# Shift Work and Metabolic Syndrome Updates: A Systematic Review

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## Abstract

Shift work can cause circadian cycles disturbances and misaligns the endogenous rhythms. The physiological variables are driven by the circadian system and, its misalignment, can impair the metabolic functions. Thus, the main objective of this study was to evaluate the metabolic alterations as a result of shift work and night work reported in articles published in the last 5 years, using the eligibility criteria both gender and indexed articles in English language. In order to execute this work, we perform a systematic review according to PRISMA guidelines and searched about Chronobiology Disorders and Night Work, both related to metabolism, in Medline, Lilacs, ScienceDirect and Cochrane. Cross-sectional, cohort and experimental studies with low risk of bias were included. We found a total of 132 articles, and, after the selection process, 16 articles remained to be analyzed. It was observed that shift work can cause circadian misalignment and, consequently, some metabolic parameters alterations such as an impaired glycemic control and insulin functioning, cortisol phase release, cholesterol fractions imbalance, changes in morphological indexes and melatonin secretion. There are some limitations, such as heterogenicity in used databases and the 5 years restriction period, because the effects of sleep disturbance may have been reported earlier. In conclusion, we suggest that shift work interferes with the sleep-wake cycle and eating patterns, which cause crucial physiological alterations that, together, can lead to metabolic syndrome.

**Keywords**

- Metabolic syndrome
- shift work
- sleep disruption
- eating patterns

## Introduction

The internal temporal system is organized as a network of oscillators and drives the biological rhythms. The suprachiasmatic nucleus of the hypothalamus is considered the central oscillator,[1] which receives direct luminosity information, and is able to synchronize the peripheral oscillators.[2,3] Under normal conditions, the behavioral cycle and endogenous timing system are synchronized at an appropriate phase angle, and the more stable these phase relationships, better the anticipation of circadian rhythms, like hormone balance and sleep.[1] In consequence, molecularly, the temporal system regulates the expression and the activity of enzymes and hormones involved in metabolism, improving the metabolic function.[1]

When the phase relationships are unstable, for example changes between consecutive days, causes a circadian misalignment, a mismatch between the endogenous and exogenous circadian cycles of environmental and behavioral variables, such as light-dark cycles, sleep-wake, rest-activity,

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and food-fast cycles.[4] The circadian misalignment can occur between any two variables considered, with different consequences. This phenomenon is commonly observed in shift workers – people who maintain an unstable or rotating work schedule, including two or more shifts per day or night.[5] Similar circadian disturbance can be observed between the night workers – people who work only in night shifts, usually in alternate nights (12h work x 36h rest).[5] Thereat, the night workers are submitted to a chronic sleep deprivation once they are allowed to sleep only in nights off, what usually corresponds to alternated nights.[5,6] Both work regimens impaired the circadian organization and commonly they adopt an irregular feeding time, eating during their shifts, even if it is nighttime.[5,6]

The circadian system reacts differently to the environmental cues, depending on the internal phase and the relationship with the *zeitgeber* (time-giver, in German), for example, the phase response curve to the light-dark cycle stimuli can be individually modulated.[7] *Zeitgebers* are diverse and include some social clues, such as working time, feed schedule and the light-dark cycle, and they are an important stimulation to entrain the clock phase, and thereafter, the circadian system.[8] The feed schedule can synchronize the behavior, not only the feeding time, but also the food quantity and quality.[6] And the opposite also works: behavior can affect the metabolism.

Alterations in the circadian cycle commonly have physiological consequences, for example, the night work with sleep deprivation can decrease the melatonin levels and may be linked to cardiometabolic and body alterations.[8–10] Sleep deprivation is a loss of night's sleep[11] or when the total sleep time per night is not enough, sleep is considered shorter than need. On average, short sleep lasts less than 5 or 6 hours a day.[12,13]

Chronic sleep deprivation can alter the sleep architecture,[14] which may provoke changes in secretory profile of some hormones, such as cortisol and melatonin,[15] as well as alterations in immune system elements[14] and in the glucose control.[14] The lack of glycemic control, including insulin secretion,[14] insulin resistance[14] and hyperglycemia[14] can lead to obesity and hypertension, making the individuals more prone to Metabolic Syndrome (MetS).[16–20]

MetS is considered an epidemic,[21] and there are some morphophysiological variables to consider. The International Diabetes Federation includes gain in waist circumference (WC) plus two of the following: dyslipidemia, increased Blood Pressure (BP) or hyperglycemia[21] to be considered with MetS. On the other hand, the World Health Organization consider MetS the one who presented insulin resistance (IR) in addition to two of the following criteria: central obesity, Body Mass Index (BMI) $> 30\,kg/m^2$, hypertriglyceridemia, hypercholesterolemia and/or microalbuminuria.[22]

Considering the vast literature about the MetS as a consequence of circadian disruption, the main objective of this study was systematically reviewing the literature to evaluate the metabolic variables that lead to the MetS, as a result of shift work (SW) and/or night work reported in articles published in the last 5 years.

