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REVIEW ARTICLE

How sleep influences type II diabetes: an integrative review

Como o sono influencia na diabetes mellitus tipo 2: uma revisão integrativa

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ABSTRACT

The relationship between type 2 diabetes *mellitus* (T2D) and sleep is well-established, as extremes in duration and poor quality are strongly associated with an increased risk of developing this metabolic disease. Chronic sleep dysregulation leads to increased insulin resistance, disrupts the balance of the hormones that control appetite and satiety, and thus affects glucose metabolism. The present review sought to understand the relationship between lack of sleep and an increase in the propensity of T2D. Based on an analysis of publications from 2014 to 2024 available on the PubMed, SciELO, and BVS platforms, it was possible to see that both short and long sleep durations, as well as low quality sleep, are associated with increased insulin resistance, which elevates the propensity for disease development. Furthermore, in the materials studied, associations were also seen between the dysregulation of the circadian cycle and its substances, and the development of the metabolic disorder studied. Thus, we realize the importance of further studies for a better understanding of the observed relationships and the indication of changes in sleeping habits, complementary to the already indicated good diet and physical exercises, to prevent and treat type 2 diabetes *mellitus* in adults.

Keywords: Type 2 diabetes *mellitus*; Dyssomnias; Circadian cycle.

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RESUMO

A relação diabetes *mellitus* tipo 2 (DM2) e o sono, especialmente quanto aos extremos de duração e má qualidade, estão fortemente associados a um risco aumentado de desenvolver essa doença metabólica. Com a desregulação constante de sono, há um aumento da resistência à insulina, desequilibrando hormônios que controlam o apetite e a saciedade, afetando o metabolismo da glicose. A presente revisão buscou entender se havia relação entre a falta de sono e o aumento na propensão de DM2. Baseado na análise das publicações, datadas de 2014 a 2024, encontradas na plataforma PubMed, SciELO e BVS, foi possível perceber que há um entendimento científico de que a falta, assim como o excesso, de sono e de boa qualidade no sono pode aumentar a resistência à insulina, o que aumenta a propensão ao desenvolvimento da doença. Além disso, nos materiais estudados também foram vistas associações entre a desregulação do ciclo circadiano, e de suas substâncias, e o desenvolvimento do distúrbio metabólico estudado. Assim, percebemos a importância de mais estudos para melhor compreensão da relação observada e da indicação de mudanças no hábito de dormir, complementares à já indicada boa alimentação e aos exercícios físicos, para se evitar e tratar a Diabetes *mellitus* tipo 2 em adultos.

Palavras-chave: Diabetes *mellitus* tipo 2; Transtornos do sono; Ciclo circadiano.

Introduction

Type 2 diabetes *mellitus* is a set of metabolic alterations that occurs due to hyperglycemia, hyperinsulinemia, and peripheral insulin resistance – which is when there is a lower supply of glucose in peripheral tissues despite the increase in insulin secretion[1,2].

These changes, resulting from multiple genetic and/or environmental factors, affect 16.8 million Brazilians, according to the Brazilian Diabetes Society, a rate that grows every year, as the WHO warns. Health agencies are concerned about this disease due to its high risk of severe complications. These include microvascular and macrovascular disorders, such as neuropathies, nephropathies, retinopathies, and cardiovascular diseases. Furthermore, the condition is frequently linked to psychiatric morbidities, including anxiety and depression, and sexual health issues, such as erectile dysfunction[3].

All these complications require treatment expenses, which exceeded 15 billion dollars in Brazil in 2019, including direct medical and non-medical expenses, such as transporting patients to appointments, and indirect expenses, such as early retirement[4].

Given its significant socioeconomic consequences, the Brazilian Ministry of Health has prioritized prevention strategies and early screening for at-risk individuals. This high-risk population is defined by one or more of the following characteristics: age over 40 years, a family history of T2D, overweight or obesity (in particular the android or central type), triglycerides or HDL cholesterol above the reference values, arterial hypertension, vascular atherosclerotic disease before the age of 50, hyperglycemia or previous glycosuria, use of medications such as corticosteroids and contraceptives. For women, specific criteria include a history of miscarriage, prematurity, polyhydramnios, gestational diabetes, and perinatal mortality, and delivering a newborn weighing more than 4kg[2].

But, in addition to these risk factors, the current scientific literature warns of the influence of sleep alterations on the increased chance of developing diabetes in the long term[5,6,7,8,9,10,11,12,13].

