

Melatonin, Circadian Rhythms, and Type 2 Diabetes Mellitus: A Comprehensive Review of Epidemiology, Molecular Mechanisms, and Therapeutic Implications

Ms. Kajal Tiwari¹, Riddhi Tiwari², Dr. Archana Tiwari³

^{1,2}Student, UTD, RGPV, SOBEBT, Bhopal

³Director, UTD, RGPV, SOBEBT, Bhopal

Abstract

This extensive review delves into the epidemiology, risk factors, historical background, and molecular mechanisms of Type 2 Diabetes Mellitus (T2DM). The term "diabetes mellitus" dates back to ancient times and the Greek physician Aertaeus is credited with coining the term. T2DM, which is defined by hyperglycemia, insulin resistance, and relative insulin deficiency, is a global public health concern that affects millions of people worldwide. A combination of genetic, environmental, and lifestyle factors play a role in the development of T2DM. The distinction between Type 1 and Type 2 diabetes was established in 1936, and Type 2 diabetes was identified as a component of the metabolic syndrome in 1988.

T2DM is becoming more and more common; it is expected to affect 552 million people by 2030, which means that research and interventions are desperately needed. The risk factors for T2DM include age, genetics, obesity, sedentary lifestyle, and components of the metabolic syndrome. Prediabetes, which is a precursor to T2DM, must be detected early in order to reduce the risk of progression. This review explores the physiological and molecular mechanisms underlying T2DM, with a focus on the complex interactions between melatonin, circadian rhythms, and diabetes.

Melatonin, this is primarily synthesized by the pineal gland, is essential for the regulation of circadian rhythms and many other physiological processes. Research has shown how melatonin affects insulin secretion and glucose metabolism, suggesting that it may have therapeutic uses in the treatment of diabetes. Circadian rhythm disturbances, particularly those brought on by shift work, are linked to a higher risk of type 2 diabetes, underscoring the importance of comprehending these intricate relationships.

The review highlights the need for more research to fully understand the complex relationships between melatonin, circadian rhythms, and diabetes. Pharmacological interventions, such as the synthetic melatonin agonist agomelatine, offer promising avenues for therapeutic exploration. Thapsigargin, an antagonist of sarco-endoplasmic reticulum Ca^{2+} -ATPase (SERCA), reveals the role of calcium signaling in diabetes research.

Keywords: T2DM, Melatonin, Agomelatine, Thapsigargin, Sarco-endoplasmic reticulum, Antagonist etc...

Introduction

The Egyptians are credited with originally describing diabetes, which is characterized by polyuria and weight loss. Yet, the term "diabetes mellitus" was first used by the Greek doctor Aertaeus (OM). Diabetes is a Greek term which means "to pass through," and mellitus is a Latin word that means "honey" (referring to sweetness). With roughly one fatality every ten seconds, diabetes is a major contributor to long-term illness and untimely death. It also claims more lives each year than HIV/AIDS (Kaul et al., 2013). One of the earliest diseases that humans have ever known is possibly diabetes mellitus (DM). Over 3000 years ago, an Egyptian book was the first to mention it (Ahmed, 2002). The distinction between type 1 and type 2 DM was defined in crystal plain terms in 1936 (Olokoba et al., 2012). And In 1988, type 2 diabetes was initially identified as a part of the metabolic syndrome (Olokoba et al., 2012). High blood glucose levels brought on by deficiencies in insulin production (insulin deficit), insulin action (insulin resistance), or both define the group of disorders known as diabetes mellitus. The pancreas produces the hormone insulin. Foods are transformed into a type of sugar called glucose when consumed, which then enters the bloodstream. Glucose must be transported into the body's cells by insulin before it can be used as fuel. Excess glucose is then stored in the liver and fat cells. Blood sugar levels rise and significant amounts of glucose are discharged in the urine when insufficient amounts of functional insulin are present. High blood sugar levels harm blood vessels and nerves and increase the risk of heart disease, stroke, high blood pressure, renal disease, blindness, amputations, and dental problems. The most prevalent kind of diabetes is type 2 diabetes, sometimes referred to as non-insulin dependent diabetes (NIDDM), which is characterized by hyperglycemia, insulin resistance, and relative insulin shortage. When genetic, environmental, and behavioral risk factors intersect, type 2 diabetes results (Alam et al., 2014),

The main features of T2DM are examined in this review, along with the molecular mechanisms, pathways, and connections involved in insulin metabolism and T2DM pathogenesis. In this review, we discuss the prevalence of T2DM worldwide and the contributions of the main risk factors, including obesity, lifestyle choices, inherited susceptibilities, gut dysbiosis, epigenetics, and mitochondrial dysregulation. We emphasize the physiological and molecular processes that cause T2DM and its side effects.