## Material and Methods

The present study was performed according to PRISMA guidelines[23] and registered in PROSPERO database (CRD42022300745). The search, selection and evaluation process were done by two independent researchers in parallel. Both searched in the four databases (Medline, Lilacs, ScienceDirect and Cochrane), excluded duplicates, read the titles and abstracts, and applied the exclusion and inclusion criteria independently, as described in ►**Figure 1**. Finally, we analyzed the remaining articles independently, and also, the selected variables described in the International Diabetes Federation (gain in WC, dyslipidemia, increased BP and hyperglycemia[21]) and in the World Health Organization (IR, central obesity, BMI, hypertriglyceridemia, hypercholesterolemia and/or microalbuminuria[22]) to report in this review.

The first search on Medline, with Chronobiology Disorders, used the descriptor "Chronobiology Disorders/metabolism" [Mesh] to refine the search and intersect with metabolism. The second search on Medline, with Night Work, did not use the MeSH descriptor because the term was not introduced in MeSH, so the search bar with "Night Work" AND metabolism was used. Both used the following filters: published in the last 5 years and human subjects. Lilacs' research was done using "Chronobiology Disorders" AND metabolism; "Night Work" AND metabolism, both with filters: published in the last 5 years and humans. In ScienceDirect searches, we used "Chronobiology Disorders" AND metabolism; "Night Work" AND metabolism, both using articles from 2016 to 2021 which corresponds to the last 5 years, and the research articles, short communications, and news were included in the results. The last search was done in Cochrane and used "Chronobiology Disorders" AND metabolism; "Night Work" AND metabolism, in articles published between 2016 and 2021.

After these searches, we filtered the results by reading the titles and abstracts, respectively, looking for articles that dealt with topics on chronobiology, chrononutrition, metabolic syndrome, diabetes, and obesity. The inclusion criteria were articles published in English and in indexed journals in the last 5 years. Cross-sectional, cohort and experimental studies were included in this work. According to PICOS study design, the selected participants were working-age adults of both genders and interventions were the clinical course of SW and night work patients with MetS. The control population was the general population working during daytime and reported as a day worker. Finally, clinical data, original and research articles, and short communication articles were analyzed, while review articles, systematic reviews and meta-analyses were excluded.

After selected the studies, we performed three bias analysis tools: AXIS for cross-sectional studies,[24] ROB2 for random trial or experimental trial[25] and NEWCASTLE-OTTAWA SCALE[26] for controlled or random cohort. We performed the bias analysis independently and equally divided between both researchers. After performing the analysis, we compared and checked the results found.

 

The searches in all databases were done in February 2021.

## Results

The search was done in a systematic way, outlined in ►**Figure 1**. The search for "Chronobiology Disorders" on Medline returns 50 articles. Of them, 22 were excluded and 28 articles remained to be analyzed. The second search on Medline, with the descriptor "Night Work," returns 35 results. Applying the exclusion criteria, 5 articles were excluded, remaining 30 papers. Searches at Lilacs obtained 1 article with the "Chronobiology Disorders" descriptor, and 2 articles with the "Night Work" descriptor, with no exclusions. The ScienceDirect research results in 3 articles with the term "Chronobiology Disorders", with one exclusion, and 34 with "Night Work", with 2 exclusions, remaining 32 papers. In Cochrane, "Chronobiology Disorders" had 5 results, with 3 studies still in progress and being excluded, leftover 2; and "Night Work" brought 9 results, of which 5 studies were in progress and 2 duplicates were discarded, resulting in 2 articles remaining. We count a total of 93 articles after adding all results and excluding duplicates.

The next step was to filter the results by reading the titles. We included the studies that dealt with topics on chrononutrition, metabolic syndrome, diabetes, or obesity. This process resulted in 36 papers. Then, we read their abstracts and looked for those that best fit the same topics used to filter the titles, and 16 articles remained. We classified the results according to the main approaches and reported the results.

