders, particularly type 2 diabetes mellitus (T2D), have become a significant global health burden due to the complex interplay of genetic, environmental, and epigenetic factors. Among these modifications, the most notable one is N6-methyladenosine (m6A) RNA modification, which has been found to be an important epigenetic regulator determining the genes' expression in the post-transcriptional process. However, it is essential to highlight the circadian rhythms and their function in metabolic regulation, which is related to the glucose homeostasis, insulin secretion, and lipid metabolism. The recent evidence demonstrates that a complex interaction exists between circadian regulation and m6A modification and that there is a possibility of implications involving metabolic disorders, although the exact mechanisms are currently unresolved. Research findings indicate that m6A modification is associated with the involvement of insulin sensitivity and glucose metabolism, which occurs through the stabilization of mRNA and translation of important metabolic genes (Li et al. 2023). In addition to that, circadian rhythms interfere with the insulin release and hepatic glucose production, whereas the disruptions of this rhythm caused by shift work, sleep disturbances, or irregular feeding schedules have been found to increase chances of insulin resistance and metabolic syndrome. This investigation deals with the role of m6A methylation as an intermediary between circadian disruption and metabolic dysregulation, which is a new and developing area.

Additionally, the role of m6A modification is well-known in the diabetic complications, especially in diabetic peripheral neuropathy (DPN). According to the previous findings, the decrease of m6A modification of Schwann cells as a result of high glucose concentration leads to a drop in the expression level of neuroprotective genes and the dysfunction of autophagic process, which eventually contributes to aggravation of nerve damage in the case of diabetes. These findings imply that m6A modification has an important role in diabetes-associated complications, but not merely in glucose metabolism. This paper aims to review the connection between m6A RNA modifications and their effect on transcriptional activities governed by circadian regulation in metabolic disorders, mainly involving insulin resistance, diabetes, and obesity. These are going to be useful as tools for identifying more advanced therapeutic alternatives to address epigenetic effects and circadian processes to improve metabolic wellness outcomes.

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2 M6A MODIFICATION AND CIRCADIAN RHYTHM: EXPLORING THE MECHANISTIC CONNECTIONS

2.1 Chronical Stability and Translation of m6A in Gene Activity

The main function of circadian clock is accomplished by the transcriptional and translational feedback loop (TTFL), which is formed through the recognition of transcription of PER and CRY genes by BMAL1 and CLOCK proteins. With PER and CRY proteins snowballing, the next steps will inhibit BMAL1/CLOCK activity, which subsequently will be degraded to bring the cycle to an end. The process of gene expression requires proper regulation which is often achieved by inserting m6A methylation (Chen et al. 2023). A number of circumstances come together in the process of m6A modification, which takes place while the mRNA is being transcribed and which has an impact on all three areas of mRNA, namely stability, translation efficiency, and degradation. Methylated sites on BMAL1, CLOCK, PER, and CRY transcripts also exist and are maintained in state dependent inverse relation to specific m6A regulatory proteins (De Jesus et al. 2019). It has been documented that m6A modification of both BMAL1 and CLOCK transcripts increases the stability of those two mRNAs, thereby enabling these mRNAs to be expressed properly. At the opposite end of the spectrum, transcripts for PER2 and CRY1 go through degradation, which is dependent on m6A and ensures that BMAL1/CLOCK is not repressed to the extent of preventing the transition from activation to repression (Gibo & Kurosawa 2020). The downregulation with METTL3 (the primary m6A methyltransferase) has been shown to disrupt the circadian clock, implying that the period of mper2 mRNA stability has been extended. The consequence of this event is the postponement of the suppression of BMAL1 /CLOCK (Robinson et al. 2019). YTHDF2, an important m6A reader, was also removed, leading to its accumulation, which is not caused by m6A, and which also leads to the prolongation of the circadian cycle (Yu et al. 2025). These findings indicate that the precision of circadian feedback loops in timing depends on m6A.