Diabetes Mellitus: An Overview

An absolute or relative shortfall in insulin synthesis or action results in hyperglycemia, which is the hallmark of the varied group of illnesses known as diabetes mellitus. The retina, kidney, neurological system, heart, and blood vessels are just a few of the end organs that are harmed, dysfunctioned, or fail as a result of the chronic hyperglycemia of diabetes mellitus. The prevalence of diabetes mellitus worldwide was projected by the International Diabetes Federation (IDF) to be 366 million in 2011 and was expected to reach 552 million by 2030 (Alam et al., 2014).

Although the two basic etiopathogenetic categories of type 1 and type 2 DM account for the majority of instances of diabetes, this rigorous classification may not be appropriate in all circumstances. Classifying people based on the following criteria is standard clinical practice and frequently depends on the clinical presentation at diagnosis.

1. Age at diabetes beginning
2. The suddenness of hyperglycemia
3. ketone bodies present at presentation
4. Obesity severity
5. The diagnosis of insulin requirement (Alam et al., 2014).

Type I DM:

Absolute lack of insulin is the cause of type 1 diabetes, which has an autoimmune foundation. Before diabetes mellitus was reclassified based on etiopathology, this illness was known as insulin-dependent diabetes mellitus (IDDM). The condition is characterized by immune-mediated death of β cells, and hyperglycemia only develops after 90% of β cells are destroyed (Alam et al., 2014). T1DM, formerly known as insulin-dependent diabetes or juvenile onset diabetes, is an autoimmune condition in which the pancreatic islets are invaded by macrophages and activated CD4+ and CD8+ T cells, which cause cell death. The first signs of T1DM typically appear between the ages of 35 and 40. It is recognized that both genetic and environmental variables affect this diabetes' vulnerability (Kaul et al., 2013). The HLA (human leucocyte antigen) gene on chromosome 6 has been linked to T1DM, according to genetic studies. The immune system uses the HLA proteins on cell surfaces to distinguish between the body's normal cells and foreign infectious and non-infectious substances. An autoimmune response against the cells occurs in T1DM as a result of an alteration in the HLA proteins. Another gene near the HLA plays a significant role in T1DM, called DR (Gorodezky et al., 2006).

Maintaining normal blood glucose levels as close to normal as feasible while preventing its significant variations is the biggest challenge in treating T1DM because doing so will help to prevent the onset of microvascular and arterial problems. Individuals with T1DM are treated with insulin, which may be given orally, intravenously, or even through inhalation, as well as through cutting-edge nanotechnology-based delivery systems (Zarogoulidis et al., 2011) (Chaillous et al., 2000).

Type II DM:

The development of Type 2 Diabetes Mellitus (T2DM), one of the most prevalent metabolic illnesses in the world, is primarily brought on by the interaction of two main factors: impaired insulin production by pancreatic β -cells and impaired insulin sensitivity in tissues (Roden & Shulman, 2019). The molecular processes involved in the production and release of insulin, as well as the insulin response in tissues, must be strictly regulated in order for it to perfectly satisfy the metabolic requirement. As a result, flaws in any of the pathways can result in a metabolic imbalance and T2DM (Galicia-Garcia et al., 2020). In comparison to type 1 diabetes mellitus (T1DM) and gestational diabetes, type 2 diabetes mellitus (T2DM) is by far the most prevalent of the three primary kinds of diabetes, accounting for more than 90% of all occurrences (DeFronzo et al., 2015, p. 2). Its primary cause is increasing impairment of pancreatic cells' ability to secrete insulin, which typically occurs in the context of pre-existing insulin resistance in skeletal muscle, the liver, and adipose tissue (DeFronzo, 2009). Genetic and lifestyle factors work together to cause T2DM. Toxins from the environment may also be a factor in the recent increases in the rate of T2DM. The likelihood of developing T2DM increases significantly in families with T2DM-affected members. Along with any genetic component, environmental factors, particularly diet and obesity, significantly contribute to the development of T2DM. Insulin resistance is the inability of human tissues to react to insulin as intended. Contrary to Type I diabetes mellitus, insulin resistance is

