Circadian Glucocorticoid Signaling Promotes the Use of Cardiac Glucose via the Regulation of Intrinsic Cardiomyocyte Genes

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Abstract

Treatments for cancer have advanced greatly lately, yet the side effects can still reduce what the patient enjoys in life. Because of this, chronopharmacology now exists to help match cancer treatments to the patient's circadian cycles. It investigates how the circadian clock relates to cancer susceptibility, the actions of clock genes in both cancer prevention and suppression and how timed medications might improve specific types of cancer therapies. Additionally, it reviews how findings on circadian rhythms can be used in palliative medicine and hormone treatments, as well as how treatments can be adjusted to meet the needs of each patient. Regulatory and ethical aspects related to chronopharmacology are studied. By relying on chronopharmacology, doctors may provide better and more personalized cancer treatments that help improve patient quality of life.

Keywords: ***Chronopharmacology, Glucocorticoids, Circadian Rhythm, Cardiomyocyte, Glucose Metabolism, Glucocorticoid Receptor (GR), Heart Metabolism, Gene Transactivation, Metabolic Regulation, Chronotherapy, Cardiac Energetics.***

1.Introduction

Diabetes mellitus is affecting more people than ever and cardiovascular issues are still the biggest reason behind death and poor health outcomes among those with diabetes. As a result of diabetes, metabolic changes in the body are considered especially dangerous for the heart and may result in diabetic cardiomyopathy, a disorder that involves impaired heart metabolism and steady worsening of its functions(1). Although the heart disease in diabetes has various features, chiefly it is caused by poor handling of glucose and reliance on an abnormal metabolism of lipids. Unable to use energy efficiently results in stress for cells and weakened heart function.

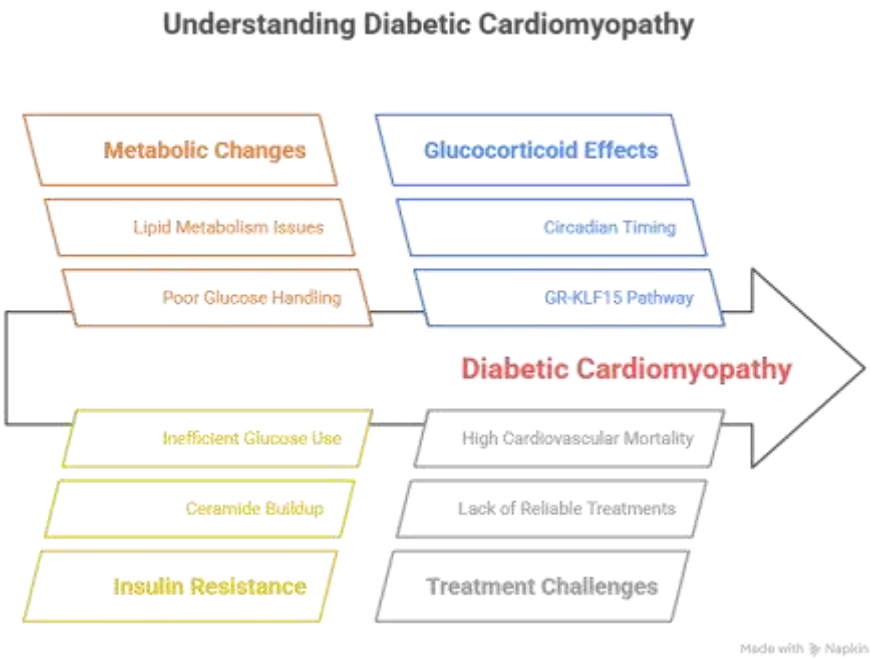

FIGURE 1 Understanding Diabetic Cardiomyopathy

This form of diabetes, more than any other, fuels insulin resistance in heart cells, making it hard for them to use glucose correctly. The added difficulty of bad glucose metabolism comes from the buildup of ceramides, lipids that disturb insulin signals and also negatively affect the heart. While we have made huge progress in learning about the molecules involved in diabetic heart disease, reliable treatments to repair metabolism and heart functions are still lacking. Despite the recent success of SGLT2 inhibitors and GLP-1 receptor agonists, 40% of diabetes deaths globally are caused by cardiovascular disease.