Sleep is a biological behavioral process that regulates the circadian cycle, body homeostasis, and neural and hormonal activities[5]. Its classification and categorization vary from study to study, period, and region. In 2017, the National Sleep Foundation of the United States classified that a good night's sleep is related to constancy and sleep architecture[14], with this architecture consisting of 5% stage 1, 16% to 20% slow wave sleep (SWS), and 21% to 30% rapid eye movement (REM)[14]. Sleep represents 20% to 40% of the human day[15]. Regarding sleep duration and its historical variation, Chaput reports that, in 1960,

modal sleep duration was 8 to 8.9 hours, while, in 2004, 30 percent of adults aged 30 to 60 years studied had an average sleep of 6 hours[16]. The cause for this reduction is, according to the author, modern lifestyle factors such as: increases in environmental light, longer work days/longer commuting time, night work, television, personal computer, or internet use. These changes, combined with physiological and hormonal changes, impact metabolic and endocrine dysfunctions, weight gain, and an increased risk of impaired glucose tolerance[16].

This review was based on these definitions of sleep and diabetes, to try to gather the most recent studies that seek to understand whether there is an association between changes in the biological sleep pattern and diabetes. So that, if true, this factor can be included by doctors in the screening of patients at risk, improving prevention.

Methods

To meet the objectives of the project, we searched for papers published in the last 10 years (2014 to 2024) on the PubMed, BVS, and SciELO platforms between January and February 2023 and in January 2024. The terms "sleep" and "type 2 diabetes" were searched on the platforms, in some of which the terms in Portuguese ("sono" and "diabetes") and Spanish ("soño" and "diabetes") were included to expand the results found.

Initially, 412 articles published between 2014 and 2024 were found that were related to the terms, namely: 187 in PubMed, 144 in SciELO, and 81 in BVMS. Of these, those that were repeated in the databases, that did not deal directly with the subject of this review, that had their free access blocked, or that did not follow the same definition of type 2 diabetes *mellitus* that was presented in the introduction of this study were excluded. At the end of the exclusions, made by reading the abstract or the full text, 20 systematic review articles or cohort studies that will be cited in this integrative review were included in the study. Figure 1 shows the flowchart of the studies selected for the study.

Results

The articles selected for study were grouped in the following table. In it, the relevant characteristics of the studies analyzed in this review are exposed:

Discussion

In their systematic review, Antza et al. (2022)[6] draw attention to the U-shaped relationship between the amount of sleep and type 2 diabetes *mellitus*: patients who sleep 5 to 6 hours a night are twice as likely to develop the disease, while patients who sleep more than 9 hours a night are 60% more likely to have the pathology than those who sleep 7 to 8 hours. The studies cited by him and his collaborators indicate that this relationship is stronger in men than in women, and that it was not affected by metrics such as BMI and age. Among the possible causes, Antza et al. (2022)[6] publicizes the higher consumption and lower caloric expenditure of patients who have short and long sleep, compared to those who sleep 8 hours/day. In addition, studies reveal a greater release of ghrelin, leptin, and GH in the individuals observed, which seems to the researchers to be related to a long-term alteration in pancreatic beta cells, which generates deficiency in insulin production and resistance. This review says there is no relationship between increased sleep duration and prevention of type 2 diabetes *mellitus*, as the studies analyzed did not prove it.

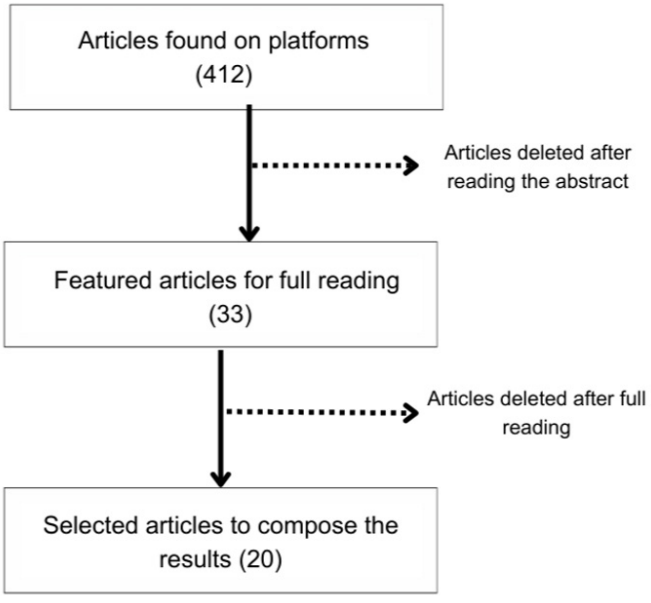

Figure 1. Article inclusion/exclusion flowchart.

Source: Authors' elaboration (2024).

Table 1. Selected scientific articles and their characteristics. By publication year, from lowest to highest.