typically caused by insulin receptors in the cells that do not respond to insulin in a proper manner rather than a problem with the production of insulin (Ginter & Simko, 2013). The World Health Organization (WHO) defines T2DM as having elevated glucose levels on two occasions: either during a glucose tolerance test two hours after an oral dose with a plasma glucose of 11.0 mmol/L or during a fasting plasma glucose of 7.0 mmol/L. T2DM onset can be delayed with a healthy diet and consistent exercise. Current research has connected insulin resistance in the brain and neurodegeneration to obesity and type 2 diabetes.

Pre-diabetes is the precursor to long-term hyperglycemia (Abdul-Ghani et al., 2006) is a high-risk condition that puts people at risk for developing T2DM, Impairment of glucose tolerance (IGT), impaired fasting glucose (IFG), or elevated levels of glycated hemoglobin A1c (HbA1c) are the three main indicators of prediabetes. Fasting plasma glucose levels that are greater than normal are present in people with IFG levels, even though they do not match the requirements for a diabetes diagnosis. While people with IFG levels have hepatic insulin resistance and impaired early (first phase) insulin secretion, IGT is characterized by insulin resistance in muscle and impaired late (second-phase) insulin secretion after a meal (Abdul-Ghani et al., 2006). HbA1c concentrations in those with prediabetes range from 5.7 to 6.4%; they are clinically quite different and represent a pathophysiological complex group. Prediabetes to T2DM conversion rates range from 3% to 11% annually (Gerstein et al., 2007).

In this thorough analysis this review highlights the need for more research to fill in the knowledge gaps regarding the complex relationships between melatonin, circadian rhythms, and diabetes. The knowledge gleaned from these studies could lead to the creation of novel therapeutic approaches for the treatment and management of diabetes."

Melatonin serves a variety of purposes, including regulating circadian activity, which is generally thought to have a sleep-promoting effect. In addition, melatonin administration causes hypothermia and heat loss through the distal skin regions in both healthy individuals and those with circadian rhythm disruptions, ranging in age from younger children to elderly people (Tordjman et al., 2017). stabilize sleep-wake cycles, Melatonin stimulates several anti-oxidative enzymes and acts on bone metabolism (Reiter et al., 2000).

Melatonin is a hormone that is primarily synthesized by the pineal gland. It is important for controlling circadian rhythms as well as impacting numerous biological processes. It is synthesized in vertebrates, which include both mammals and non-mammals, and its synthesis is closely linked to the circadian clock. Melatonin operates on the body through G-protein coupled receptors, MT1 and MT2, which are distributed across the body and influence circadian harmony, sleep, blood pressure, and reproductive processes. It is also important when it comes to glucose metabolism and insulin secretion, which makes it a major factor in the epidemiology of diabetes (Arendt & Aulinas, 2022).

The connection among diabetes, melatonin, and circadian rhythm is becoming more and more clear as studies investigate how behavioral and environmental cycle disruptions—like shift work—affect the probability of type 2 diabetes. Over 20% of American workers are employed in shift work, which has been associated with a 9% higher risk of diabetes, with exposure duration playing a further role in risk assessment. These findings demonstrate the complex interactions among circadian disruptions and metabolic health (Gan et al., 2015) (Vetter et al., 2018) (Pan et al., 2011).

Within this intricate terrain, A pharmacological treatments such as agomelatine, a synthetic agonist of melatonin, present promising avenues for therapeutic intervention. Through its targeting of melatonin receptors MT1 and MT2, agomelatine influences circadian sleep cycles and alertness signals, demonstrating its potential to improve the quality of sleep. Additionally, the use of thapsigargin, an antagonist of sarco-endoplasmic reticulum Ca²⁺-ATPase (SERCA), sheds light on the role of calcium signaling in diabetes. Thapsigargin's capacity to regulate intracellular calcium release highlights its potential as a tool for researching cellular signaling pathways in diabetes research(Dubovsky & Warren, 2009).

This review paves the way for a more thorough investigation of the complex interrelationships among melatonin, circadian rhythms, and diabetes, highlighting the significance of comprehending these connections for the creation of novel therapeutic approaches in the field of diabetes treatment and management."