The bias analyses were done using three different tools, as explained in methods, for each type of article. 10 studies are cross-sectional studies and were analyzed by AXIS tool, 2 studies are random trial or experimental trial and were analyzed by ROB2, and finally, 4 studies are controlled or random cohort and were analyzed by NEWCASTLE-OTTAWA SCALE. We find low bias risk for all selected studies and no one article was excluded.

The whole searching process is described in ►**Figure 1**.

We found the sleep deprivation in shift workers and night workers, on average, was 1.6 hours higher when compared to exclusive day workers,[27] and it was often related to worse glycemic status[12] and increased risk of diabetes.[5,28] Also, there is a higher prevalence of MetS among night workers when compared to day workers.[27] We suggests that an hypothesis is the eating patterns disruption could lead to MetS development.[29]

### Metabolic Syndrome

The prevalence of MetS in workers exposed to night shifts for up to 10 years was 37.5% higher when compared to diurnal workers.[27] Also, people who work at night for more than 10 years had a prevalence of MetS of 50% higher when compared to regular diurnal workers.[27] Besides, there was no difference between sleep duration on workdays and days off for diurnal workers without sleep debt.[27] However, the night workers showed a 1.6 hours' sleep debt per workday and about 1 hour shortened sleep duration compared to day and former night workers.[27]

Participants with MetS present a worse dietary pattern, poor sleep quality and more smokers than the general

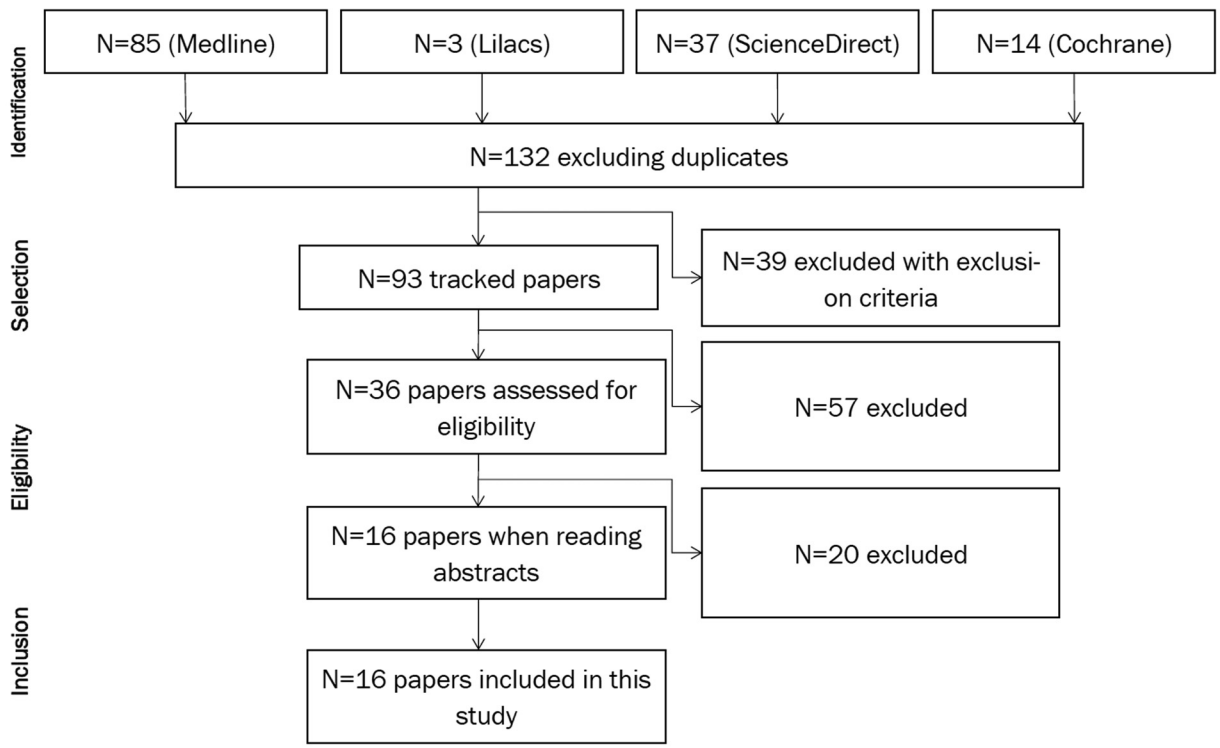


**Fig. 1** The search map of the articles selected to be discussed in this systematic review.

 

population.[27,30] There were no differences in the leptin levels (a hormone associated with a satiety feeling) and sleep duration on working days and days off in relation to MetS individuals.[27] In addition, the levels of total cholesterol and triglycerides decreased significantly in night workers, and high-density cholesterol (HDL-c) increased in accordance with the sleep duration in regular daytime workers, but there was no difference between regular and shift workers.[5] Night shift workers had higher oxidative stress and fewer antioxidants compared to day shift ones.[9]

