



## **Association between Chronotype and Type 2 Diabetes: A Literature Review**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Chronotype is an individual attribute of a person regarding circadian rhythm. Past literature denotes that the evening chronotype individuals are more prone to obesity, sleep problems, unhealthy diet and lifestyles. This review investigates original research studies on association between chronotype and diabetes. Total 28 articles were reviewed which were published in four research databases. Evening or later chronotype was associated with diabetes and poor glycemic control. Dietary practices like breakfast skipping, percentage of calories consumed at night to total daily calories were found to partially mediate the association. There is need to study how several risk factors of diabetes and the circadian disruptors influence this association. The abstracts of the shortlisted articles were further studied and relevant articles were shortlisted. Finally, total 28 articles were selected for the review. Articles published in English language only were included. The decision to include or exclude a study; was taken by agreement of all authors.

**Keywords:** Chronotype; diabetes; prediabetes; Insulin; glycemic control.

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## 1. INTRODUCTION

The World Health Organization (WHO) (2020) mentions Diabetes as one of the first ten causes of global mortality. The prevalence of Diabetes is steadily increasing since past few decades. The number of people living with Diabetes are estimated to rise from 463 million in 2019 to 700 million in 2045 [1]. It has been observed that the blood glucose levels are stable throughout the night in normal weight non-diabetic individuals. Glucose tolerance and insulin sensitivity in a healthy person are at lower levels in evening than in morning period [2]. Such phenomenon occur due to the internal biological clocks in human body. These clocks cause periodic fluctuations and set rhythms in various physiological processes in the periodic manner. Such processes include sleep and awakening, hormone secretions, body temperature and certain metabolic processes. The rhythmic fluctuations occurring at the interval of 24 hours are called as 'Circadian Rhythms'. That a central clock in the brain i.e. hypothalamic Suprachiasmatic Nucleus (SCN) generates these rhythms. Additionally, the organ-level or cellular-level peripheral clocks set rhythm for various functions of that organ. The peripheral clocks are regulated by the SCN as well as environmental and behavioural stimuli like timing of food ingestion, exercise, etc. When a person is not able to synchronize daily activities with his own circadian rhythm; the phenomenon is called as 'Circadian Disruption' or 'Circadian Misalignment' [3]. Globalization has caused vast amount of changes in human lifestyles such as late night or shift work, irregular meal timings, increased exposure to artificial light through mobile phones or computers. These factors are potential disruptors of circadian rhythms. The short term episodes of circadian disruptions can disturb glucose metabolism; and repeated disruptions can be responsible for development of various cardiometabolic disorders. The relationship between circadian disruption and metabolic disorders may also be influenced by individual variabilities [4]. The circadian disruption may also be causally associated with various cardiometabolic disorders [5]. The association between circadian disruptions and diabetes has been observed in previous studies. They are able to produce impairments in pancreatic beta cell functions, have adverse impact on glycemic control and hence, predispose the person to higher risk of diabetes. More the disruption, more is the risk. Additionally, there is need to explore

that how circadian disruptions can impact glycemic control in diabetes patients.

Chronotype is considered as a person specific attribute which reflects circadian phase of an individual. It can also be described as behavioural preference of the internal circadian clock of a person [6]. A person can be considered to be of Morning chronotype i.e. 'Early Larks' or of Evening chronotype i.e. 'Night Owls'. The 'Early Larks' are characterized by early awakening, sleep early in the evening and being mentally and physically at their finest at morning time. The 'Night Owls' awake comparatively at a later time than larks, stay up late at night, sleep at comparatively later time than larks and are mentally and physically at their finest during late afternoon or evening time. A person can be placed on a continuum from morningness (earlier chronotype) to eveningness (later chronotype). Chronotypes are often classified as 'Morning', 'Evening' and/or 'Intermediate' i.e. neither morning nor evening' type [7]. These classifications have been defined according to the cut-off points on the continuum measured by various chronotype measurement scales. These scales primarily measure self-reported behavioural preferences related to sleep and wake, alertness and activeness.

These scales have been widely used in epidemiological research. Past studies have observed that the persons with the attribute of eveningness, are associated with unhealthy dietary practices and lifestyles as well as obesity. [8] mentions that the later chronotype persons can be at risk of poorer glycemic control because of possibility of disruption of circadian rhythms. However, mentions that a subgroup of later chronotypes has characteristics similar to the morning chronotype, such as good sleep. The need for exploring association of chronotype with various dietary patterns has been mentioned. states that there is lack of clarity on how people with different chronotypes adapt to the shift work. Similarly, other factors related to glucose metabolism and circadian disruptors should also be studied for their interactions with glucose metabolism in persons with different chronotypes. This review study was undertaken with the objective of exploring findings of the previous studies about the association between chronotype and diabetes; and role of risk factors of diabetes and circadian disruptors in the association.