Epidemiology

T2DM has grown to be a significant global public health issue. According to the World Diabetes Federation, 382 million persons between the ages of 20 and 70 had T2DM in 2013, with 80% of those affected residing in low- and middle-income nations(Home et al., n.d.). By 2035, this figure is anticipated to reach 592 million. China and India are severely damaged by this condition, as the prevalence of T2DM has increased significantly while the considerably lower rate of obesity(Hu, 2011). Asians are more probable to have a greater percentage of body fat mass, more abdominal obesity, and less muscle mass, which may contribute to their increased likelihood of acquiring type 2 diabetes (Chan et al., 2009).

Risk factor of T2DM:

Our understanding of the behavioral, lifestyle, and biological risk factors for type 2 diabetes has gotten better because of epidemiological studies, the table below explains such risk factors in detail.

Table 1

Risk Factor	Description
Older age	Advanced age increases the risk of T2DM.
Non-white ancestry	Certain ethnic backgrounds have a higher risk.
Family history of T2DM	A family history of T2DM can increase risk.
Genetic factors	Genetics play a role in T2DM risk.
Metabolic syndrome components	Includes increased waist circumference, high blood pressure, high triglyceride levels, low HDL cholesterol, and small dense LDL particles.
Overweight or obesity (BMI ≥ 25 kg/m ²)	Excess body weight is a significant risk factor.
Abdominal or central obesity (independent of BMI)	Excess abdominal fat can increase risk.
Polycystic ovary syndrome	Women with PCOS are at higher risk.
History of atherosclerotic cardiovascular disease	Prior heart disease can raise T2DM risk.
Unhealthy dietary factors	Includes sugary beverages and low fiber intake.
Cigarette smoking	Smoking is associated with T2DM risk.

Sedentary lifestyle	Lack of physical activity is a risk factor.
History of gestational diabetes or large newborns	Previous gestational diabetes or large babies can increase risk.
Acanthosis nigricans	Skin hyperpigmentation can indicate increased risk.
Some medications	Certain medications may increase T2DM risk.
Short and long sleep duration and rotating shifts	Irregular sleep patterns and shift work can raise risk.
Psychosocial and economic factors	Stress and economic status can influence risk.

The single biggest risk factor for T2DM is growing adiposity, which is shown by increased BMI values. Physical inactivity is a significant behavioral risk factor, and both weight training and aerobic exercise are advantageous (Grøntved et al., 2012). Risk increases with sedentary behavior, including prolonged television viewing (Grøntved & Hu, 2011). Rotating shift work, and short sleep duration (5 hours per night) or long sleep duration (9 hours per night) are both linked to increased risk (Cappuccio et al., 2010) (Pan et al., 2011). In addition, smoking cigarettes significantly increases the likelihood of developing T2DM, regardless of body weight and other risk factors (Hu, 2011). Despite the fact that genetics is a major factor in T2DM development (Barnett et al., 1981). Novel genetic changes are insufficient to account for the current diabetes epidemic; instead, the epidemic of obesity accounts for the majority of it (Wang et al., 2011). Even so, our sensitivity to environmental changes is influenced by our genes, and vice versa.

Glucose Metabolism:

A multitude of systems and pathways work together in the human body to create and sustain a healthy physiological state, the ability of the organism to maintain a continuous, stable condition, or homeostasis, is the fundamental basis of these activities.

Following a meal, the combined effects of hyperinsulinemia and hyperglycemia promote insulin secretion and decrease glucagon secretion. Glucagon-like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP), two incretin hormones released by the gut's L cells and K cells, respectively, are responsible for 60–70% of the insulin secretion. Together, the variations in blood sugar, insulin, and glucagon levels restrict lipolysis, increase muscular glucose uptake, and suppress hepatic glucose synthesis. The latter reduces the blood's concentration of free fatty acids, which strengthens the effect of insulin on the liver and muscle. Major disturbances in all of the aforementioned physiological responses are linked to type 2 diabetic mellitus, including impaired insulin secretion, increased fasting plasma glucagon levels, abnormal basal hepatic glucose production, abnormally impaired muscle glucose uptake, increased fasting plasma free fatty acid levels, abnormally abnormal post-meal glucagon levels, and abnormal post-meal glucagon levels. Yet, the stimulatory effects of both GLP1 and GIP on insulin production are severely resisted by cells (DeFronzo et al., 2015, p. 2).