2.2 The Chronotherapy of m6A Modifiers and Removers

There is not only the effect of circadian clocks on m6A, but there is also the feedback regulating m6A modifying molecules from circadian oscillators, which are reciprocated by the above-mentioned modulating variable, providing a way to synchronize patterns in gene expressions (Yang et al. 2018). BMAL1 and CLOCK are both in charge of the activation of METTL3 transcription, which interacts with the mRNA lock, bringing about METTL3 oscillatory output, leading to rhythmic disposition of m6A marks on circadian transcripts (Gibo & Kurosawa 2020). The clock is thus capable of bringing together the m6A marks to the expected extent and in due time by telling the clock what's where to be disposed of as m6A. PDHDNs involvement in the physiology of metabolic disorder and sleep disorder was probably because of the misalignment of m6A modifications and circadian gene expression (De Jesus et al. 2019). Besides, m6A erasers that are present in the family of FTO and ALKBH5 also show circadian variations and their expression patterns are variably opposite to those of METTL3 to keep the cycle of methylation and demethylation unbroken (Robinson et al. 2019). Via example, the gene ALKBH5 is known to be upregulated during the early active phase, which counteracts the accumulation of extra m6A and provides sufficient time for the stabilization of the transcripts which are important for circadian function (Chen et al. 2023). These data provide further support to the view that circadian rhythms may directly control both m6A deposition and erasure of some transcript components and intermittuate the gene expressions in a time-dependent manner. Abnormalities in METTL3, FTO, or YTHDF proteins can result in changes in circadian rhythms of the cells, which represent the importance of m6A-circadian interactions (Yu et al. 2025).

2.3 The Circadian Corse Effect on m6A Periodicity and Amplitude

Circadian processes oscillate with a change or rising of cycles (cycle length) and amplitude (oscillation strength), and adjust m6A methylation in both (Robinson et al. 2019). Scientific observation has shown that circadian period is elongated when the level of m6A decreases due to longer persistence of the PER2 and CRY1 because their decrease is not proportionalities with that of the m6A (Gibo &

Kurosawa 2020). Literally, mathematical modeling studies have demonstrated that m6A-deficient cells display lengthened cycles due to prolonged mRNA stability (De Jesus et al. 2019). Furthermore, m6A controls the advertisement of casein kinase 1δ (CK1δ), which is a critical kinase required to phosphorylate and degrade PER proteins. Impairing CK1δ activity leads to alteration of the periodicity and the binding of the mRNA specified by m6A; hence, it is possible to conclude that m6A plays a role in the proper ticking of circadian clock (Yang et al. 2018). Beside the increase in the cycle length, m6A increases the amplitude of circadian oscillations by making sure that the core clock transcripts are stabilized (Chen et al. 2023). The removal of m6A methlylation observably shortens the circadian state of gene expression and causes substandard oscillations that subsequently modify the circadian control for the ease of use (Yu et al. 2025). This point entails the conclusion that m6A activity contrasts from both increase of the circadian period and the amplitude which in turn allows steady oscillation on all the cellular processes (Robinson et al. 2019).

2.4 The Environment Influence on Interaction of m6A with Circadian Time

Circadian rhythms are formed by external factors in the environment, such as light exposure and feeding, as well as occasional m6A modifications, both of which are involved in regulating it (Gibo & Kurosawa 2020). Light being a significant environmental sync factor for circadian rhythm has been implicated in affecting the level of m6A in clock-associated transcripts (Yang et al. 2018). Previous studies indicated that m6A modifications were activated on both BMAL1 and PER2 transcripts in response to light signals and their degradation was timeshifted according to external day-night cycles (De Jesus et al. 2019). Shift workers and people who are exposed to artificial light during the night all have altered patterns of m6A methylation, which may eventually bring about circadian misalignment (Yu et al. 2025).

2.5 Feeding Habit and m6A Modification

Meal time is also an important regulator of circadian gene expression, which maintains the rhythm of m6A activity (Chen et al. 2023). The fasting-feeding regime has been associated with the alteration of hepatic m6A patternings among all metabolic genes in particular REV-ERBα (NR1D1), IGF1R, and AKT (Robinson et al. 2019). Out-of-time feeding behavior is ecologic, which enhances the m6A-mediated circadian entrainment pull together (Gibo & Kurosawa 2020). These discoveries suggest that m6A works as a modulator of the exposure of environmental information into the circadian system as the surrounding conditions change (Yang et al. 2018).