Author/Year	Title	Type of Research	Objective of the study	Key findings	Journal	Database
Ferrie JE, et al. (2015)[8]	Change in Sleep Duration and Type 2 Diabetes: The Whitehall II Study.	Cohort study	To examine whether changes in sleep duration are associated with the development of T2D.	Individuals who increased their sleep time had an increased risk for developing diabetes. The group's weight gain partially explains this association.	Diabetes Care	MEDLINE
Leproult R, et al. (2015)[21]	Beneficial Impact of Sleep Extension on Fasting Insulin Sensitivity in Adults with Habitual Sleep Restriction.	Interventional study	To analyze whether the relationship between sleep duration under real-world conditions is a beneficial intervention for adults with chronic sleep restriction and metabolic glucose disorders.	There were beneficial effects on insulin sensitivity when these healthy, sleep-restricted adults had their sleep extension modified.	Sleep	PUBMED
Reutrakul S, et al. (2015)[23]	Relationships among sleep timing, sleep duration and glycemic control in Type 2 diabetes in Thailand	Prognostic study	To highlight findings from laboratory studies on the impact of experimenting with sleep manipulation, such as restriction and fragmentation, on the control of energy balance and/or glucose metabolism.	It was concluded that insufficient sleep is a risk factor for obesity, insulin resistance, and T2D, suggesting that an optimization in sleep duration and quality may benefit metabolic effects. As for T2D, fragmented sleep has a smaller body of evidence, but has consistency in terms of risk in development of disease.	Chronobiology International	MEDLINE
Shan Z, et al. (2015)[5]	Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies	Study of etiology	To analyze the dose-response relationship between sleep duration and T2D	Reveals a U-shaped relationship between sleep duration and disease development, with lower risk for people who sleep 7-8 hours	Diabetes Care	MEDLINE
Cespedes EM, et al. (2016)[7]	Long-term changes in sleep duration, energy balance and risk of type 2 diabetes.	Study of etiology	To examine the relationship between long-term changes in sleep duration, diet, and eating, and subsequent diabetes.	Increased sleep duration was modestly associated with the development of diabetes in older women. Changes in BMI and physical activity patterns did not explain the relationship.	Diabetologia	MEDLINE
Forrestel AC, et al. (2016)[17]	Chronomedicine and type 2 diabetes: shining some light on melatonin	Systematic review	Review the role of the biological clock in controlling, and detail the influence of melatonin on glucose metabolism. In addition to understand the hormone's contribution to the treatment of people with T2D.	Low melatonin secretion is associated with insulin resistance in diabetics. In addition, the drop in the circulation of the hormone can increase the predisposition to diabetes and sleep disorders.	Diabetologia	PUBMED

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Author/Year	Title	Type of Research	Objective of the study	Key findings	Journal	Database
Li Y, et al. (2016)[10]	Association between sleeping difficulty and type 2 diabetes in women	Cohort study	To see if the association between diabetes and lack of sleep is independent of other factors, such as cardiovascular disease and sleep disorders.	Women who reported sleep disturbances were four times more likely to develop type 2 diabetes.	Diabetologia	MEDLINE
Lin C L, et al. (2016)[11]	Associations between sleep duration and type 2 diabetes in Taiwanese adults: A population-based study	Cohort study	To analyze the association between sleep duration and diabetes risk in Taiwanese adults.	Short sleep duration is linked to the development of diabetes, especially in young adults.	Journal of the Formosan Medical Association	MEDLINE
Nuyujukian DS, et al. (2016)[12]	Sleep Duration and Diabetes Risk in American Indian and Alaska Native Participants of a Lifestyle Intervention Project	Observational study	To examine the association between sleep duration and the incidence of diabetes in Native Americans.	Few hours of sleep, but not long hours, are associated with an increased risk of developing T2D.	Sleep	MEDLINE
Jike M, et al. (2018)[19]	Long sleep duration and health outcomes: a systematic review, meta-analysis and meta-regression.	Systematic review, Meta analysis, and Meta Regression	To assess and identify whether long-term sleep is associated with health adversities using the same methodology for all complications.	Long-term sleep duration is related to a higher risk of the incidence of several diseases, including diabetes.	Sleep Medicine Reviews	PUBMED
Reutrakul S, et al. (2018)[24]	Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes	Systematic review	To highlight findings from laboratory studies on the impact of experimenting with sleep manipulation, such as restriction and fragmentation, on the control of energy balance and/or glucose metabolism.	It was concluded that insufficient sleep is a risk factor for obesity, insulin resistance, and type 2 diabetes, suggesting that an optimization in sleep duration and quality may benefit metabolic effects. As for T2D, fragmented sleep has a smaller body of evidence, but has consistency in terms of adverse effects on diabetes risk.	Metabolism Clinical and Experimental	PUBMED