Melatonin

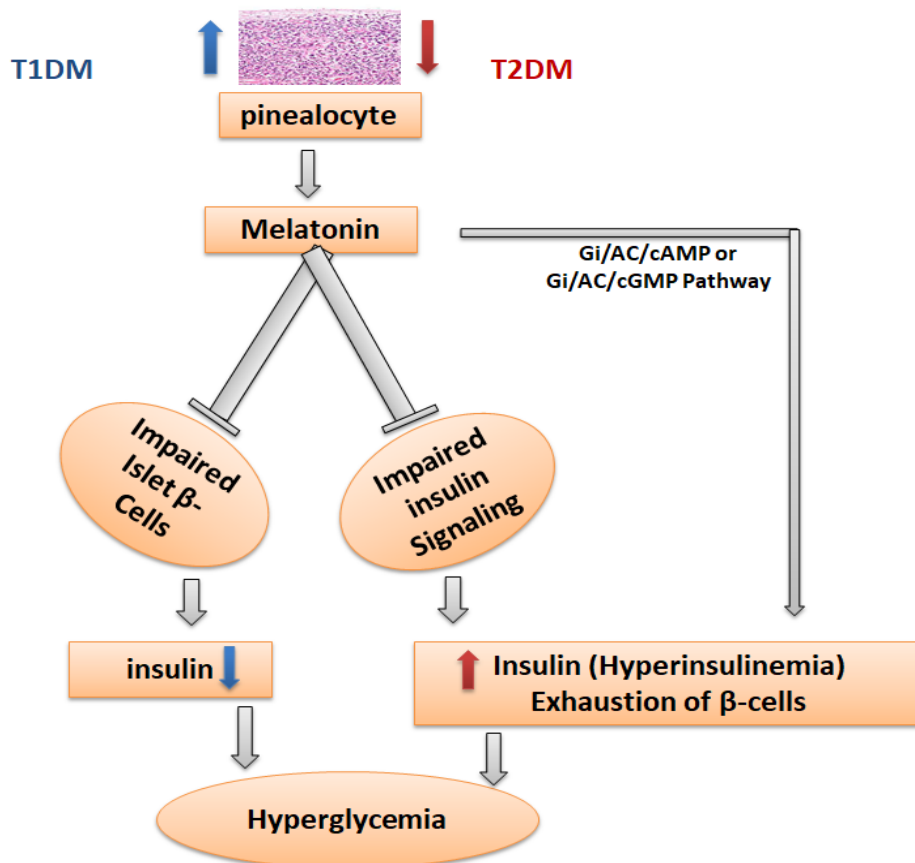
A hormone called melatonin is mostly produced by the pineal gland in vertebrates. During the night, four distinct enzymes work together in a rather simple biosynthetic route to produce melatonin. The synthesis of pineal melatonin is directly regulated by the circadian clock found in the pinealocytes in many vertebrates, including fish, amphibians, reptiles, and birds, as opposed to mammals, where the synthesis of melatonin is regulated by a circadian clock found in the suprachiasmatic nucleus (SCN) of the hypothalamus. Because melatonin is a lipophilic substance, the pineal gland cannot store it. Instead,

it diffuses into the blood and cerebral spinal fluid, where its concentration reflects that of its synthesis(Tricoire et al., 2002).

Melatonin operates on a variety of different cell types in the body, where it functions either directly through its G-protein coupled receptors known as melatonin receptors 1 (MT1) and 2 (MT2) or as an antioxidant and free radical scavenger. The expression of MT1 and MT2 is found all over the body, where they control the coordination of circadian rhythms, sleep, blood pressure, and reproductive processes(Owino et al., 2019).