## 2. METHODOLOGY

The literature review was conducted electronically by searching the four electronic databases; 'SCOPUS', 'Web of Science', 'PubMed' and 'ScienceDirect'. The search terms used were 'Chronotype' combined with 'Diabetes', 'Prediabetes', 'Insulin' and 'Glycemic Control'. We included only original research articles, and excluded review articles, book chapters, conference abstracts and editorials. The literature search was done during the time period of 13<sup>th</sup> April to 27<sup>th</sup> April 2020 [9]. Out of total 1003 search results; only 471 were original research articles. The studies which describe association or relationship between Chronotype and Diabetes Mellitus, Prediabetes, Insulin resistance, Glycemic control or any other related aspects; were selected. The titles of the articles were read and relevant articles were shortlisted. The process of selection of research articles for review is described in Fig. 1. Out of the 28 studies, we could find out full text of only 25 studies electronically.

## 3. RESULTS

All the selected studies were published in the time period of 2011 to 2020. Majority of the studies were from United States of America (36%); followed by various European countries (32%), followed by Asian countries (29%). Remaining one study was undertaken in Canada. Chronotype assessment was mainly done by the 'Morningness Eveningness Questionnaire (MEQ)' scale, by calculation of 'Mid Sleep Time on free day method' and a self-reporting single

question about self-perception of own chronotype; each by 25% of the total studies [10]. 18% of the studies used 'Composite Scale of Morningness (CSM)' and one study used 'Children's Morningness-Eveningness Preferences Scale'. We could not identify chronotype assessment method of one study which used data from a previously conducted study. The list of the studies which were selected for the review and their major findings are given the Table 1.

The evening chronotype was significantly associated with diabetes and had comparatively elevated levels of impaired blood glucose and insulin levels in various studies. The significant association was not found in all studies. significantly higher values of fasting insulin and fasting blood glucose levels in evening chronotype participants compared to morning chronotype participants. Similarly, could not found any association between evening chronotype and fasting blood glucose, fasting insulin or HOMA-IR levels in an adult population [11].

The evening chronotype participants also had significantly higher Glycated Haemoglobin (HbA1c) values i.e. poorer glycemic control in prediabetic and diabetic patients did not found such association in a group of prediabetic and recently diagnosed untreated diabetic patients. Similarly, evening chronotype participants did not have significantly higher HbA1c levels than morning and 'neither evening nor morning' chronotype participants in diabetic patients.