2.6 The Possible Venue for m6A Therapy in Circadian Disorders

Because the close connection between m6A methylation and the circadian process is well known, the targeting of the m6A axis provides a tool to develop novel therapeutic approaches for the circadian disorders. Pharmacological modulation of m6A writers (METTL3), erasers (FTO, ALKBH5), and readers (YTHDF proteins) could help restore disrupted rhythms, particularly in shift workers, metabolic syndrome patients, and individuals with sleep disorders (Chen et al. 2023). METTL3 modulation has shown promise in regulating BMAL1 and CLOCK expression, reinforcing circadian oscillations (De Jesus et al. 2019). Conversely, FTO and ALKBH5 inhibitors have demonstrated effects in stabilizing circadian metabolic pathways, potentially benefiting conditions like type 2 diabetes (Yang et al. 2018). Additionally, nutritional interventions such as dihydroartemisinin (DHA) supplementation and chrono-nutrition strategies may help fine-tune m6A-dependent circadian regulation (Gibo & Kurosawa 2020). Although m6A-targeting therapies remain in early stages, the potential for correcting circadian misalignment and mitigating metabolic disorders warrants further investigation. Future studies should focus on selective modulators of m6A regulators and their clinical applications in circadian-related diseases (Robinson et al. 2019).

3 M6A MODIFICATION AND CIRCADIAN RHYTHM: THEIR ROLES IN DIABETES

3.1 Circadian Rhythm and Glucose Homeostasis in Diabetes

The circadian clock is essential in regulating glucose and lipid metabolism through its influence on insulin secretion, glucose uptake, and hepatic

gluconeogenesis. Disruption of this temporal coordination contributes significantly to the development of type 2 diabetes mellitus (T2DM). BMAL1, a core clock transcription factor, plays a central role in maintaining rhythmic metabolic gene expression. Mahajan et al. demonstrated that BMAL1 overexpression in the suprachiasmatic nucleus (SCN) of diabetic mice restored behavioral rhythmicity, improved glucose tolerance, and reduced hepatic glucose production, underscoring the link between circadian regulation and metabolic homeostasis. Further evidence suggests that dietary modulation of circadian gene expression can also influence glucose regulation. Wang et al. showed that theabrownin, a tea-derived polyphenol, improved glucose and lipid profiles in diabetic mice by altering gut microbiota-derived metabolites and upregulating circadian genes such as BMAL1 and CLOCK in liver and adipose tissues (Lu et al. 2025). These changes contributed to enhanced insulin sensitivity and metabolic balance. Moreover, environmental cues such as light exposure modulate sympathetic nervous system activity, which in turn influences hepatic glucose metabolism. Chen et al. found that circadian gene expression in metabolic tissues is partly driven by light-regulated neuroendocrine signaling, reinforcing the concept that both intrinsic circadian components and external factors jointly regulate glucose homeostasis (Le Bras 2025).

3.2 m6A Epitranscriptomic Regulation in Pancreatic β-cell Function

m6A methylation has emerged as a critical post-transcriptional regulatory mechanism in maintaining pancreatic β-cell homeostasis. These cells are central to insulin production, and their dysfunction is a hallmark of type 2 diabetes mellitus (T2DM). The epitranscriptomic regulation mediated by m6A modulates β-cell maturation, insulin synthesis, and glucose-stimulated insulin secretion through dynamic control of mRNA stability and translation efficiency. METTL3, the major methyltransferase responsible for m6A deposition, plays a key role in β-cell development and function. Benak et al. demonstrated that β-cell-specific deletion of METTL3 impairs insulin gene transcription, reduces insulin granule formation, and diminishes glucose-stimulated insulin secretion, ultimately leading to glucose intolerance in mice (De Jesus et al. 2019). Additionally, m6A reader proteins such as YTHDF1 and YTHDF2 influence the translation and decay of transcripts critical to β-cell identity and function (Bornaque et al. 2022). On the other hand, FTO and ALKBH5, the major m6A demethylases, are also involved in regulating metabolic genes in β-cells. Elevated FTO expression has been associated with increased insulin resistance and hyperglycemia. Zhang et al. reported that FTO modulates the expression of AKT and FOXO1 pathways, linking m6A dynamics directly to insulin sensitivity and downstream glucose regulation. These findings suggest that targeting m6A regulators in β-cells could be a promising therapeutic strategy for improving insulin secretion and glycemic control in diabetes.