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Author/Year	Title	Type of Research	Objective of the study	Key findings	Journal	Database
Seo JA, et al. (2019)[13]	Habitual late sleep initiation is associated with increased incidence of type 2 diabetes *mellitus* in Korean adults: the Korean Genome and Epidemiology Study	Study of etiology	Studying the impact of sleep onset time on the development of T2D.	The impact of sleeping late on the development of the disease is greater in the elderly.	Sleep	MEDLINE
Schipper SBJ, et al. (2021)[15]	Sleep disorders in people with type 2 diabetes and associated health outcomes: a review of the literature.	Literature review	To review the prevalence of sleep disturbances in people with T2D, and the association between sleep disorders and health effects.	Evidence suggests a bidirectional relationship between sleep problems and type 2 diabetes. Insomnia, obstructive apnea, and restless legs syndrome have been found to be more frequent in people with T2D than in normoglycemic patients, and these diseases, added to circadian cycle disturbances, negatively affect glycemic control.	Diabetologia	PUBMED
Wu IH, et al. (2021)[26]	Sleep duration and type 2 diabetes risk: A prospective study in a population-based Mexican American cohort	Study of etiology	To estimate the effect of sleep duration on the risk of developing T2D, considering demographic characteristics, at follow-up periods, and having body mass index (BMI) as a mediator and moderator.	The results highlighted the role of BMI and its effect on T2D risk in the early follow-up of those without obesity. T2D prevention and management for Mexican-American adults should consider the role of chronic sleep loss.	Sleep Health	MEDLINE
Antza C, et al. (2022)[6]	The links between sleep duration, obesity and type 2 diabetes *mellitus*	Systematic review	Understanding how sleep manipulation can help prevent diabetes and obesity.	Sleep is an independent risk factor for developing T2D and obesity.	Journal of endocrinology	PUBMED

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Author/Year	Title	Type of Research	Objective of the study	Key findings	Journal	Database
Johnson JM, et al. (2022)[20]	The effect of slow-wave sleep and rapid eye-movement sleep interventions on glycaemic control: a systematic review and meta-analysis of randomised controlled trials.	Systematic review	Synthesize the evidence on how alterations in specific stages of sleep influence glucose percentages.	Insulin resistance was higher than control when the slow phases of sleep were interrupted. There was no significant difference between pre- and postprandial glucose levels during the experiments.	Sleep Med	MEDLINE
Quadra MR, et al. (2022)[22]	Influência do sono e da crononutrição na hipertensão e diabetes: um estudo de base populacional	Cross-sectional study	To evaluate the influence of sleep and chrononutrition on SAH and T2D in the adult population of Criciúma-SC.	Poor sleep quality and fewer meals are associated with the diagnosis of diabetes and hypertension.	Caderno de Saúde Pública	SCIELO
Sondrup N, et al. (2022)[25]	Effects of sleep manipulation on markers of insulin sensitivity: a systematic review and meta-analysis of randomized controlled trials.	Systematic review and Meta analysis	To observe how sleep manipulation interferes with insulin markers, and the potential underlying mechanisms that potentially explain the effects of sleep manipulation and changes in insulin sensitivity.	It was concluded that the duration, timing, and quality of sleep influence metabolic function. Most of the studies analyzed revealed a negative effect of sleep restriction on insulin sensitivity.	Sleep Medicine Review	PUBMED
Fritz J, et al. (2023)[18]	Sleep duration, plasma metabolites, and obesity and diabetes: a metabolome-wide association study in US women.	Cross-sectional study	To assess the differences between metabolites from women with short, medium, and long-term sleep.	Short and long sleep generates different patterns in blood metabolites, with increases in lipids mostly. However, the study was not able to link these observations with the increased risk for T2D.	Sleep	MEDLINE
Kurnool S, et al. (2023)[9]	Sleep Apnea, Obesity, and Diabetes - an Intertwined Trio.	Systematic review	To synthesize the existing literature on the relationship between sleep disorders, obesity, and diabetes.	Sleep deprivation is related to the development of diabetes and should be recognized as a risk factor in the treatment of the disorder.	Current Diabetes Reports	MEDLINE

Source: Elaboration by the authors (2024).

The study, conducted by Cespedes et al. (2015)[7], followed women aged 55 to 83 years between 1986 and 2000. The meta-analysis also found a U-shaped association, in which sleep extremes are unfavorable to disease prevention: women who reported changes in sleep had higher body mass indexes, lower physical activity indexes, and worsening diet quality. In addition, they reported smoking habits, high blood pressure, hypercholesterolemia, and family history of the disease more frequently than women who slept 7-8 hours a day. The research was not able to perceive, however, whether the improvement in temporal sleep indices would bring metabolic benefits. As a hypothesis for the perception of the association, the researchers brought the increase in inflammatory cytokines and decrease in melatonin levels, which seemed to affect good metabolic performance in blood glucose control.