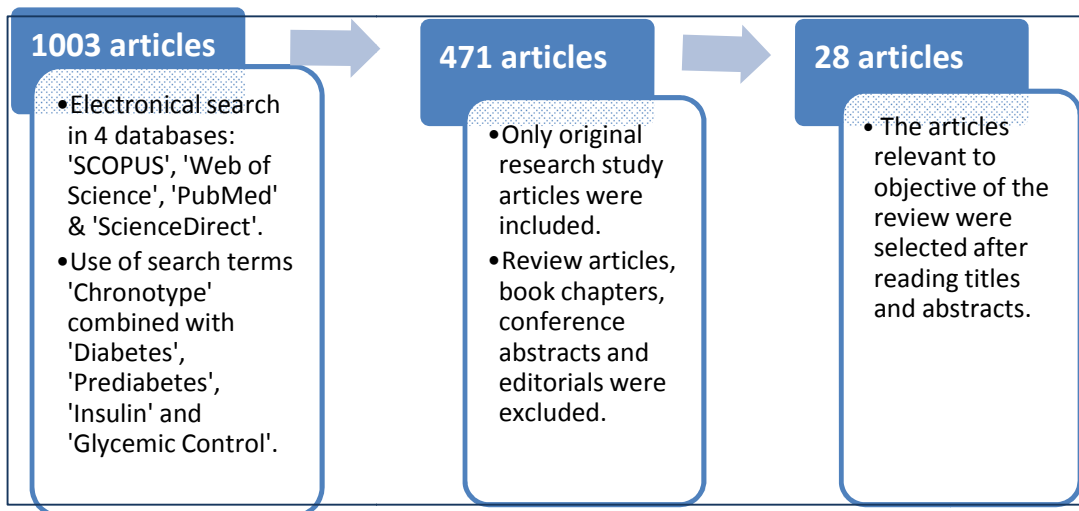


Fig. 1. Process of selection of research articles for review

**Table 1. List of the studies selected for review and major findings**

<b>Sr. No.</b>	<b>Authors</b>	<b>Year of publication</b>	<b>Major findings</b>
1	Kelly <i>et al.</i>	2020	A significant relationship was found between eveningness and poor glycemic control in diabetic patients; but only in patients who had more than 90 mins of Social Jet Lag (SJL).
2	Tan <i>et al.</i>	2020	Late chronotype was significantly associated with diabetes independent of MTNR1B risk allele.
3	Saetung <i>et al.</i>	2019	Eveningness was significantly associated with depression in diabetic patients in two cohorts from two different countries.
4	Mokhlesi <i>et al.</i>	2019	Chronotype was not associated significantly with glycemic control in prediabetic and recently diagnosed, untreated diabetes patients.
5	Hulsegge <i>et al.</i>	2019	No significant differences in risk of diabetes was observed in shift workers versus daytime workers; in any group of participants of particular chronotype.
6	Ritonja <i>et al.</i>	2019	Evening chronotype participants having night shifts had significantly more risk of diabetes than evening chronotype participants working only in day shifts.
7	Adams & Neuhausen	2019	Morning chronotype was significantly associated with lower values of total fatty acids, and healthy fats like Mono Unsaturated fatty acids and Omega-3 fatty acids. Higher levels of Total fatty acids and healthy fats were associated with lower risk of diabetes.
<b>Sr. No.</b>	<b>Authors</b>	<b>Year of publication</b>	<b>Major findings</b>
8	Jones <i>et al.</i>	2019	No causal association was found between morning chronotype and risk of diabetes.
9	Nimitphong <i>et al.</i>	2018	Later timing of breakfast consumption mediated the relationship between evenignness and Body Mass Index (BMI), in group of diabetic patients.
10	Vera <i>et al.</i>	2018	Evening chronotype was significantly associated with diabetes. A risk score based on genetic variants of chronotype was not significantly associated with diabetes.
11	Dong <i>et al.</i>	2018	A composite dimension of good quality of sleep was not significantly associated with diabetes in eveningness oriented adolescents.
12	Škrlec <i>et al.</i>	2018	Intermediate chronotype was significantly associated with diabetes comorbidity in a population of Myocardial Infarction patients.
13	Knutson and Schantz	2018	Later chronotype had significantly higher risk of diabetes than earlier chronotypes.
14	Anothaisintawee <i>et al.</i>	2017	Significant association was present between eveningness and poor glycemic control in prediabetic patients.
15	Knutson <i>et al.</i>	2017	Evening chronotype was significantly associated with higher HOMA-IR values in a combined population of diabetic patients and non-diabetic persons.
16	Jones <i>et al.</i>	2016	No causal association was seen in chronotype and diabetes.
17	Reutrakul <i>et al.</i>	2015	Evening chrontype was significantly associated with poor glycemic control in diabetic patients.
18	Vetter <i>et al.</i>	2015	Evening chronotype persons working with no night shifts had significantly higher risk of diabetes than Morning and Intermediate chronotype persons working with no night shifts. The risk of diabetes significantly and positively correlated with increasing years of night shifts in morning chronotype participants.
20	Lucassen <i>et al.</i>	2013	Evening chronotype persons did not have significantly higher levels of fasting glucose and fasting insulin compared to morning chronotype persons.
21	Merikanto <i>et al.</i>	2013	Evening chronotype participants had significantly higher risk of diabetes than morning chronotype participants.

The role of various factors in the association was also studied. These factors included risk factors of diabetes like obesity, unhealthy dietary practices, physical inactivity; potential circadian disruptors like sleep disturbances and working in shifts; as well as other factors like age, sex and ethnicity.

The association was found to be independent of various sleep related problems like sleep duration [12]; It perceived sleep debt adopted a comprehensive strategy to study the role of sleep through development of a composite sleep health score consisting of various dimensions of sleep; in an adolescent population. The composite score was not associated with presence of diabetes for previous one year; though better sleep health score was found to be associated with significantly reduced risk of emotional ( $p \leq .001$ ), cognitive ( $p=.01$ ) and social ( $p=.04$ ) health [13].

The intensity and duration of shift work were found to influence the association in a study done. In this study, the evening chronotype participants who were working in rotating shifts had significantly higher levels of fasting blood sugar compared to the evening chronotype participants working only in day shifts [14]. It was also found that amongst groups of intermediate and evening chronotypes; those who were working for more than three consecutive night shifts had higher fasting blood sugar levels than intermediate and evening chronotype persons working for less than three consecutive night shifts or doing only day shifts. Hence, harmful effect of shift work was observed in evening chronotypes for impaired blood sugar levels. On the contrary, found that late chronotype participants who never worked in night shifts had significantly higher risk of diabetes compared to the morning and intermediate chronotype participants who never worked in night shifts. Additionally, the risk of diabetes significantly and positively correlated with increasing years of night shifts in morning chronotype participants. Similar results were observed for incident diabetes cases too. However, did not find significantly higher risk of diabetes in shift workers versus daytime workers; in any group of participants of a particular chronotype [15].