In controlled studies, individuals with no sleep rebound presented a higher prevalence of MetS components, 27.46%, compared to 19.87% for individuals who had a sleep rebound,[29] such as glucose increase, abdominal obesity, and high cholesterol levels.[29] Among participants who slept less than 6 hours on weekends, the MetS risk was 0.655 times lower.[29] The optimal duration for weekend sleep rebound was between 40 min and 360 min,[29] and more MetS components were associated with individuals without sleep rebound.[29] Withal, participants without MetS had similar weekend sleep as those with MetS, but with about 9% longer duration.[16]

Further, the MetS patients presented anthropometric alterations in BMI and WC. There was a relationship between BMI and sleep deprivation, the shorter the sleep duration, the greater were the tendencies of high BMI.[9,31] Also, BMI is increased in subjects with sleep deprivation,[31] and this factor is independently associated with poor sleep quality and short sleep duration.[31]

Moreover, sleep deprivation can be associated with social jetlag.[31] The social jetlag is caused by the mismatch between social rhythms, such as work, and endogenous rhythms, such as sleep-wake cycle. It becomes more pronounced on weekends, days when you sleep late to compensate for the slight sleep deprivation of workdays.[31] While this phenomenon was observed more frequently in youngsters,[30] the subjects that exhibited poor sleep quality were significantly older, about 6.7 years,[28] predominantly men, high BMI, and a substantial proportion with hypertension as comorbidity.[28]

Nevertheless, excluding subjects with diabetes, systolic blood pressure decreases significantly according to sleep duration,[5] suggesting the sleep deprivation increases the blood pressure.[28]

## Glycemia Control

Abnormal sleep duration is associated with uncontrolled glucose metabolism.[5] Fasting blood glucose level varies according to sleep duration: short sleep duration was associated with higher levels and long sleep duration was associated with decreased levels of fasting blood glucose in shift workers.[5] In these subjects, fasting blood glucose showed different levels across sleep duration: 93.3 mg/dL for short duration, 92.3 mg/dL for normal duration and 88.5 mg/dL for long duration.[5]

But, on the contrary, other study affirms that in general, for each additional hour, the adjustments of fasting blood glucose were 0.79 mg/dL higher.[31] For example, healthcare shift workers had higher fasting glucose and fasting insulin when compared to healthcare non-shift workers, they also present higher Homeostatic Model Assessment Insulin Resistance (HOMA-IR) index, with a positive association between increasing values of HOMA-IR and SW.[32] In this aspect, the glucose oxidase in night workers was 17 mg/dL higher than diurnal workers, independently of the sleep duration.[9]

In addition, some problems such as elevated number of wakes after the sleep onset and short sleep duration, or other parameters of poor sleep quality with an activity index $\geq 50$ by actigraphy, are associated with impaired insulin secretions and sensitivity to insulin (SI).[28] In a selected study[28] about the people with actigraphy $\geq$ 50%, 28.3% presents glucose tolerance, 41.3% presents reduced tolerance and 30.4% presents type 2 diabetes (T2D).[28]

Thus, experiments with four nights of simulated night work, participants who ate at night presented an increase of 27% on the glucose area under the curve (AUC) during the simulation.[33] On the other hand, participants who did not eat at night presented a 12% increase in the glucose AUC response to breakfast on days in simulation.[33] In the same study,[33] insulin AUC was increased in both groups, 11% for who ate at night and 18% for who not, when compared the previous night to the simulation.[33] It suggests that the glycemia curve is altered due to feed schedule, while the insulin secretion is influenced by the sleep-wake cycle.