Jane Ferrie et al. (2015)[8] examined whether there was a relationship between 5 years of sleep change and the development of T2D over the next 5 years. To do this, they followed 10308 nurses, aged 35 to 55 years, since 1985: they answered a questionnaire, "how many hours of sleep on average do you sleep per night during the week?" and underwent a clinical examination with Oral Glucose Tolerance Test (OGTT) and HbA1c tests to monitor the presence of type 2 diabetes *mellitus*. The study revealed a nonlinear relationship between sleep duration and disease development: the persistence of short sleep duration and an increase of two hours in sleep for 5 years, compared to 7 hours of constant sleep, are associated with increased risk for type 2 diabetes *mellitus*.

For Ferrie et al. (2015)[8], the possible causes can be diverse. Regarding short sleep, laboratory studies have shown that sleep restriction increases appetite, especially for high-calorie-dense foods, by a drop in satiety and an increase in appetite-stimulating hormones. This is revealed in higher calorie intake, which generates weight gain and favors the development of the disease in the long term. In addition, prolonged sleep deprivation also increases inflammatory pathways, which has also been associated with the development of the disease, and reduces melatonin levels, which plays an important role in glycemic control, indicating a relationship between decreased levels of the hormone and the development of T2D.

Long-term sleep, on the other hand, is associated with other risk factors for diabetes, such as depression, poor socioeconomic status, and sedentary lifestyle. In addition, it can indicate the presence of disorders, such as obstructive sleep apnea (OSA), of which moderate and severe types are associated with type 2 diabetes *mellitus*[11]. The author points out that the use of self-reported measures of sleep time, in addition to ignoring chronotypes, the presence of disorders, and the quality of sleep of the participants, may have influenced the results, since these factors are associated with T2D in isolation[8].

Forrestel et al. (2016)[17] sought explanations for the relationship between the reduction in melatonin levels and the increase in the risk of developing the disease. In this review, they exposed studies showing that 50% of diabetic patients report insomnia, and that the use of Metformin and adequate glycemic control seems to improve the quality of sleep of these patients. In addition, 4 or 5 days of changes in the sleep pattern of healthy individuals resulted in the appearance of postprandial glycemic uncontrol, a sign of T2D.

In the searches with animals, cited by the authors, the influence of melatonin on blood glucose control was more detailed. One hour after the application of the substance, the activity of AMPK was increased, an enzyme that potentially increases the sensitivity of the liver to insulin, which also happens in elderly rats after continuous supplementation for 8 to 12 weeks. In addition, melatonin appeared to activate inhibitory G-proteins, which reduces cAMP production, activating A kinases and thereby decreasing the secretion of the hormone. Furthermore, Forrestel et al. (2016)[12] draw attention to another observed effect: the neurotransmitter seems to decrease the concentration of intracellular calcium and stimulate phospholipase C and IP3, which increases insulin secretion. Agonist effects occur at different concentrations. Another study showed that the deletion of melatonin receptors generates a drop in glycemic levels and decreases the response of the animals' liver to insulin.

Also, according to the authors, the effects of melatonin on blood glucose control and the liver's response to insulin have indicated to some researchers the possibility of using the neurotransmitter as a treatment for type 2 diabetes *mellitus*. In this regard, Forrestel et al. (2016)[17] drew attention to a study that showed the recovery of beta cells in rats with T2D induced by Streptozotocin that received 1mg/kg/day of the substance. It is not clear, however, how and if this application would work in humans.

Fritz et al. (2023)[18] brought the results of a study conducted by the Broad Institute of MIT and Harvard University, which used gas chromatography coupled with mass spectrometry to analyze blood samples from the groups. They were separated according to the answers given to a form that asked: sleep habits, age, ethnicity, BMI, snoring habit, physical activity, diet quality, alcohol habit, and whether there was a diagnosis of diabetes, depression, or dyslipidemia. The objective was to see if there was a similarity or increase in the frequency of common metabolites in the samples, and for this, they considered those that appeared in at least 50% of them.

It was noted that people who sleep little have a different metabolic composition in their plasma than those who sleep regularly and who sleep many hours[18]. In the first group, a greater presence of lipids and triglycerides in the blood was observed, in addition to other metabolites that had already been associated with obesity and diabetes. However, despite the similar relationship in the group that sleeps little, this does not explain the higher incidence of type 2 diabetes *mellitus* in the long term. This is because the study was not able to prove that adjustments in the levels of these metabolites reduce the risk of acquiring the diseases (obesity and T2D). Meanwhile, when looking at the group that reported having long sleep duration, the associations

between the metabolites that appear in sleep were much less robust: there was some difference between the lipids that appeared in the group – diacylglycerol and triacylglycerol were increased in relation to individuals who slept 7-8 hours or less, but were not able to relate it to the onset of diseases[18].

In summary, Fritz et al. (2023)[18] shows that different sleep habits show different metabolic relationships in plasma, with a difference in metabolites between groups that sleep more, less, or 7 to 8 hours per night. But this difference did not seem to explain the relationship between sleep time and increased risk for obesity and T2D.