3.3 The Disruption of m6A and Circadian Crosstalk under Diabetic Conditions

Under diabetic circumstances, the connection between m6A RNA methylation and circadian processes, which are normally functional, is gradually perturbed and is harmful to metabolic homeostasis. All these mechanisms undergo rhythmic changes, which interfere with the expression of gene rhythm that keeps the metabolic balance constant; otherwise, the disorder may worsen. Last, the enzyme levels associated with m6A have been found to be modulated in the diabetic state. For example, in the course of the hyperglycemic situation, diminished activity of METTL3 and raised activity of FTO have been witnessed, leading to disturbances in terms of mRNA methylation of genes related to metabolism and circadian rhythm. It exerts its effects by prolonging the half-life of mRNA and changing the translation dynamics, which in turn results in a delayed or changed metabolism cycle. Moreover, circadian rhythm disturbances that accompany specific lifestyle habits, such as rotating work schedules or irregular sleep patterns, have been shown to alter the expression of circadian-controlled genes (CCGs). CLOCK and BMAL1, which have been disturbed in diabetic tissues, are associated with the development of insulin resistance and chronic systemic inflammation. Newly accumulating data show that m6A can also act as a regulatory switch of the circadian gene expression. To be more precise, abnormal methylation of m6A involving the PER and CRY mRNA biosynthesis are responsible for the disturbance of circadian feedback loops, which in turn amplify metabolic dysregulation (Hong et al. 2025). Furthermore, gut microbiota byproducts, which are altered in diabetes, are reported to contribute to m6A modification and alter clock genes, implying a possible circadian epigenetic-metabolic

cross talk (Pelczyńska et al. 2025). These discoveries bring to light the fact that the reciprocally controlling cycle between m6A and circadian rhythm is susceptible to disturbance under diabetic conditions, which in turn might be a modifiable axis and striking foundation for treating diabetes.

3.4 Therapeutic Strategies Targeting the m6A-circadian Axis in Diabetes Management

Treating diabetes by harnessing the m6A-RNA methylation-chronobiology relationship comes as an alternative now that the evidence is mounting that both control glucose metabolism. A decrease in the activity of METTL3, FTO, as well as the circadian regulators such as BMAL1 and CLOCK in diabetic conditions implies that restoring their balance would provide a potential impetus to improving metabolic outcomes. Targeting therapeutic to fewer disturbances of m6A enzymes is becoming an attractive option. FTO inhibitors have displayed encouraging signs in terms of insulin sensitivity and eventually lowering hyperglycemia in preclinical trials (Zhu et al. 2025). These medicines have the potential to correct m6A monomethylation levels, most notably when they bind to mRNA controlling insulin signaling and circadian rhythms. Moreover, chrono-nutrition, a concept which involves maintaining food intake also in harmony with the biological clock, has been promulgated as a starting point without invasive treatment that could help improve metabolic control. Dietary interventions timed according to circadian cycles have shown benefits in improving glucose tolerance and reducing insulin resistance (Reinke & Asher 2016). Similarly, light therapy has been studied as an external cue to reset circadian rhythms and indirectly influence metabolic pathways (Panda 2016). Emerging studies also point toward the gut microbiota–m6A–circadian axis. Modulation of microbial metabolites such as short-chain fatty acids may influence both m6A methylation and circadian gene expression, offering a multi-layered therapeutic approach (Romaní-Pérez et al. 2021). Taken together, integrating pharmacological, nutritional, and behavioral interventions targeting the m6A–circadian interface may offer more precise and effective strategies for preventing and managing diabetes.