The glucose after eating food, the postprandial glucose, was 6.5% higher in the biological night compared to the morning, in chronic night workers,[4] with lower insulin levels for those with evening chronotype, indicating reduced function of the β cells.[4,34] Postprandial glucose is also higher in those of the evening chronotype if compared to morningness, indicating insufficiency in the response of pancreatic β cells.[35] About behavioral cycles, no differences were found,[35] suggesting a similar function of β cells of the pancreas in day and night workers.[4] The functions of pancreatic β cells were 19.1% reduced on the biological night compared to the biological day.[34] However, there were no significant effects of circadian misalignment on pancreatic β cells function, but SI was 16.5% lower in circadian misalignment.[34]

Thereon, the glucose after eating food of chronic night workers was 5% higher at dinner than at breakfast,[4] with a relative tolerance to glucose in the meal time and suggested reduced SI.[4] Postprandial glucose was 5.6% higher in the condition of circadian misalignment than in alignment,[4] but ones with morningness chronotype did not have their postprandial insulin altered in misalignment condition, and those of the eveningness chronotype presenting an increase in circadian misalignment.[4]

There were no significant correlations between changes mediated by circadian misalignment in postprandial glucose, postprandial insulin from the previous or later phase and alterations mediated by circadian misalignment in total sleep time or at any stage of sleep.[4] Although, using the 75 g oral glucose tolerance test (75gOGTT), coupled with poor sleep quality may exhibit high tendencies of T2D.[28]

In other glucose test, the glycated hemoglobin (HbA1c) test, useful in detecting abnormal plasma glucose levels, is

 

formed in non-enzymatic reactions between hemoglobin and plasma glucose, occurring naturally in the entire population and markedly in individuals with uncontrolled diabetes. In this aspect, individuals with sleep duration <5 and 8> hours presented high values of HbA1c: 5.84% for less than 5 hours and 5.85% for more than 8 hours, compared with subjects with 7-8 hours of sleep, with 5.74% of HbA1c.[31] However sleep quality, daytime sleepiness, and obstructive sleep apnea risk were not significantly associated with HbA1c.[31]

In other study about the sleep parameters, obstructive sleep apnea patients had high levels of HbA1c, but sleep duration and quality were not associated with the level of HbA1c.[35] Therewithal, a higher BMI, increased triglyceride levels and presenting risk for obstructive sleep apnea were independently associated with higher levels of HbA1c.[35–37] HbA1c was associated with elevated triglycerides as well as evening chronotype, whereas social jetlag was not significantly related to HbA1c levels.[35]

In addition, individuals with an evening chronotype, who prefer to sleep and eat later, are independently associated with higher concentrations of HbA1c in patients with prediabetes.[35] Two hours of drag on the mid-sleep time on a free day adjusted for sleep debt have the same effect as about 74% of a BMI unit, one of the strongest risk factors for diabetes.[35] Moreover, some factors such as age, educational level, smoking, and depressive symptoms were not significantly associated with HbA1c levels.[35]

### Cortisol

The circadian misalignment did not affect cortisol levels,[4] but it did change the phase of cortisol release.[4] Cortisol levels in circadian misalignment reach the acrophase at the end of the waking period,[4] instead of at the beginning of the waking period in the aligned condition.

The individuals with both T2D and diabetic retinopathy (DR) have significantly higher salivary cortisol at various time points than those who haveT2D without DR.[38]

### Retinopathy

Additionally, we found a curiously variable evaluated inside the theme: retinopathy. Pupillometry showed that T2D with DR significantly reduced the intrinsically photosensitive retinal ganglion cell function, as reflected by the lower relative amplitude of post illumination pupil.[38] There were significant associations between worse control and lower post illumination pupil response amplitude and greater variability in sleep duration.[38] Smaller post illumination pupil amplitudes were also associated with greater insomnia symptoms.[38]

The participants with T2D, with and without DR, had more signs of peripheral neuropathy, as well as autonomic neuropathy.[38] In comparison with those with an evening time dim light melatonin onset, those without an evening time dim light melatonin onset had lower urinary overnight urinary 6-sulfatoxymelatonin,[38] along with more severe neuropathy. The absence of an increase in melatonin levels in patients with DR is not due to light suppression because the dim light melatonin onset was measured in low light conditions.[38]

T2D people with DR showed significantly greater insomnia symptoms and greater nocturnal variability in sleep duration.[38] Also, T2D and DR produced less nocturnal overnight urinary 6-sulfatoxymelatonin excretion.[38] The sleep breathing disorders were more severe in T2D with DR, compared to T2D without DR.[38]