Role of Melatonin and Melatonin receptor in Glucose Metabolism:

The pancreatic β -cells' melatonin receptors (MT1 and MT2) are generally responsible for their actions. Melatonin prevents β -cells from secreting insulin through the GC/cGMP or AC/cAMP pathway. This reduces hyperinsulinemia and shields β -cells from functional overstrain in T2D. Conversely, melatonin preserves T1D-related β -cell activity (regeneration/proliferation, apoptosis prevention). Melatonin is involved in glucose homeostasis, and altered melatonin circadian rhythms account for altered insulin levels and hyperglycemia. High amounts of melatonin and reduced plasma insulin levels are shown in T1D (blue arrows); in T2D, on the other hand, lower levels of melatonin and higher insulin levels are seen (red arrows)(She et al., 2014)



Melatonin is predominantly produced and released by the pineal gland in a circadian manner, influencing endogenous circadian rhythms and impacting various physiological functions. Both MT1 (encoded by MTNR1A) and MT2 (encoded by MTNR1B) G-protein-coupled receptors in mammals play a role in mediating melatonin's effects. Extensive in vivo and in vitro studies have provided evidence

supporting melatonin's significant involvement in regulating glucose metabolism and contributing to diabetes pathogenesis. Recent investigations into human genetic variants of MTNR1B have further confirmed its relevance. Notably, there is a suggested link between genetic variations within MTNR1B and the direct impact on β -cell function, specifically insulin secretion. This implies a functional connection between MT2 and the risk of Type 2 Diabetes (T2D) at the protein level, representing a prominent mechanistic pathway through which impaired melatonin signaling contributes to metabolic disorders and heightens the risk of T2D. The findings suggest that melatonin and its receptors may offer a novel therapeutic approach for diabetes (She et al., 2014).

Research points to melatonin's involvement in the etiology of type 2 diabetes (T2D) in people and animals through regulating glucose metabolism (Peschke & Mühlbauer, 2010). Insulin resistance and glucose intolerance were brought on by pinealectomy, which stopped the generation of melatonin. These conditions might be reversed with melatonin supplements (Zanquetta et al., 2003). This demonstrated definitely that melatonin is important for maintaining glucose homeostasis. The bodies of elderly rats have impaired insulin signaling due to a decrease in melatonin production; nevertheless, melatonin administration improves insulin sensitivity and delays the onset of age-related insulin resistance (She et al., 2014). In neonatal streptozotocin (STZ)-induced diabetic rats, Melatonin therapy corrected metabolic abnormalities and adipocytes' insulin responsiveness, or glucose utilization (de Oliveira et al., 2012). Also in one of the studies it is found that melatonin activated the hypothalamus-liver communication by suppressing hepatic gluconeogenesis and activating hypothalamic Akt in rats with intracerebroventricular injection. This further indicated a possible physiopathological connection between circadian abnormalities in metabolism and the lower melatonin levels observed in T2D patients (Faria et al., 2013). Melatonin regulates circadian rhythms by acting on melatonin receptors in many peripheral organs. The circadian system controls glucose metabolism in the same way as it does other physiological processes (She et al., 2014).

Interplay of Melatonin, Circadian Rhythm, and Diabetes: Insights into Receptors, Shift Work, and Pharmacological Interventions:

Melatonin and Circadian rhythm:

The suprachiasmatic nucleus (SCN), also known as the master circadian pacemaker, is responsible for preserving the 24-hour cycle that governs a variety of biological processes, including immunological response and sleep. Significant and crucial regulatory effects on the SCN are mediated by the hormone melatonin (5-methoxy-N-acetyltryptamine), which is mostly synthesized in the pineal gland and released during the hours of darkness or subjective night. It is well known that melatonin transduces photoperiodic information, which determines how long the night is (Dubocovich et al., 2003) (Dubocovich & Markowska, 2005) (Reiter, 1991) (Reiter, 1993) (Borjigin et al., 1999). And At least two high-affinity melatonin receptors, MT1 and MT2, are expressed by the SCN. These receptors coupled to G-proteins co-localize within the SCN and have unique molecular structures, chromosomal position, and pharmacological properties (Reppart et al., 1996). The MT1 and MT2 melatonin receptors have varied affinities for various ligands, allowing these ligands to be used to functionally characterise melatonin receptors in natural tissues (Dubocovich et al., 1997). Melatonin receptors MT1 and MT2 are connected to the activation of various signalling pathways (Dubocovich, 2007).

Melatonin is a naturally occurring hormone that regulates circadian rhythm (Reppert et al., 1995). Melatonin appears to play a role in glucose regulation. MTNR1b is a receptor expressed in the SCN, although Langerhans islets and pancreatic β -cells have also been identified as locations of expression. Melatonin inhibits insulin release, which is ordinarily driven by glucose (Hunt et al., 2001) (BOUATIA-NAJI et al., 2009) (Peschke et al., 2006).