These steroid hormones called glucocorticoids have recently become known for their complicated roles in how the heart uses fuel. In the presence of glucocorticoids, the GR, a transcription factor, mediates their influence on cells such as cardiomyocytes. Specifically, the GR has a strong influence over using nutrients and keeping energy levels in balance. Current studies reveal that the circadian clock governs the activity of the GR in heart cells.

Circadian timing of glucocorticoid signaling adds a time element to the effects of drugs on the heart, showing that the moment these drugs are taken matters. Giving prednisone in the morning reduces cardiac problems, but taking it at night can lessen the drug's help. The interaction of the GR with KLF15 which is a circadian metabolism-related transcription factor, is why this phenomenon appears. Both proteins in the GR-KLF15 axis play a role in changing how the heart uses substrates, functions and responds to insulin(2).

While circadian timing of glucocorticoid effects is now understood, the exact targets in the GR-KLF15 pathway that influence metabolism in the heart are not fully known. A lack of understanding is particularly important in diabetic cardiomyopathy, since metabolic problems are common and treatment is not completely successful at the moment. Recognizing the effect of when glucocorticoid therapy is given on cardiomyocyte metabolism could lead to medicine that targets the biological clock and boosts treatment benefits.

To reach this goal, new studies have investigated both gene expression and epigenetic patterns in genetically altered mice in which cardiomyocytes do not produce GR or KLF15. These methods have pointed out Adipor1 and Mpc1 and Mpc2 as the main downstream targets of the GR-KLF15 complex that control glucose uptake and oxidation. When activated, Adipor1 increases cells' ability to use glucose by helping to reduce ceramide molecules, reducing lipotoxicity and promoting flexibility in the metabolism. The pyruvate carrier in mitochondria is important to transport pyruvate into those organelles for the effective oxidation of glucose and making ATP.

As a result, timed doses of glucocorticoids during daylight hours in obese diabetic mice show that the therapy can restore glucose metabolism and enhance heart function, demonstrating the promise of chronopharmacology for treating metabolic heart disease. Combining the knockdown of GR and KLF15 removes these benefits, showing just how much they influence glucocorticoid results. It is clear from these results that universal cardiotoxicity from glucocorticoids is not accurate and that circadian-based mechanisms can help protect the heart instead.

This introduction points out that using chronobiology may now become a part of treating diabetic cardiomyopathy and other metabolic cardiovascular diseases. By working with the natural circadian rhythm of the heart and controlling when glucocorticoids are given, researchers could help prevent heart failure in people with diabetes. Further study of the GR-KLF15 axis and what it leads to may find new medicines we can use and better plans for treating the heart's complex metabolism(3).

2. Decoding Cardiomyocyte-Specific Glucocorticoid Receptor and KLF15 Interactions in Cardiac Metabolism Regulation

Cardiac metabolism depends strongly on how glucocorticoids and circadian signals affect transcription in cardiomyocytes. When this occurs, the heart's metabolism is guided by the actions of these two regulators: the glucocorticoid receptor and Krüppel-like factor 15. To know how influence heart function under metabolic stress, we need to better understand the mechanisms of circadian-controlled glucocorticoid signaling in the body.

Genomic and epigenomic techniques have revealed the important roles of GR and KLF15 in controlling gene transcription in cardiomyocytes. By using mice that can turn on or off GR or KLF15 in the heart only, researchers found that both genes play a direct role in modulating cardiac genes and metabolism. Since these models let scientists timely remove a gene, they can study the impacts of loss without interference from the body's development or general changes.

Myocardial tissue treated with glucocorticoids was used to perform ChIP-seq to assess the locations of GR and KLF15 on the genome. The results indicate that GR and KLF15 are linked to promoters that carry GREs and KREs, showing that they control transcription at these sites. Especially, applying glucocorticoids at the optimal time (ZT0)

increases the strength and number of these binding events without creating imbalances in where they occur on the genome and signals more about transcriptional activation than changes in the types of genes controlled.

GR-KLF15 complexes mainly target two important genes: Adipor1 for adiponectin receptor 1 and mitochondrial pyruvate carriers Mpc1 and Mpc2. Adipor1 is important for letting insulin push glucose into muscle and other cells by giving the ceramidase enzyme the chance to get rid of damaging ceramides linked to insulin resistance and fat buildup. Additionally, the heteromeric complex made up of Mpc1 and Mpc2 takes in pyruvate and helps oxidize glucose in cardiomyocytes.