The association was found to be independent of various unhealthy dietary practices like later breakfast time, later dinner time, later midpoint of food intake, composite score of inappropriate eating behaviours, emotional eating, higher

triglyceride levels and composite score of healthy eating [16]. Mediating role of certain dietary practices in the association was observed statistically. By application of regression models, amount of calories ingested at dinner were found to minimally partially mediate the relationship between evening chronotype and poor glycemic control in an adult diabetic population. In a study on diabetic patients; earlier breakfast time mediated the association of morning chronotype with lower BMI in a diabetic population found that the later chronotype acted as a partial mediator for association between not having daily breakfast and lower glycemic control in diabetic patients. However, evening chronotype was associated with elevated levels of Mono Unsaturated Fatty Acids (MUFA) and Omega-3 fatty acids; which had protective effects against diabetes.

The association was found to be independent of BMI in various studies. The association between eveningness and poor glycemic control were observed to be independent of SJL in a Thai prediabetic population. In contrast to this finding, [17] found such significant association only in those diabetic participants who reported SJL of more than 90 minutes. Several studies found the association to be independent of age factor However, age and sex related variations were also found in few studies. The association of evening chronotype with insulin resistance was observed in participants above age of 35 years. Significant association was however seen only in age group of 56 to  $\leq 70$  years for fasting blood glucose levels in this study. Sexwise differences were observed such that the association was found only in female intermediate chronotype participants. Total percentage of the evening chronotype participants was only 0.5% of the total study population in this study. The association between fasting blood sugar level and Diabetes Mellitus was observed only in men. The evening chronotype was significantly associated with higher depression in two separate cohorts of diabetic patients from USA and Thailand. However, the association between evening chronotype and diabetes was found to be independent of various depression related symptoms in three studies. The association was also found to be independent of other factors in various studies like ethnicity, less physical activity, smoking and alcohol consumption.

Causal association between chronotype and diabetes was studied in genetic context by using Mendelian Randomization techniques in two

Genome wide analysis studies which were conducted on an identical biobank dataset [18]. In these studies; the chronotype was not found to be causally associated with diabetes and fasting insulin levels. A risk score based on the genetic variants accounting for chronotype (GRS) is formulated. The GRS was found to be significantly associated with chronotype measurement by MEQ scale; but it was not significantly associated with the fasting blood glucose, fasting insulin levels and HOMA-IR values. The results denoted that the GRS could represent the chronotype, but was not helpful to associate with metabolic risk. found that later chronotype was associated with diabetes independent of MTNR1B receptor risk allele, which is related to inhibition of insulin secretion. However, the association was also observed to differ across MTNR1B rs10830963 genotypes.

#### **4. DISCUSSION**

Apart from being associated with risk factors of diabetes like obesity; additional circadian disruption can put persons at more risk of diabetes. In the studies selected for the review; the evening chronotype was associated with diabetes, impaired blood glucose and insulin levels as well as poorer glycemic control. Also, the risk for diabetes, and levels of blood sugar and insulin were comparatively higher in later chronotypes than earlier chronotypes. However, few studies could not find such associations, or the association was found to be influenced by other factors. It is still unclear that whether evening chronotype can be more adaptive to night shifts according to their later sleep timings and later phase of alertness. The selected studies also found varied types of influence of shift work on the chronotype and its association with impaired glucose metabolism. The evening chronotype persons are comparatively more associated with unhealthy dietary practices like delay in meal timing, breakfast skipping, nocturnal eating, lesser consumptions of proteins and vegetables, and increased consumption of sucrose, sweets, caffeine and alcohol [19]. Similar to this, our studies also found association between the evening chronotype and various unhealthy dietary practices. Later chronotypes are found to make up sleep debt in weekends more than earlier chronotypes and also have more sleep related issues than earlier chronotypes. But, this did not seem to influence the association as the association was found to be independent of various sleep related

problems in most of our studies. Though, obesity is a major risk factors of diabetes; many of the included studies found the association to independent of higher BMI [20]. Mediating role of only few of such factors like the calories consumed at dinner time later breakfast timing and breakfast skipping have been studied statistically in past studies.

#### **5. CONCLUSION**

Significant association between later chronotype and diabetes as well as poor glycemic control was observed in the studies selected for the review. As most of the available studies had adopted cross sectional design; prospective design studies should be undertaken to explore the association and related variables. Only few of dietary practices were statistically investigated for their mediating role in the association. Considering multidimensional nature of diabetes; mediating role of other risk factors of diabetes and potential circadian disruptors in the association needs to be investigated. Additionally, there is need to explore how people with different chronotypes respond to various anti-diabetic interventions. Exposure to artificial and natural light is one of the major circadian disruptor, but no study investigated its role in the association. As diabetes; mediating role of various risk factors needs to be examined. The role of ethnicity also need to be explored by undertaking studies in different parts of the world and in different ethnic populations.

#### **CONSENT**

It is not applicable.

#### **ETHICAL APPROVAL**

Not applicable.

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#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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