## Discussion

Sleep duration has been progressively reduced in the last 50 years and, simultaneously, MetS has grown in prevalence, and it became a public health concern.[39] At the same time, there is much evidence linking the short sleep duration with metabolic disorders[39–42] by circadian misalignment, where the social rhythms are in discordance with the biological rhythms.[43] The circadian misalignment can also occur when the central oscillator is out of sync with the peripheral oscillators in an organism, i.e., the suprachiasmatic nucleus presents alterations in the phase angle with the peripheral clocks or when the sleep-wake or feeding cycles changes the phase angle enormously in relation to the environmental cycles.[35]

The peripheral oscillators (or peripheral clocks) usually act in circadian alignment and are synchronized through autonomic outputs.[44] In consequence, the autonomic sympathetic nervous system is affected by sleep restrictions, causing disruption of neurohumoral parameters, decreasing SI and insulin secretion in patients with type 1 and 2 diabetes; also reduces plasma leptin and elevating ghrelin and cortisol, which regulate satiety and hunger, respectively.[45–50] These hormones may contribute to the BMI and WC increase and play an important role in the association of short sleep and diabetes.[44,46,51–53]

Furthermore, peripheral appetite regulating systems are modulated by circadian rhythms through sympathetic and parasympathetic action.[54] However, the irregular work schedules can disturb this, which may clarify the unregulated maintenance of xenin and ghrelin, which can influence the appetite, contributing to body adiposity,[32] as supported by animal models with specific disturbances in the clock genes in liver or skeletal muscle increasing the risk of MetS.[32]

In addition, reducing the light exposure at night may be important to maintain the circadian system regularity,[55] and the low color temperature in light spectrum, in consequence low light intensity, reduce antioxidants such as glutathione peroxidases, catalase and other enzymes evolved in the metabolic pathways.[9,10] We find in the analyzed papers that genetic, environmental, psychobehavioral, endocrine, cultural and socio-economic factors also influence metabolic problems, like diabetes and hypertension, moreover, changes in the light-dark cycle cause disruptions in other rhythms, increasing the propensity for chronic diseases.[44]

The circadian system plays a role in glucose metabolism and can be mediated by two mechanisms: 1) reduced function of pancreatic β cells, 2) decreased SI and RI oscillatory cycle.[4,34,56] Besides, glucose tolerance varies widely

 

throughout the day in healthy people, with a peak in the morning.[34] Because this variation, inappropriate eating times can impact glucose metabolism, and food restriction at night can prevent these unwanted effects[33] and limits the impact of circadian misalignment on glucose metabolism in rodents.[57] As consequence of circadian disruption, in the first week of this condition, the concentration of glucose and cortisol became higher, and the levels keep higher up to the third week of exposure but fasting insulin levels increase only after the third week, but the glycemia does not suffer any alteration.[58]

Moreover, higher insulin secretion and disrupted growth hormone may cause IR, which could lead to reduced utilization of glucose and contribute to increase in blood glucose concentration.[46,59,60] For the variation of glucose tolerance throughout the day and sleep restriction, night work has a significant direct effect on glycemic level,[60] there is an increase in IR.[58,61,62] Besides, the IR is higher at night, causing a reduction in glucose tolerance in this phase.[53] Also, SW may be correlated with IR in healthy individuals under 50 years of age.[32]

In a study with actigraphy data from patients with untreated diabetes, sleep quality was shown to be significantly linked to insulin secretion but not to SI.[28] Beyond, reduced sleep time is associated with an evening chronotype, especially on working days,[63] and together with poor sleep quality, it is related to IR, glucose intolerance and increased risk of diabetes.[64] In contrast, too long sleep duration is also related with glucose intolerance and was positively associated with fasting blood glucose.[31] SW with irregular sleep schedules resulting in sleep deprivation have an increased risk of diabetes relative to day workers.[14,65,66] But there were factors that may confound these data such as chronic disease, depressive symptoms, socioeconomic status, and a low level of physical education.[46,58,67,68]

Withal, adverse effects on blood glucose, sleep restrictions contribute to development of MetS, which is popularly defined as a group of IR markers, such as high BP, impaired glucose metabolism, high serum triglycerides and low serum HDL concentration, which results in triggering resistance to insulin-stimulated glucose uptake.[69] Metabolic disorders associated with IR have a wide spectrum, such as T2D, dyslipidemia, hypercoagulability and inflammatory markers, cardiovascular disease, and chronic diseases.[70–73]

Insufficient sleep duration increases the risk of fasting hyperglycemia in day workers, but the sleep extension can provide a beneficial impact on fasting blood glucose in shift workers.[5] Short sleep duration or poor sleep quality, in studies with self-reported questionnaires, may increase the risk of developing poor glycemic control in T2D,[74,75] we also found that it may trigger an increased risk of developing diabetes in non-diabetic people.[76] In addition, chronic night workers experience recurrent circadian misalignment, which may partly explain the increased risk for T2D.[77]