No rise in Adipor1 or Mpc1/2 transcripts occurs in hearts with GR or KLF15 deleted from cardiomyocytes when exposed to glucocorticoids. Based on these results, we conclude that none of these genes can be activated without first having GR and KLF15 present. Using ChIP-qPCR, it was possible to confirm that the transcription factors occupy the promoters of Adipor1 and Mpc directly, demonstrating collaboration to control important elements of cardiac glucose metabolism.

Changes in transcription guided by GR and KLF15 are important for cellular metabolism. Treatment with glucocorticoids at ZT0 decreases ceramide content in the heart which probably comes from Adipor1 activation and greater ceramide breakdown. Lower ceramide levels decrease harmful stress on fat and help cardiomyocytes become more responsive to insulin. This helps explain why hearts treated in these studies take in more 2-deoxyglucose than untreated controls when observed in vivo. When GR or KLF15 are knocked out only in cardiomyocytes, these benefits no longer happen, proving they are essential(4).

In addition to improving glucose uptake, expressed Mpc1 and Mpc2 support more pyruvate movement into mitochondria which leads to increased glucose oxidation. Under ADP stimulation, mitochondria taken from glucocorticoid-treated hearts reveal both increased respiration and better control ratios which suggests greater efficacy in creating ATP. As well as maintaining low energy during rest, these benefits also enhance the heart muscle's energy when it is needed for extra work.

It is worth noting that glucocorticoid stimulation causes similar transcriptional and metabolic changes in both males and females and there were no differences seen in assays of glucose and mitochondrial function between male and female tissues. It seems that both genders use this system to control heart metabolism, however, the authors agree more research on bigger groups might be needed to find out if there are indeed slight sex-specific patterns.

Assessments using echocardiography indicate that exposing wild-type mice to glucocorticoids at ZT0 time of day provides benefit for their hearts by improving both fractional shortening and stroke volume. Such improvements are missing in mice where GR function is limited to cardiomyocytes or where KLF15 has been removed, revealing that these transcriptional effects play a key role in cardiac function. Knockout mice are found to carry their heart weights further up the tibia, showing that altering genes in heart cells leads to harmful results and strengthens their protective roles.

In addition, removing GR or KLF15 from the cells results in trouble with both diastolic and systolic function, shown by increased left ventricular diameter and lower ejection fraction trends. It shows that these transcription factors are important for protecting the structure and function of the heart by affecting metabolism. There are no functional benefits of glucocorticoid treatment in knockout mice, confirming that the GR-KLF15 axis in cardiomyocytes is needed for treatment to produce any results(5).

Results from these experiments help explain how glucocorticoid effects are gated by circadian rhythms. When glucocorticoids are provided during ZT0, when Klf15 is present in the highest levels, the effects from GR interactions with KLF15 are significantly increased. Most likely, the heart's intrinsic clock, controlled by the transcription factor BMAL1, plays a key role in this rhythm. Cardiac energy and function benefit from glucocorticoid signaling cooperating with circadian transcription factors which enable metabolism to work best during the day.

Manually curating these data highlights that, guided by the GR-KLF15 axis, cardiomyocytes in the heart execute a complex program that brings together glucocorticoid and circadian effects for better sugar metabolism. This means the program helps insulin shoot glucose into cells, clears ceramide by using Adipor1, increases glucose oxidation and raises pyruvate carriers in mitochondria, ending up with better mitochondrial respiration and the production of more ATP.

This research shows that when given based on the body's clockwork, glucocorticoids may prevent cardiac issues and could actually benefit the heart. By recognizing important molecules and signaling routes in the process, this work helps design fresh and effective chronotherapies targeting GR-KLF15 to regain metabolic adaptability and maintain heart health in illnesses such as diabetic cardiomyopathy.

The results suggest that managing glucocorticoid therapy according to both timing and molecular targets could bring

radical changes to the way cardiac metabolic disorders are treated. It is possible that upcoming approaches could design modulators that help the beneficial part of the GR-KLF15 network without causing systemic glucocorticoid side effects and also optimize timing administration to benefit from circadian rhythms(6).