Jike et al. (2018)[19] pointed to a relevant association between long-term sleep, type 2 diabetes *mellitus*, and obesity, as well as increased mortality and cardiovascular diseases when in values greater than eight to nine hours of sleep. As for durations of less than six hours, the risk is associated with diabetes and coronary heart disease, as well as obesity and cardiovascular disease. Combining these two extremes, the "U-shaped" relationship between duration and potential associated diseases is evident.

Johnson et al. (2022)[20] synthesized the relationship between manipulations in the sleep stage and glycemic control. In this experiment, participants had one night of unchanged sleep and one night with pink noise stimulation, which was transmitted by headphones, when slow wave (NREM) sleep began. The authors did not notice a significant change in postprandial glucose or insulin levels in any of the experiments when compared to the control group. However, a significant increase in insulin resistance was noticed in the group that had altered sleep. In addition, when the change time was increased, there were changes in glucose and insulin levels, which, according to the authors, suggest a dose-dependent relationship.

This, Johnson et al. (2022)[20] reports, shows that changes in NREM sleep increase insulin resistance, but do not significantly alter postprandial glucose and insulin levels.

Kurnool et al. (2023)[9] synthesized the literature on the associations among sleep disorders, obesity, and T2D, highlighting that assessing sleep health is a crucial component of the treatment of obese and diabetic patients. The authors point out that these disorders are often poorly recognized and, therefore, are not treated. And that the treatment of obstructive sleep apnea (OSA), for example, can improve sleep quality and reduce the risk of developing obesity and T2D.

In this work, Kurnool et al. (2023)[9] explains that OSA seems to worsen the diabetic condition. This is because it causes hyperglycemia by inciting catecholamines and other regulatory hormones. However, studies on the treatment of sleep disorders with CPAP have been unclear on how resolution of the condition improves glycemic control in these patients[9]. The author concludes that, since type 2 diabetes *mellitus* is associated with abnormalities in respiratory control and neuromuscular effects, the disease can alter respiratory mechanics and worsen obstructive sleep apnea[9].

Leproult et al. (2015)[21] demonstrated a metabolic improvement in six weeks of sleep extension for adults usually with restricted sleep time. Inter-individual variability was highlighted, but the correlation between increased sleep and improvements in insulin sensitivity indices was reinforced, even with the addition of only one hour of sleep. Six weeks were used in this study to allow sufficient time for a potential physiological change observed in studies related to hypertension. Through an objective evaluation using actigraphy and polysomnography, it was found that with the addition of one hour in sleep, there was an increase in time in stage 2 of NREM and REM sleep, in addition to unchanged sleep efficiency, indicating that this is an adequate amount that preserves sleep quality and brings improvements in insulin metabolism.

Li et al. (2016)[10] documented a study that sought to follow 121,700 women, nurses, between 30 and 55 years of age, for 10 years, to understand the associations between sleep disorders and cardiovascular diseases and type 2 diabetes *mellitus*. The authors sought to quantify how the effects of diabetes on sleep quality are related to BMI, hypertension, or depression, and other factors, such as: night work, difficulty sleeping, few hours of sleep, and sleep disorders (snoring and apnea). In 10 years of follow-up, 6407 cases of T2D were reported, the definition of which took into account the participants' statements and, after 1998, the criteria of the National Diabetes Data Group.

It was observed that women who had difficulty sleeping had an increased risk of developing type 2 diabetes *mellitus*, even disregarding other risk factors, such as: menopause, use of hormonal medications, vitamins and aspirin, family history, and lifestyle habits (physical exercise, diet, alcoholism, smoking, and social factors)[10].

However, this difficulty was not independent of three other factors: hypertension, obesity, and depression. When adjusting for these variables, the statistics on the relationship between difficulty sleeping and the development of the disease decreased considerably. Alone, these three factors together increased the chance of developing the disease by 46%[10].

In addition, a relationship was observed between the risk for the disease and the practice of frequent night work. And the risk was also increased in women who reported sleeping sickness: the presence of one, two, or three conditions gradually increased the chance of developing the disease. All of the findings proved consistent with other previous studies, Li et al. (2016)[10] says.

To explain the relationships found, the author proposes some hypotheses. First, that difficulty sleeping can alter the circadian rhythm and physiological functions: sleep restriction appears to alter the function of hormones that regulate appetite, leading to weight gain and thus increasing the risk of developing diabetes. In addition, the author recalls that sleep changes are frequent symptoms in depressive patients, a disease that has also been associated with type 2 diabetes *mellitus* in previous studies. And, they conclude that the increase in risk for the disease is not determined by an isolated factor: hypertension, obesity, and depression also contribute to the process and have previously been associated with difficulty sleeping. Experimental sleep restriction is

said to reduce glucose tolerance, compared to those who are completely rested[10].