Animal studies with long-term circadian interruptions, such as the knockout of clock genes and constant exposure to light, showed dysfunction in β cells in rodents.[58,61,62] Circadian regulation of pancreatic β cells may provide an explanation for the poor glycemic control in people who usually eat at night.[34] The findings support that avoiding high glycemic index meals at night reduces postprandial hyperglycemia, reducing the risk for T2D.[78]

Besides, glucose tolerance is lower in the biological afternoon than in the morning, regardless of the behavioral cycle, therefore, mealtimes can be a crucial factor to be considered.[4] There were divergences in all bibliography analyzed because of an existent confounder factors like physical activity and dietary habits, but in both genders shift workers are not adept at healthy habits in general.[79]

The health effects of SW have been investigated and associated with many non-communicable diseases, such as metabolic disorders, cancer, and dementia.[45,80–88] Indeed, the MetS has been more related to eating habits,[46] for example, night workers tend to distribute food intake throughout the night.[46] The literature is conflicting regarding the practice of physical activity and obesity among shift workers.[27]

In addition, metabolic stimuli and oxidative stresses are correlated with changes in chronobiological rhythms, which results in cytokine production.[32,89–91] There was a C-reactive protein level increase, which is a nonspecific inflammatory marker produced by liver and has an association between night work and low-grade inflammation, which could be used to monitor metabolic risk in this group.[9,92] The positive correlation between C-reactive protein and HOMA-IR in patients with T2D may contribute to the cardiovascular disease risk.[93] Also observed significantly higher levels of thiobarbituric acid, a substance with antioxidant effects, in these subjects.[9]

Another point, shift workers and night workers experience are an extreme form of misalignment, linked to chronic sleep deficit, and are at increased risk of obesity,[94] hypertriglyceridemia,[52] MetS,[27,95] with adverse effects on glucose tolerance and cardiovascular function.[96] Consequently, these misalignments are associated with higher levels of HbA1c.[32,35,97] Moreover, evening chronotype is associated with higher risks of all these problems, even if they are non-shift workers,[98–100] maybe by extending the eating phase until late.

Apparently, there is a relationship between circadian misalignment and MetS, but the causal mechanisms have not been fully understood yet.[32] As a possible marker of this nexus of MetS, BMI is inversely proportional with sleep duration. As an example of circadian misalignment, SW showed an increase of BMI in subjects with prediabetes and untreated participants with existing T2D[101] and, among female nurses in SW, it was observed an increase in BMI only after 1000 nights of work.[101] About the BMI parameters, it has been discussed if it may or may not be related with obesity risk, because it cannot separate the lean mass from the fat mass, but BMI and WC showed strong correlation with subcutaneous and visceral adiposity.[102] Abdominal circumference measures have been studied in association between abdominal adiposity and breast cancer and they are promising predictors.[103]

Indeed, in SW and night work, food consumption in later hours predicts a higher BMI and reduces the effectiveness of weight loss programs.[104] In this sense, it has been suggested that aspects of food consumption and circadian

 

misalignment may help to explain the effect of SW and night work on weight gain and increased abdominal obesity and WC and may lead to overweight and obesity.[36] Mechanistic hypotheses can explain weight gain among night workers,[27] such as the breakdown of appetite-related hormones homeostasis, such as ghrelin, leptin, GLP-1, oxyntomodulin and xenin, and consequently the energy balance.[54] Even, serum leptin levels remain controversial in the literature.[27]

However, some factors linked to the SW are involved, such as adverse feeding times for digestion and prolongs the eating duration delaying the feeding phase during the night.[66] Therefore, inappropriate time for food increases the risk of developing diseases related to chronic obesity.[32,33] A meta-analysis suggested that a relationship between SW and T2D in men is stronger than in women,[14] even though women are more exposed for night work, but both genders demonstrated significant effects mediated by WC.[60] The internal circadian time is an important factor to consider determining the meal's time in SW, added to this factor, changes in lifestyle, such as exercise, sleep quality, diet and stress control are important in MetS managing.[105–108]