3. Harnessing Chronopharmacology

Diabetic cardiomyopathy is a major complication of type 2 diabetes and includes difficulties in metabolizing, growing insensitive to insulin and weakening of the heart. Mainly, the problem is with cardiomyocyte glucose uptake and oxidation, plus a rise in using lipids which leads to lipid toxicity and damaged mitochondria. Although there are many efforts to improve treatment, picking up from lab findings and using them to help diabetes has been challenging and heart disease continues to be a big cause of poor health and death in diabetics(7).

Recent work in chronobiology suggests that when drugs are taken can strongly affect both their therapeutic results and their side effects. If given at the wrong time relative to the body's daily rhythms, glucocorticoids could have negative effects on the heart. In this section, researchers demonstrate that timing glucocorticoid treatment improves glucose absorption by the heart in a mouse model of diabetes which could help turn circadian research into clinical applications.

As a common model used to study obesity-related type 2 diabetes, the db/db mouse shows characteristics of diabetic cardiomyopathy such as weaker diastolic function, smaller stroke volume and enlarged heart tissue. The hearts of these mice show limited response to insulin and impaired drug glucose use inside the mitochondria, similar to human disease. Notably, as in db/db mice, glucocorticoid levels are still high but change less regularly, suggesting a problem with how steroids are regulated that could lead to worse metabolic problems.

Researchers studied if glucocorticoid treatment could help control diabetic cardiomyopathy by giving prednisone to mice once every week at either ZT0 or ZT12. The interaction between GR, metabolism and circadian factors such as KLF15 and BMAL1, both of which have daily fluctuations in expression, is the principle of this design.

Only the ZT0 glucocorticoid approach led to significant improvements in a number of heart function measures in db/db mice. On the echocardiogram, ZT0 prednisone lowered diastolic dysfunction by reducing the E/e′ ratio,, increased stroke volume to levels observed in healthy littermates and decreased the size of the heart as a proportion of tibia length. However, prednisone given at ZT12 did not have these positive effects, indicating that timing is an essential factor in making the most of glucocorticoid cardioprotection.

Simultaneously, important metabolic functions were rebuilt during these functional improvements. A rise in glucose uptake into myocardial cells after ZT0 but not ZT12 prednisone treatment was detected using 2-deoxyglucose, showing insulin-sensitive routes of glucose transport were revived by ZT0 prednisone. The same result was found in isolated heart cells from treated db/db mice which showed greater use of glucose, better mitochondrial respiration and enhanced ATP synthesis, confirming improved respiration and cellular energy availability(8).

Glucocorticoid treatment at the molecular level led to elevated protein levels of adiponectin receptor 1 (ADIPOR1) as well as subunits of the mitochondrial pyruvate carrier (MPC1/2) in the heart of diabetic animals. This pair of proteins is controlled by the GR-KLF15 system and both help clear ceramides and move pyruvate into the mitochondria. An increase in ADIPOR1 helps reduce the buildup of harmful lipids called ceramide which in turn makes insulin work better and higher MPC1/2 improves the use of pyruvate in energy production by cells. All these molecular changes together lead to the improved cardiac metabolism seen after ZT0 dosing.

Importantly, cardiac metabolism and function improved in all groups, but despite this, neither glucocorticoid treatment affected the body weight or blood pressure of the mice beyond what was expected from their genetic trait. Because the metabolic and functional improvements were not affected by systemic blood flow or obesity, this strengthens the idea that autonomous actions on the heart directly benefited cardiomyocytes.

To show that the GR-KLF15 axis is key, researchers selectively reduced the levels of GR and KLF15 in muscle and cardiomyocytes using special AAVs. ZT0 prednisone did not provide any metabolic or functional improvement in diabetic mice if GR and KLF15 were knocked down together. In particular, the elevation of ADIPOR1 and MPC1/2 proteins was prevented, less glucose was taken up and mitochondrial respiration did not increase. Furthermore, reduced diastolic function, a lack of stroke volume and enlarged hearts persisted in the knockdown mice, despite glucocorticoid treatments, proving that the GR-KLF15 program is required for the therapeutic benefits.