In short, Li shows that difficulty sleeping is associated with type 2 diabetes *mellitus*, which is partially explained by its relationship with hypertension, obesity, and depression. The risk increases when these factors are added to sleep disorders[10].

Lin et al. (2016)[11] sought to analyze the association between sleep duration and the risk of developing T2D in Taiwanese adults. In a cross-sectional study that had Taiwanese residents as its target population: 1533 adults aged 19-64 years participated in the survey. Of these, 6.1% slept for 5 hours, and 10.1% slept for 9 hours.

The authors concluded that the risk of developing T2D for young participants (19 to 44 years) who slept for 5 hours was 2.04 times higher than for those who slept for 7 to 8 hours. This relationship was not present when comparing the oldest (44 to 64 years). In addition, those who slept for 9 hours also did not show an increased risk, compared to those who had an ideal sleep time. In this work, Lin was unable to define the cause of this association[11].

Nuyujukian et al. (2016)[12] published a longitudinal study that included 1,899 participants recruited from January 2006 to July 2009 and sought to examine the association between sleep duration and the incidence of diabetes in the native prediabetic population of Alaska. After adjusting for age and sex variables, Nuyujukian et al. (2016)[12] concluded that those who slept less than 7 hours were more likely to be diagnosed than those who slept longer[12]. In addition, the study also showed that this group had lower health quality indexes: they smoked more and did less physical exercise than those who had ideal sleep time.

Unlike short-term sleep, in this study, those who had a long duration of sleep did not have a higher risk of acquiring T2D or significant differences in diet and physical activity, compared to those who slept between 7 and 8 hours. The study points out, however, that long sleep duration may be associated with psychosocial factors, such as depression, which have previously been associated with type 2 diabetes *mellitus*[12].

The author recalls that the cause of this association is still unclear. Poor sleep duration seems to have an influence on hormones that regulate appetite, such as leptin and ghrelin, in addition to altering glycemic factors and the circadian cycle, and worsening sleep apnea, which have already been linked to insulin resistance. These factors, together, can contribute to the development of the disorder[12].

Quadra et al. (2022)[22] published a study carried out in Brazil, in the city of Criciúm/SC. The study interviewed 820 individuals over 18 years of age and residents of the city, and classified them according to their sleep duration as: short duration (less than 7 hours), adequate duration (7 to 8 hours), and long duration (more than 9 hours). In this group, having poorer sleep quality was associated with a higher presence of hypertension and diabetes. According to the researcher, this may be related to the fact that the peripheral clocks of the circadian cycle – liver, pancreas, muscle, intestine, and adipose tissue – are also closely related to the control of insulin secretion and the maintenance of glucose levels.

Thus, changes in this cycle, such as the lack of adequate hours of sleep, represented mainly by the women in the group and those who worked, can harm the proper maintenance of blood glucose by increasing the circulation of inflammatory cytokines, dysfunction of adipocytes, and reduction in the metabolic rate at rest. All of these situations seem, in the long term, to be related to reduced glucose tolerance and insulin resistance, which increases the risk of developing type 2 diabetes *mellitus*[22].

Reutrakul et al. (2015)[23] conducted a study in 2015 of 210 adults with type 2 diabetes *mellitus* who were not shift workers in Thailand. Sleeping later on weekends was found to be associated with nocturnal preference, shorter duration, and lower glycemic control in individuals with T2D.

In 2018, the same author examined studies of sleep-restricted, fragmented, and extended nights, and their relationship to type 2 diabetes *mellitus* and insulin resistance[23]. When compared to a 12-hour fully rested condition in bed, the four-hour sleep restriction resulted in a 24% decrease in insulin sensitivity. In restrictions of four to five and a half hours in bed, there was a reduction in insulin sensitivity ranging between 16 and 32%. Regarding fragmented sleep, in a study by Reutrakul et al. (2018)[24] , in which the duration was maintained, but without contiguity, for three nights, there was a reduction in insulin sensitivity by 25% and glucose tolerance by 23%. Regarding sleep extension, an improvement in fasting insulin sensitivity was observed when there was an objective increase in sleep.

Schipper et al. (2021)[15] analyzed different sleep alterations and their associations with some diseases, including glycemic control. For diseases such as insomnia, circadian rhythm disorders, and OSA, the existence of a bidirectional relationship between these disorders and type 2 diabetes *mellitus* was evidenced, suggesting a vicious cycle between these two factors. There is also a relationship between insomnia, for example, and the use of medications such as Metformin for glycemic control. In addition, the three disorders mentioned above have been found to be more prevalent in diabetics than in the general population.