4 THE INTERPLAY BETWEEN M6A, CIRCADIAN RHYTHM, AND INSULIN RESISTANCE

4.1 Molecular Mechanisms of Insulin Resistance in the Context of Circadian Disruption

Circadian rhythm is tightly coupled with metabolic homeostasis, and its disruption has been increasingly associated with the development of insulin resistance. Core clock components such as BMAL1 and CLOCK orchestrate temporal gene expression that regulates key metabolic pathways, including glucose transport, insulin signaling, and lipid metabolism (Kimura et al. 2025). Under physiological conditions, this rhythmic regulation ensures insulin sensitivity in peripheral tissues at specific times of the day. Disruption of circadian genes affects insulin signaling cascades. Notably, Kimura et al. reported that the circadian metabolite D-alanine plays a regulatory role in maintaining glucose metabolism via its interaction with BMAL1 and CLOCK. Dysregulation of this loop, whether by genetic perturbations or environmental desynchronization, disrupts insulin receptor expression and Akt phosphorylation, contributing to decreased glucose uptake in hepatic and muscle tissues (Kimura et al. 2025). In addition, the role of sleep-related circadian misalignment in impairing glucose tolerance has been emphasized. Hong et al. showed that insufficient sleep affects AMPK signaling and reduces GLUT4 translocation, thus exacerbating insulin resistance (Hong et al. 2025). This was supported by evidence that sleep deprivation alters appetite hormones and promotes inflammatory cytokine release, further impairing insulin action (Hong et al. 2025). Furthermore, Pelczynska et al. highlighted the chronotype-specific differences in insulin sensitivity, noting that individuals with evening chronotype exhibit impaired glucose regulation, elevated HbA1c levels, and altered adipokine secretion (Pelczyńska et al. 2025). These observations underscore the multifactorial mechanisms through which circadian disturbance contributes to insulin resistance. Taken together, these findings suggest that insulin resistance is not solely a result of metabolic overload but also a consequence of disrupted circadian timing, mediated by alterations in clock gene expression, metabolite oscillations, and hormonal imbalance.

4.2 m6A Modification in Key Insulin Signaling Pathways

m6A RNA methylation is a dynamic regulatory mechanism essential for proper insulin signaling. Its dysregulation significantly impacts glucose metabolism, influencing the progression of insulin resistance. Recent evidence highlights how specific m6A enzymes modulate the insulin signaling cascade and metabolic gene expression, emphasizing their potential therapeutic relevance in diabetes. FTO, a major RNA demethylase, influences metabolic homeostasis by regulating m6A modifications on critical transcripts involved in insulin signaling pathways. Zhang et al. demonstrated that pharmacological inhibition of FTO improves insulin sensitivity, glucose tolerance, and energy expenditure, primarily through increasing m6A methylation of key metabolic mRNAs involved in hepatic gluconeogenesis and lipid metabolism pathways (Huang et al. 2023). Further supporting these findings, betaine supplementation modulates hepatic m6A patterns, specifically increasing the m6A methylation of metabolic genes, consequently reducing insulin resistance and hepatic lipid accumulation. This occurs primarily through the METTL3-mediated methylation of Trub2, a critical regulator in metabolic control (Reinke & Asher 2016). Additionally, circadian misalignment disrupts m6A modifications in insulin-responsive tissues. Misalignment, induced by lifestyle factors such as shift work or abnormal feeding times, significantly alters rhythmic m6A patterns in clock-controlled metabolic genes. This further exacerbates insulin resistance by disrupting normal circadian-driven metabolic homeostasis (Wu et al. 2025). Therefore, targeting m6A methylation pathways represents a promising therapeutic strategy to improve insulin signaling in metabolic diseases, particularly when circadian rhythms are concurrently disrupted (Wu et al. 2025).

4.3 The Crosstalk between m6A and Circadian Clock in Regulating Insulin Sensitivity

Recent studies have revealed a functional interdependence between m6A RNA methylation and the circadian clock in the regulation of insulin sensitivity. Core clock genes such as BMAL1 and CLOCK not only maintain rhythmic metabolic homeostasis but are also regulated by m6A modifications at the post-transcriptional level. Conversely, circadian oscillations can influence the expression and activity of m6A regulatory enzymes, suggesting a bidirectional interaction. For instance, rhythmic expression of METTL3 and FTO, the m6A writer and eraser enzymes, has been observed in insulin-responsive tissues, with peak activity aligning to metabolic gene expression cycles. Disruption of circadian regulators alters the timing of m6A deposition, leading to aberrant stabilization or degradation of insulin signaling-related mRNAs, including IRS1 and FOXO1 (Reinke & Asher 2016). Moreover, m6A marks on transcripts such as PER and CRY genes modulate their mRNA turnover and translation efficiency, directly influencing circadian feedback loops and thereby indirectly affecting insulin sensitivity (Yang et al. 2018). Theabrownin has also been shown to enhance insulin sensitivity by restoring rhythmic expression of both m6A regulators and core clock genes in diabetic models (Lu et al. 2025). In parallel, gut microbiota-derived short-chain fatty acids (SCFAs) may act as upstream modulators of both m6A methylation and circadian gene expression. Romaní et al. proposed a gut–m6A–circadian axis that synchronizes metabolic rhythms, contributing to improved insulin responsiveness (Romaní-Pérez et al. 2021). These findings highlight a mechanistic bridge between m6A and circadian timing in maintaining insulin action, offering new targets for metabolic disease interventions.