These findings question the common notion that all glucocorticoids hurt heart metabolism and show that timing plays a key role(9). If drugs are given along with the body's peak activity of circadian regulators, they can enhance the cardiovascular benefits of steroid hormones. These results strongly suggest that breaking up steroid doses may help reduce possible side effects, including hypertension, difficulty with using insulin and muscle loss, that are connected to taking steroids every day.

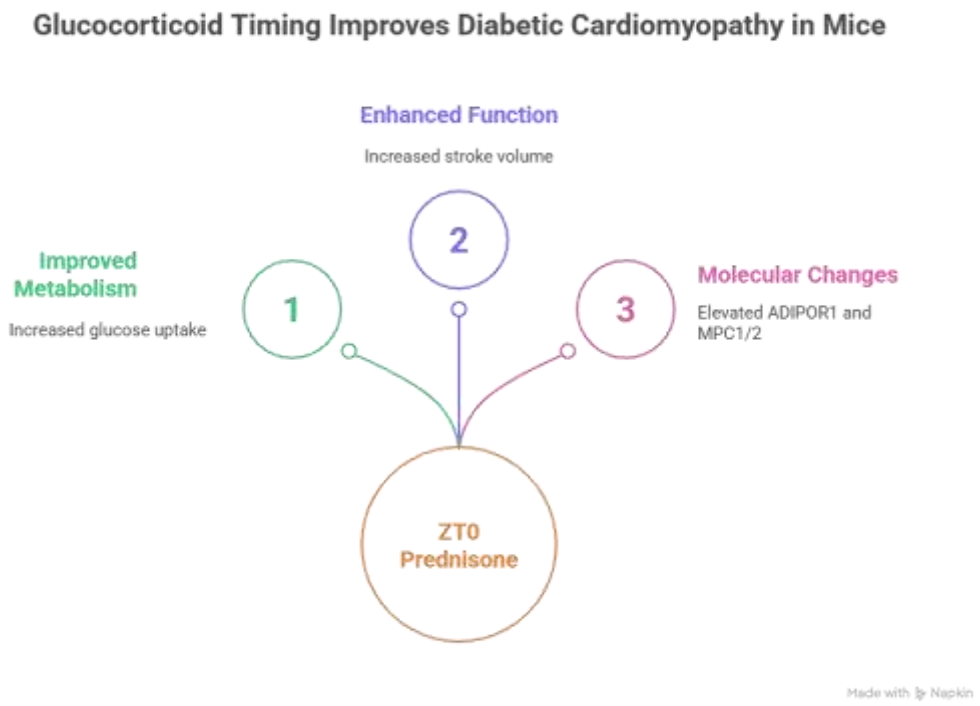

FIGURE 2 Glucocorticoid Timing Improves Diabetic Cardiomyopathy in Mice

Overall, what we observed brings attention to the link between circadian biology and metabolic disease therapeutics. The way the heart works throughout each day is carefully regulated by daily rhythms for selecting its fuel, contracting and repairing itself. When timing is broken, as in diabetes and similar diseases, it can cause serious changes and problems in the body. Methods that strengthen or fix the body's internal clock are showing promise for treating diseases.

On the clinical front, what science has found could help doctors manage diabetic cardiomyopathy and heart failure better. Patient care could be improved by using timed glucocorticoid therapy to aid cardiac metabolism and avoid serious side effects in the body. In addition, strategies that concentrate on ADIPOR1 and MPC complex components such as using small drugs or gene therapy, may provide different or supportive options. Using information about circadian rhythm can help customize treatments for people based on their body's rhythms.

Further studies are needed to see if these conclusions apply to humans and to investigate whether other elements that affect the circadian rhythm such as eating, exercise and sleeping, influence how well glucocorticoids work in humans. The possible interaction between glucocorticoid chronotherapy and existing diabetes drugs should be examined to design more effective combined treatment strategies(10).

4.Cutting-Edge Methodologies for Unraveling Circadian Influences on Cardiac Metabolism and Glucocorticoid Signaling

Understanding the effects of circadian glucocorticoids on the heart's metabolism calls for an all-round and multidisciplinary approach to research. Combing in vivo, ex vivo, molecular and omics approaches, researchers have built a strong platform to identify how and when cardiomyocyte metabolism changes. The following section describes the detailed methods applied to show the influence of the GR and KLF15 on glucose uptake and metabolism in the heart.