Circadian Rhythm and diabetes type 2:

So apparently studies focusing on lifestyles linked to a mismatch in environmental, behavioural, and/or circadian cycles have revealed a link between type 2 diabetes risk and circadian disturbances. Also in one of the studies we Shift work is a common cause of circadian disturbance; in the US, over 20% of workers work nights, rotate shifts, or follow alternative schedules than traditional day/evening shifts (Mason et al., 2020). And according to a meta-analysis of observational data, people who work shifts are 9% more likely to develop diabetes than people who have never worked shifts (Gan et al., 2015). This risk is also strongly correlated with the length of exposure to shift work, with a 5% rise in risk for every five years of shift employment, per a longitudinal study utilizing the Nurses' Health cohorts (Pan et al., 2011). Crucially, research has also revealed that employees who work rotational shifts are significantly more likely to develop diabetes than those who perform regular night shifts (Vetter et al., 2018) (Gan et al., 2015).

Agomelatine relation with Melatonin receptor and circadian rhythm:

Agomelatine is a synthetic agonist of melatonin, a naturally occurring chemical that is released by the pineal gland and has a role in controlling sleep patterns and circadian rhythms. Agomelatine acts as an agonist on melatonin MT1 receptors, which reduces alertness signals to the cortex, and MT2 receptors, which causes a change in phase in the circadian cycle of sleep. Taking agomelatine at night to simulate the circadian pattern of melatonin production greatly enhances the quality of sleep (Norman, 2021).

Also agomelatine, a melatonin analogue, has a high affinity for the MT1 and MT2 receptors. IP₃, a hydrophilic molecule that is essentially formed from a lipid moiety, can bind to IP₃R on the endoplasmic reticulum (ER) and raise the Ca²⁺ level as a result. A specific Ca²⁺ ion channel in the plasma membrane is called the calcium release-activated channel (CRAC). The CRAC channel is triggered to gradually replace Ca²⁺ when it is depleted in the ER, a significant Ca²⁺ reserve in pancreatic β -cells. The internal membrane-bound enzyme known as sarco/endoplasmic reticulum Ca²⁺-ATPase (SERCA) uses the free energy of ATP to move Ca²⁺ across a concentration gradient. Cytosolic Ca²⁺ is sequestered by SERCA into membrane-bound intracellular compartments, which is its physiological function. It is possible to release this held Ca²⁺ as a general messenger for cellular signalling by using the medication thapsigargin, an antagonist of SERCA (Rochester & Akiyode, 2014).

Thapsigargin and Calcium signalling:

One of the main components of the roots and fruits of the Mediterranean plant *Thapsia garganica* L. is the sesquiterpene lactone thapsigargin. The initial pharmacological actions of thapsigargin were identified in 1978, and its whole structure was clarified in 1985. Not too long later, the general mechanism of the apoptotic-inducing Sarco-endoplasmic reticulum Ca²⁺-ATPase (SERCA) inhibition was uncovered. Thapsigargin is frequently employed to research Ca²⁺-signaling because of its strong antagonistic impact on the SERCA (Andersen et al., 2015).

The medication thapsigargin, an antagonist of SERCA, will primarily be used to maintain the concentration of Ca²⁺ in the cytoplasm by inhibiting the incorporation of Ca²⁺ ions into the ER. It may be utilized to release this stored Ca²⁺ as a general messenger for cellular signaling¹¹. 2-APB is a membrane-permeable regulator of intracellular calcium release triggered by inositol triphosphate (IP₃)¹². Although there are many different diabetic treatments available, their usage is severely restricted by side effects, low effectiveness, and high cost. A novel strategy for the development of diabetes therapies is suggested by the existence of circadian regulation over pancreatic function and the low levels of melatonin found in type 2 diabetic patients (Rochester & Akiyode, 2014).

In one of the studies done by (Sharma & Singh, 2022) it is found that The process behind insulin secretion is not directly correlated with thapsigargin but when it comes to inhibiting the ubiquitous SERCA proteins in mammalian cells, thapsigargin is the most utilized inhibitor.

Future prospects:

Several important prospects can direct the course of investigations in this field. A thorough examination of Type 2 Diabetes Mellitus (T2DM), its associated risk factors, and the developing role of melatonin and circadian rhythms opens up exciting avenues for future research and therapeutic development.