In addition, the parameters of food intake (energy, protein, and carbohydrates) during the workday point to the increased intake associated with higher HDL levels,[4,109] and the variation in HDL levels can work as another MetS mark. In nights of work, the quantity and quality of the meals collaborate to an increase in night worker's triglycerides and LDL cholesterol levels and increase even more the total cholesterol levels. It is noted that participants with sleep deprivation are more prone to more caloric food,[109–111] and this may be due to the accumulation of amyloid β plaques and neurofibrillary tangles, which makes individuals more impulsive.[11] Moreover, neurotoxins are eliminated during sleep, especially slow wave sleep, as well as the suppression of the growth hormone release, responsible for metabolic and homeostatic reactions.[29] These subjects tend to distribute food intake throughout the night.[54] So, redistributing mealtimes to night workers can be a strategy to improve the health of this population.[33]

According to our readings, experimental circadian misalignment in healthy volunteers with shifted times of sleep and eating showed greater intolerance to glucose, high blood pressure (BP), and inflammatory markers.[38,106,112] In SW, BP is reduced during the sleep, this occurs due to a lower sympathetic output during the nocturnal sleep. Current night workers are more prone to diastolic arterial hypertension than day workers and former night workers, as well as hypertriglyceridemia,[27] two risk factors for MetS in the IDF classification. Night work time is an important parameter, as more than 10 years of work at night shows a higher risk,[27] but evidence suggests that discontinuing night work after 10 years reduces the risk prevalence,[27] that is, discontinuing night work even after 10 years can reduce the prevalence of MetS risk factors.[27]

Furthermore, sleep recovery can have an effect by neutralizing these influences of sleep deficit, stabilizing the carbohydrate metabolism and endocrine function[113]; and a sleep recovery weekend produces positive changes in cardiovascular disease biomarkers, such as IGF-1 and myeloperoxidase, recovering immunity processes and inflammatory parameters.[29] In addition to decreased glucose tolerance, circadian breakdown is associated with inflammatory markers, suggesting metabolic risk.[58,66,77,114,115]

About the circadian cycle, melatonin, a neurohormone secreted by the pineal gland, is related to the night phase and sleep, also affects glycemic metabolism, and there is evidence that sleep deprivation and circadian disorders are associated with poor glycemic control in patients with diabetes,[75,116,117] which can lead to a vicious metabolic cycle and complications in DR.[38] Dysfunction in the intrinsically photosensitive retinal ganglion cells can reduce the effectiveness of the photonic entertainment of the central circadian clock, leading to abnormal rhythm of melatonin release (or secretion). Evidence shows that patients with DR have less melatonin secretion overnight[118–120] and lower urinary overnight 6-sulfatoxymelatonin levels along the night, associated with disturbed sleep.[118]

Thus, melatonin supplementation will be beneficial in patients with DR to improve sleep,[121–124] reduce systemic inflammation[121–124] and the lipid profile,[122,123] but with mixed effects on glycemic control.[121–124] In the same way, low nocturnal melatonin secretion is a predictor of IR and diabetes.[125,126] Abnormal melatonin regulation can lead to poor signaling and reduced ability to maintain a regular sleep schedule.[35] The action of this hormone regulates the expression of the type 4 glucose transporter and phosphorylation triggers on insulin receptors,[32] that is, a decrease in melatonin levels may be related to higher levels of IR.[32] Cellular receptors for melatonin are also found in pancreatic β cells and can modulate insulin secretion.[127]

This systematic review demonstrates limitations related to the databases used, since their search modes are not the same for all databases, and even the choice of keywords may have interfered in the results. Another point is the work schedules are not standardized between the articles reviewed here and this divergence can generate different outcomes. Besides there is heterogeneity between the methodologies used in the analyzed articles. The restricted period analyzed may be another limitation because it was only included the articles published in last 5 years, and the effects of sleep disturbance may have been reported earlier.

## Conclusion

In conclusion, we verified that SW and night work cause circadian misalignment between the endogenous and behavioral cycles, and it can affect metabolic parameters. The main parameters alterations observed in the literature comprises: (i) morphological parameters, as BMI and WC; (ii) the glucose metabolism, since the glycemia throughout the day up to insulin release, pancreatic-β cells responsiveness and HOMA-IR; (iii) the phase of cortisol release and, consequently, the cholesterol fractions balance; and (iv) neurohumoral parameters, such as melatonin secretion which reduce antioxidant effects and increase the oxidative stress. The SW interferes with the sleep-wake cycle and eating patterns,

 

resulting in crucial alterations in metabolic parameters that can lead to MetS.

Declaration of Interest
The authors declare that they have no competing financial or personal interests that could influence the work reported in this paper.

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