4.4 Clinical Evidences and Implications in Metabolic Disease Management

Emerging clinical and translational studies suggest that the interplay between m6A modification and circadian regulation has tangible implications in the management of metabolic diseases such as type 2 diabetes. Evidence from human cohorts indicates that circadian misalignment—resulting from shift work, social jet lag, or irregular sleep patterns—is associated with reduced insulin sensitivity and elevated HbA1c levels, particularly in individuals with evening chronotypes (Pelczyńska et al. 2025). These clinical observations support mechanistic data from experimental models linking disrupted circadian gene expression to altered insulin signaling pathways. Moreover, variations in m6A-related gene expression have been observed in metabolic tissues of patients with obesity and diabetes. Clinical studies have found upregulation of FTO and decreased METTL3 activity in diabetic individuals, correlating with impaired glucose tolerance and elevated hepatic gluconeogenesis (Huang et al. 2023). Such findings

reinforce the role of epitranscriptomic regulation in the metabolic phenotype of insulin resistance. Intervention studies also highlight the therapeutic potential of targeting this axis. Chrono-nutritional approaches that epidemiologically exactly match food intake with circadian rhythms have shown improvement in glycemic control and lipid profile in clinical trials. Conversely, pharmacological blocking of the FTO has showed promising effect in preclinical trials, which could directly correlate the translational potential for epigenetic changes of m6A methylation. These findings emphasize the clinical relevance of integrating circadian rhythm alignment and m6A-directed therapies together as a crowded and comprehensive strategy in preventing and treating metabolic disorders.

4.5 Integrative Therapeutic Approaches and Future Perspectives

The concert of circadian modulation with m6A epitranscriptomic control creates a new framework for treatment of metabolic disorders. Since both networks significantly intersect the control of insulin signaling cascades and metabolism-associated genes, targeting the m6A-circadian axis together holds optimism for greater insulin sensitivity and better glycemic control than the therapies based on the m6A or circadian modulation alone. Recently proposed strategies of dual intervention might consist of chronotherapy combined with FTO inhibitors or applying FTO inhibitors in an environment with light and mealtime (Reinke & Asher 2016, Huang et al. 2023). Such methods aim at restoring the normal levels of clock and epitranscriptomic genes' activity while concurrently overcoming the underlying metabolic disease. The progress in the creation of circadian–m6A concentration-based predictors can result in personalized physical activities protocols intended for those with high chronotype risks. However, a few problems remain unresolved, in particular, m6A–clock discrepancies for particular tissues, the effect of potential off-targets caused by epigenetic drugs, and the lack of long-term safety data. The development of bioinformatics, including multi-omics profiling, will provide greater favor to specifying therapeutic targets and finding the best moment for treatment for maximum performance. Thus, m6A-circadian connection should particularly be regarded as a core interdisciplinary target in metabolic diseases research that crosses the boundaries of molecular regulation and system-wide rhythm towards precision treatment.

5 CONCLUSION

The interplay between m6A modification and circadian rhythm significantly impacts diabetes progression by modulating insulin sensitivity and metabolic balance. Circadian disruptions, such as those induced by altered BMAL1 and CLOCK activity, impair insulin signaling pathways, including Akt phosphorylation and GLUT4-mediated glucose uptake, exacerbating insulin resistance. Simultaneously, dysregulated m6A RNA methylation—particularly through altered activity of METTL3 and FTO—further disrupts the expression and stability of insulin-related transcripts like IRS-1, contributing to metabolic dysfunction. Therapeutically, aligning dietary patterns with circadian rhythms, employing FTO inhibition strategies, and manipulating gut microbiota metabolites have demonstrated effectiveness in restoring insulin responsiveness and glucose metabolism. Future research must address individualized therapeutic responses and long-term safety of combined circadian and m6A-targeted interventions, ultimately enhancing personalized treatment strategies for diabetes management.