Experiments with Animals and Scientifically Developed Circadian Treatment

The studies are built on genetically modified mice where the genes GR or KLF15 can be removed in the heart at the researchers' command. With these models, investigators are able to delete genes later in life to avoid the problems caused by early deletion and to see the effects of changes in genes and metabolism in real time. Environmental Light/Dark cycles of 12 hours each were used to maintain mouse circadian rhythms and all treatments were carried out when animals reached a similar age to reduce random variation.

Corticosteroid treatments were carried out using prednisone, administered once each week, either at ZT0 (when lamps are switched on) or ZT12 (when lamps are switched off), to measure when signaling from these glucocorticoids took effect. Giving steroids from time to time prevents the problems linked to long-term use and allows researchers to look at the body's circadian rhythms and drug effectiveness. This system mimics different types of treatment where timing matters for better results(11).

We use transcriptomic and epigenomic analysis

We used RNA sequencing to assess how the genome responded to glucocorticoids at the transcriptional level based on samples taken 4 hours after administering glucocorticoids. This design means early activation is known before secondary effects appear elsewhere in the body. The samples were processed with Illumina; RNA was obtained and sequenced at high speed, then arranged against the known genomes to measure expression.

Direct binding sites of GR and KLF15 were discovered by using ChIP-seq to map the epigenomic region. To eliminate issues with antibody specificity, ChIP was done using FLAG-tagged, knockin mice for KLF15 as well as specific antibodies. Sonicated cardiac chromatin was immunoprecipitated, the resulting DNA was purified and the entire process was followed by high-throughput sequencing. Peak calling and analysis of motifs showed that regulatory regions important for turning on metabolic genes are marked by more GR and KLF15 factors.

To identify genes and processes altered by glucocorticoid chronopharmacology and gene deletion, these omics studies complemented PCA and pathway enrichment.

Testing at the molecular and biochemical level

Following omics analyses, we confirmed Adipor1, Mpc1 and Mpc2 gene expression by qPCR in the tissue, validating that treatment and knockouts changed their levels. Furthermore, ChIP-qPCR was performed to check how GR and KLF15 bind to nearby promotor regions of these genes, supporting the mechanisms involved.

The number and subcellular position of GR, KLF15 and metabolic effectors were quantified using western blotting. Insight into how transcription factors transit the nucleus was gained after using nuclear and cytoplasmic fractionations after glucocorticoid exposure, helping clarify why circadian rhythms affect signaling effectiveness.

Tools used for measuring metabolism and function are called metabolic and functional assays(12).

The effects of transcriptional regulation on metabolism were investigated by performing a collection of metabolic tests. To measure glucose uptake in the heart, radiolabeled 2DG assays were used and allowed for quantifying myocardial glucose transport under various genetic and treatment situations. Lipidomics studies involved the use of untargeted mass spectrometry to estimate ceramide levels, main lipid molecules associated with insulin resistance and the toxic effects of excessive lipids in cells. ADIPOR1's involvement in reducing insulin resistance through discarding ceramide was shown by these assays.

The function of mitochondria was tested by applying Seahorse XF respirometry to individual cardiomyocytes, tissues and purified mitochondria. The study tested the basal oxygen consumption rate (OCR), the response to ADP stimulation, the respiratory control ratio (RCR) and ATP production, giving a complete view of oxidative metabolism. Flux through each metabolic pathway was studied by assessing the response to glucose and pyruvate.

Measuring the Heart's Function

Echocardiography was done to change laboratory information into information about heart function by measuring fractional shortening, stroke volume, ejection fraction and diastolic function. The assessments made it possible to track the structure and performance of the heart over time while treating with a circadian glucocorticoid and ablating specific genes.

Reducing the levels of a gene by transfecting with AAV Vectors

GR and KLF15 Knockdown in diabetic hearts was done by manipulating the presence of these factors with AAV shRNA to gain insight into their roles. For the AAV treatment, the MyoAAV variant was selected for its capacity to maximally reach and affect cardiomyocytes. The combination of Nr3c1 (GR)- and Klf15-directed shRNAs was sent into the animals through injections into the orbit to achieve prolonged reduction of their target genes. Researchers showed that losing these factors stops glucocorticoids from providing important metabolic and functional benefits.