- **Precision medicine and personalized interventions:** Knowing more about the genetic components that influence the risk of type 2 diabetes opens the door to personalized interventions, wherein treatments are tailored to an individual's genetic predisposition, lifestyle, and environmental factors. This has the potential to completely transform the way that diabetes is managed.
- **Integrated Methods for Preventing Diabetes:** Multidisciplinary approaches that address lifestyle, genetics, and environmental factors may be very successful in stopping the progression from prediabetes to Type 2 diabetes. These approaches may involve behavioral changes, targeted pharmaceutical interventions, and precision medicine.
- **Comprehensive Investigation of Melatonin-Mediated Pathways:** Future studies should explore the molecular mechanisms through which melatonin affects glucose metabolism and insulin secretion. By comprehending the complexities of melatonin-mediated pathways, new therapeutic targets for the treatment of diabetes may become apparent.
- **Methods for Optimizing Circadian Rhythms:** Researching treatments that bring circadian harmony back could provide novel preventive approaches. Creating methods to optimize circadian rhythms could reduce the incidence of Type 2 diabetes, particularly in populations exposed to shift work or circadian disruptions.
- **Clinical Trials with Melatonin Agonists and SERCA Antagonists:** It is imperative to carry out carefully planned clinical trials involving melatonin agonists (like agomelatine) and SERCA antagonists (like thapsigargin). This will establish the viability of these drugs as T2DM treatment options through rigorous studies evaluating safety, efficacy, and long-term effects.
- **Technological Innovations for Diabetes Management and Monitoring:** By combining personalized interventions with wearable technology and continuous glucose monitoring systems, real-time diabetes monitoring and management could be improved.
- **Examination of the Impact of Gut Microbiota and Epigenetic Influences:** There is much to learn about the contribution of gut microbiota and epigenetic factors to insulin resistance and metabolic

dysregulation, and understanding these relationships may lead to the identification of new targets for intervention.

- **Worldwide Collaborative Initiatives:** Exchange of information, knowledge, and resources might hasten the development of context-specific therapies and our understanding of the various factors that contribute to diabetes, which is crucial in light of the growing worldwide prevalence of type 2 diabetes.
- **Patient Education and Empowerment:** Improving health literacy, encouraging lifestyle changes, and encouraging active patient participation in their care are all important aspects of empowering people with Type 2 diabetes through education and self-management techniques.

In conclusion, research on type 2 diabetes has a bright future ahead of it, with opportunities ranging from personalized medicine to novel therapeutic interventions. Through a collaborative and multidisciplinary approach, scientists can better understand the complexities of diabetes and open the door to game-changing approaches to its management, prevention, and treatment.

Conclusion:

The present review concludes that a thorough examination of Type 2 Diabetes Mellitus (T2DM) has been conducted, covering its epidemiology, historical foundations, risk factors, and complex molecular mechanisms. The evolution of diabetes research from ancient descriptions to modern classifications emphasizes the critical need to address this global public health issue, as T2DM is expected to affect 552 million people by 2030.

The discovery of risk factors—such as age, genetics, obesity, sedentary lifestyle, and components of the metabolic syndrome—highlights the intricate interaction between genetic, environmental, and behavioral factors in the development of type 2 diabetes. The identification of prediabetes as a precursor highlights the need for early detection in order to effectively intervene, underscoring the significance of preventive measures.

This review delves deeply into the newly discovered relationship between melatonin and circadian rhythms in type 2 diabetes. Melatonin is mainly produced by the pineal gland, and research reveals that it has effects on insulin secretion and glucose metabolism in addition to its established roles in regulating circadian rhythms. The complex interactions between melatonin, circadian rhythms, and diabetes are highlighted, especially when it comes to circadian disruptions brought on by factors like shift work.

Pharmacological interventions, such as the synthetic melatonin agonist agomelatine and the SERCA antagonist thapsigargin, offer intriguing avenues for future research and provide information about how circadian and calcium signaling pathways may be modulated for novel approaches to diabetes treatment.

With the prevalence of type 2 diabetes (T2DM) rising worldwide, it is critical to close the knowledge gaps regarding the complex relationships between melatonin, circadian rhythms, and diabetes. This review highlights the need for additional research to fully understand these relationships in order to develop novel therapeutic approaches for managing and treating diabetes. Through the integration of insights from molecular mechanisms, therapeutic interventions, and epidemiology, the review advances our understanding of T2DM and sets the path for future investigations in this important area.

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