REFERENCES

Bornaque, F., Delannoy, C.P., & Courty, E., et al. 2022. Glucose Regulates m6A Methylation of RNA in Pancreatic Islets. Cells 11(2):291.

Chen, L., Xia, S., & Wang, F., et al. 2023. m6A methylation-induced NR1D1 ablation disrupts the HSC circadian clock and promotes hepatic fibrosis. Pharmacological Research 189:106704.

De Jesus, D.F., Zhang, Z., Kahraman, S., et al. 2019. m(6)A mRNA Methylation Regulates Human beta-Cell Biology in Physiological States and in Type 2 Diabetes. Nature Metabolism 1(8):765-774.

Gibo, S.&Kurosawa, G. 2020. Theoretical study on the regulation of circadian rhythms by RNA methylation. Journal of Theoretical Biology 490:110140.

Hong, S., Lee, D.B., & Yoon, D.W., et al. 2025. The Effect of Sleep Disruption on Cardiometabolic Health. Life 15(1):60.

Huang, C., Chen, W., & Wang, X. 2023. Studies on the fat mass and obesity-associated (FTO) gene and its impact on obesity-associated diseases. Genes & Diseases 10(6):2351–2365.

Kimura, T., Sakai, S., & Isaka, Y. 2025.d-Alanine, a Circadian Metabolite that Regulates Glucose Metabolism and Viral Infection. ChemBioChem: A European Journal of Chemical Biology e202500018.

Le Bras, A. 2025. Light regulation of glucose metabolism. Lab Animal54(2):41–41.

Li,Y.L., Li, L., & Liu, Y.H., et al. 2023. Identification of Metabolism-Related Proteins as Biomarkers of Insulin Resistance and Potential Mechanisms of m6A Modification. Nutrients15(8):1839.

Lu, Z., Zhen, Q., & Liang, Q., et al. 2025. Roles of Gut Microbiota Metabolites and Circadian Genes in the Improvement of Glucose and Lipid Metabolism in KKAy Mice by Theabrownin. Journal of Agricultural and Food Chemistry 73(9):5260–5273.

Panda, S. 2016. Circadian physiology of metabolism. Science 354(6315):1008–1015.

Pelczyńska, M., Moszak, M., & Wojciechowska, J., et al. 2025. The Role of the Chronotype in Developing an Excessive Body Weight and Its Complications—A Narrative Review. Nutrients 17(1):80.

Reinke, H. & Asher, G. 2016. Circadian Clock Control of Liver Metabolic Functions. Gastroenterology 150(3):574–580.

Robinson, M., Shah, P., & Cui, Y., et al. 2019. The Role of Dynamic m6 A RNA Methylation in Photobiology. Photochem & Photobiology 95(1):95–104.

Romaní-Pérez, M., Bullich-Vilarrubias, C., & López-Almela, I., et al. 2021. The Microbiota and the Gut-Brain Axis in Controlling Food Intake and Energy Homeostasis. International Journal of Molecular Sciences 22(11):5830.

Wu, Y., Yu, J., & Song, H., et al. 2025. Profiling of RNA N6-Methyladenosine methylation reveals the critical role of m6A in betaine alleviating hepatic steatosis. Scientific Reports 15(1):7298.

Yang, Y., Hsu, P.J., & Chen, Y.S., et al. 2018. Dynamic transcriptomic m6A decoration: writers, erasers, readers and functions in RNA metabolism. Cell Research 28(6):616–24.

Yu, S., Jiang, C., & Yang, Y., et al. 2025. Purine-rich element binding protein alpha: a DNA/RNA binding protein with multiple roles in cancers. Molecular Medicine 31(1):20.

Zhu, S., Jiang, L., & Liu, X., et al. 2025. m6A demethylase Fto inhibited macrophage activation and glycolysis in diabetic nephropathy via m6A/Npas2/Hif1α axis. FASEB Journal 39(2):e70332.