Temporal and Epic Resolution

The experimental framework is unique because it allows the study of changing processes over time within complex reactions. When timing drug administration with information from the clock working and readings from the body, experts showed that transcription factors, gene expression and metabolism are all changed by this clock. GR bound better to gene promoters no matter when the drugs were given, yet the effects of KLF15 and the functions were greater at ZT0, indicating the close relationship between circadian regulators and steroid signals.

Points to Keep in Mind

It is important to mention the limitations of these detailed methodologies. Since samples in omics experiments were not large, there might have been limits to finding out subtle sex-related and time-related differences. Although

murine models are useful, we must exercise care when using the results for humans. Due to the side effects that chronic glucocorticoid use may have on the entire body, proper dosing is very important.

Conclusion

All of these strategies combined demonstrate how using genetic models, evaluating the timing of drug effects, omics tech and functional techniques together can explain how various biological systems function. A thorough search for how cardiomyocytes respond to glucocorticoids and their internal clocks gave key insights that help design better chronotherapies for diabetic cardiomyopathy and metabolic heart disease. Advanced experimental tools now make it more achievable to use treatments at the most effective time for the patient.

5.Navigating Challenges and Charting Future Pathways in Circadian-Based Cardiometabolic Therapies

Gaining knowledge about the timing of cardiac metabolism and glucocorticoid signaling has led us to explore new ways to treat metabolic diseases of the heart. Getting these mechanistic findings successfully into treatment plans requires careful consideration of various issues and complications. It explores the obstacles found in current studies, explores open questions and suggests important paths for making use of circadian biology for better cardiometabolic health.

One of the problems is that biological rhythms differ greatly and can be quite complex, even among individuals and species. Factors influencing a person's circadian system can be genetic, determined by the environment or due to behavioral habits and these factors often vary considerably among patients. As a result, there is not one ideal time to give glucocorticoids or chronotherapeutic treatments; timing may have to be adjusted based on a patient's personal circadian patterns. At present, most researchers use the same daily light and eating schedules for animals, even though these may not cover all the differences in human body rhythms. More research is needed that covers chronotypes and real-life differences to improve timing strategies(13).

Experimental groups are often limited by having an unequal number of males and females. In most of the discussed work, male mice were used to cut down on animal use and variability, so hormonal differences in females could produce different effects on circadian and metabolic pathways. In fact, estrogen and testosterone in the blood affect both how the heart uses energy and the body's internal clock. Although the first analyses did not spot major differences in glucocorticoid-linked metabolic effects between males and females, the findings could not pick up subtle differences. It will be important to investigate carefully, using sex-equal cohorts and hormone treatments, to find sex-specific effects and make gender-inclusive therapies optimal.

In present studies, some subjects are not included due to their mechanical focus. The need for GR and KLF15 to influence insulin sensitivity and glucose utilization by cells is clear, but the signaling and metabolic systems behind cardiac improvement require more study. How transcriptional programs cooperate with other metabolic regulators, for example, AMPK, PGC-1α or mTOR, is still not clear. In addition, the way cardiomyocytes and other cardiac cells such as fibroblasts, endothelial cells and resident immune cells interact may affect how the heart responds to variations in treatment times.

How long glucocorticoid therapy lasts and how much is prescribed creates additional difficulties. While interrupted, timed use of glucocorticoids reduces many serious effects often seen with regular therapy, yet prolonged periods of use may produce hypertension or suppress the immune system. Still, it is vital to set the right dose and dosing time that help the medicine work without raising safety risks for groups such as diabetic patients with other health problems. Mixing glucocorticoid chronotherapy with cardiovascular and antidiabetic medicines needs careful review to prevent unwanted effects and drug interactions.

Progress is hindered by the technical problems that come with adapting these findings for patients. It is still uncommon for assessment of circadian phase in patients to be overtly accurate and noninvasive, so precise timing of drugs is difficult. Biomarkers such as melatonin or temperature rhythms which capture our internal clock, look positive but they must be made more standard and accessible. New gadgets and healthcare apps intend to regularly monitor circadian activity, making it possible to change treatment times as needed. Advancing and confirming these tools is very important for personalized medicine focused on circadian rhythms.