According to the study by Seo (2019)[13], a sample of 3689 Korean participants without T2D, in the age group between 40 and 69 years old, were followed for 12 years, divided according to the time of sleep onset. 820 cases of type 2 diabetes *mellitus* were documented, and the group of late sleepers (between 1:00 and 5:59) showed an increase in insulin resistance. The impact of delayed sleep was more evident in older individuals and those with decreased beta cell function[13]. Delayed sleep was then observed as a risk factor, regardless of sleep duration and/or quality.

Shan et al. (2015)[5] presented evidence of the "U-shaped" relationship between sleep duration and risk of type 2 diabetes *mellitus*, with sleep between seven and eight hours being associated with a lower incidence of diabetes. It was found that the potential mechanisms influencing this relationship may differ between the extremities, being related to short sleep, for

example, changes in the activity of neuroendocrine systems and insulin resistance in adipocytes through the reduction of AKT phosphorylation. While the decrease in testosterone and melatonin secretion may be related to sleep disruption. For both short and long-term sleep, it was associated with increased levels of inflammation markers, which may also be a consequence of this extended duration.

Sondrup et al. (2022)[25] found that metabolic function is impaired when there are sleep disturbances, and that the effects of this sleep manipulation differ depending on the type of manipulation and the method for analyzing insulin sensitivity. For example, sleep restriction reduces insulin sensitivity when evaluated by oral glucose tolerance tests, intravenous glucose tolerance, and by the homeostatic model for insulin resistance assessment. In addition, it was found that this sensitivity is negatively altered by misalignment of the circadian cycle and suppression of slow-wave sleep, but they are not affected by REM disorders and fragmented sleep.

Finally, based on the cohort study conducted by Wu et al. (2021)[26] with Mexican Americans, it was observed that sleep duration is related to the risk of type 2 diabetes *mellitus*, with BMI mediating this relationship. Results supported the theory that excessive weight is an explanatory factor linking sleep and T2D, as well as being a serious risk factor for glycemic dysregulation. Despite this, non-obese individuals (BMI < 25) with 5 hours of sleep per night were at higher risk of T2D in the short-term follow-up, and this finding was confirmed in other studies analyzed by the authors. In conclusion, BMI is a moderator and a mediator in sleep duration and in the relationship with type 2 diabetes *mellitus*.

Conclusion

From this extensive literature review, it was possible to infer the existence of relationships between type 2 diabetes *mellitus* and sleep. For this, the multiple characteristics of the latter, such as duration, timing, quality[26], and possible sleep disorders[16], were used as variables and examined separately by the studies for greater specificity of analysis, in order to elucidate how each one interferes. This highlights the complexity of this relationship, which is not only cause and consequence, but also an interdependence of factors that interfere in the expression of diabetes and in the development of sleep as a whole. Therefore, the management of the various sleep factors should be done in order to improve the quality of life of people already diagnosed with T2D.

A U-shaped relationship between the amount of sleep and T2D was confirmed[5, 6, 7, 19], with long- and short-term sleep having the highest incidence of diabetes. A cyclical development between these two factors was also observed[15], in which one influences the maintenance and progression of the other, and vice versa, so a diabetic person is more likely to have inadequate sleep, as well as a sleep without quality, or of excessive or deficient quantity, results in changes in insulin sensitivity and glucose tolerance, for instance.

Thus, having seen the finding of an interconnection between sleep and type 2 diabetes *mellitus*, impacting the health and general quality of life of individuals, the relevance of this study becomes evident, contributing to the dissemination of knowledge on this topic.

It is worth noting, however, that only one Brazilian study was found that followed the criteria. Regarding the others, most of the studies brought were produced in English and were developed in developed and Western countries, with white people, and without much variation in ethnicity in the cohort studies.

It was not clear how much this social profile influences the results of the research, but this seemed to the authors to be a limitation, since other ways of life that are directly related to sleep behavior are excluded, in addition to influencing other spheres – such as diet and physical activity, which have previously been related to the increase in the propensity to T2D. In the analysis of long sleep duration, for example, it was noticed that it was almost always accompanied by sedentary habits, which in themselves favor the development of the disease, leaving the question of how much long-term sleep alone is a predictive factor of the disease.

Therefore, as unanimously highlighted in the studies analyzed, it is suggested that new studies be produced. These future studies should be conducted in more diversified population groups, with more objective types of tests and forms of sleep analysis, in order to expand the data for analysis. Moreover, such studies should carefully examine how additional factors, such as social factors, diet, and physical activity, may influence the U-shaped relationship between sleep duration and insulin resistance, and, with them, allow the development of an efficient intervention in order to reduce the deleterious effects of this relationship.

Author's contributions

We describe contributions to the papers using the taxonomy (CRediT) provided above: *Conceptualization, Investigation, Methodology, Visualization & Writing – original draft*: GQN Baldani; BR da Silva; BG Dias; J de O Machado; JL Ferreira; AJFS e Silva. *Project administration, Supervision & Writing – review & editing*: EA Soares, F da R Guerra.

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