Moreover, the discovery of ADIPOR1 and the mitochondrial pyruvate carrier complex as molecular targets means that new drugs can be developed using a different approach from glucocorticoid therapy. If we boost these effectors using selective agonists or genetic therapy, it may offer benefits for metabolism with limited effects elsewhere. Nonetheless, these methods need to be rigorously tested in research labs and deserve original delivery ways that reach the heart only.

Going forward, collaboration between different fields will be necessary to handle these issues. Bringing chronobiology together with cardiology, endocrinology, pharmacology and bioinformatics will make it easier to study and apply in medicine. For timed glucocorticoid therapy in diabetic cardiomyopathy and heart failure to be based on evidence, large-scale clinical trials with circadian timing are needed.

Also, involving disorders from other areas such as obesity, hypertension and atherosclerosis, may further extend the reach of chronotherapeutic strategies. Research into how adjusting timing of meals, working out and exposure to light with the help of medication will benefit treatment plans.

All in all, changing the way glucocorticoids act in the body via the circadian system could restore cardiovascular health, but it is essential to consider how much each person differs, male or female differences, treatments and new technology. Working on these problems using rigorous studies and new developments is expected to bring an era of precision cardiometabolic care where timing is a major part of designing treatments.

6.Conclusion and Future work

Such findings explain how the heart's daily cycle works together with glucocorticoid hormones to control cardiac metabolism and function when diabetes is involved. As a result, these studies discover a new way the glucocorticoid receptor (GR) and Krüppel-like factor 15 (KLF15) interact to boost insulin-dependent glucose uptake and the use of pyruvate in energy production. Restoring metabolic flexibility depends heavily on the way these molecules interact.

Circadian gating of glucocorticoid efficacy is important: it shows that if you give prednisone during the light phase (ZT0), the drug acts better, improving both the glucose metabolism and function of the heart. This research changes the old belief that glucocorticoids damage the heart and now suggests that, if used at the right times, they can have beneficial effects. At ZT0, an increased interaction between GR and KLF15 activates both Adipor1 and Mpc1/2 genes in the metabolism which decreases ceramide levels, improves how well insulin works and boosts ATP supply in cardiac muscle cells.

Importantly, disturbing the presence of GR or KLF15 in the cardiac muscle wipes out the good outcomes brought by glucocorticoids, making it clear that glucocorticoids need these factors to trigger remodeling of heart metabolism. Because of their use of inducible cardiac knockouts and gene knockdown with virus vectors, researchers now know the GR-KLF15 axis acts as a timing machine controlling how the heart changes its energy sources.

The fact that diabetic cardiomyopathy is a serious clinical challenge means these findings are especially important. Glucocorticoid treatment in the light phase restored glucose oxidation and improved how the heart transmits pressure in healthy obese diabetic mice, indicating this approach has promise. With this strategy, specialists hope to establish effective treatments that consider the daily cycle to lower risks of unpleasant effects usually seen in people treated with glucocorticoids for long periods.

Additionally, finding that Adipor1 and mitochondrial pyruvate carriers are among the targets creates chances for making medicine that selectively impacts these effectors. These strategies could be used in addition to or in place of glucocorticoid therapy which may limit the effects on a patient's entire body and improve how well they feel.

The findings here highlight the broader value of including circadian biology in the creation and use of therapies for heart diseases. The timing of physiological events plays a major role in health and disease that has gone mostly unnoticed in medicine up to now. If we time our therapeutic actions with the body's own biological schedule, we can find new ways to prevent and manage different cardiometabolic disorders.

Still, the vision can only become a reality if challenges such as variability in the body's clock, the effects of gender on circadian patterns and practical tools for assessment in medical settings are addressed. It is important that future studies examine the way cardiomyocytes connect with other cell types and factors in the heart to better understand heart metabolism.

All in all, the synergy between chronobiology and glucocorticoid pharmacology, as seen in this text, is expected to produce important results in cardiometabolic medicine. Using the timing of GR-KLF15, we can create treatments that are more exact, effective and tailored for diabetic cardiomyopathy and likely other related diseases. Because of this shift, we gain new insights and also create a better system for helping people by respecting their internal biological patterns.

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Conflicts of interest

The authors have no conflicts of interest to declare

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