

Sleep Deprivation and Its Impact on Insulin Resistance

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Abstract

Background/Objectives: Adequate sleep has a fundamental role in human health, mainly in cognitive and physiological functions. However, the daily demands of modern society have led to a constant pursuit of better living conditions, requiring more active hours at the expense of sleeping hours. This sleep deprivation has been associated with human health deterioration, namely an increase in Diabetes Mellitus incidence. This metabolic disease is a chronic pathology that imposes a big burden on health systems and is associated with the rise in insulin resistance. In this sense, the aim of this review is to analyze the relation between sleep deprivation and insulin resistance, emphasizing the metabolic parameters and hormones that may be involved in the subjacent mechanism. **Methods:** A literature review of the last 10 years was performed with specific terms related to “sleep deprivation” and “insulin resistance”. **Results:** Overall, the studies analyzed showed a decrease in insulin sensitivity in cases of sleep deprivation, even with different study protocols. In addition, an association between sleep deprivation and increased non-esterified fatty acids was also noticeable; however, other parameters such as cortisol, metanephrines, and normetanephrines showed no consistent results among the studies. **Conclusions:** This review allowed us to confirm the relationship between sleep deprivation and insulin resistance; however, despite the difficulties to monitor sleep, more research is needed to understand the related mechanisms that have not yet been clarified.

Keywords: sleep deficiency; Diabetes Mellitus; glucose homeostasis; metabolic parameters; cortisol; epidemiological studies



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1. Introduction

The human organism alternates between periods of wakefulness and sleep, with sleep itself being divided into two distinct phases: rapid eye movement (REM) and non-rapid eye movement (NREM). During a typical night, sleep cycles alternate between three stages of NREM and a fourth stage of REM, comprising the sleep architecture [1]. Sleep is essential for the maintenance of several biological functions, and its beneficial effects are achieved only when both quantity and quality are adequate. These benefits include regulation of blood pressure, heart rate, hormone secretion, immune defense, cellular repair, temperature control, and enhancement of memory and cognition [1,2].

From a cardiovascular perspective, sleep plays a crucial role, as evidenced by the occurrence of a decrease in heart rate, a reduction in blood pressure, and an increase in the predominance of parasympathetic activity within the autonomic nervous system during sleep [1]. Metabolically, sleep deprivation is associated with an increased risk of developing

type 2 diabetes mellitus (T2DM), driven by multiple mechanisms. These include alterations in cortisol and growth hormone secretion, increased production of inflammatory cytokines, sympathovagal imbalance, reduced cerebral glucose utilization, adipocyte dysfunction, and elevated circulating free fatty acids [1,3].

Regarding the cerebral function, sleep facilitates the clearance of neurotoxic proteins and metabolites via the glymphatic system and is critical for the stabilization and consolidation of long-term memories. Furthermore, a bidirectional relationship exists between sleep and psychological well-being: sleep disturbances have been shown to increase the risk of depression, and conversely, depression can lead to sleep disorders [2]. However, the deleterious effects of sleep are predominantly associated with sleep deprivation—defined as less than the recommended amount of sleep—and circadian misalignment, a condition prevalent among shift workers, which exerts a detrimental influence on metabolic and immune functions [3].

The Centers for Disease Control and Prevention (CDC) advocate that adults aged 18 to 60 years should sleep a minimum of 7 h per night, with slightly different guidelines proposed for older age groups [3]. Nevertheless, modern lifestyles, including increased use of electronic devices and shift work schedules, have contributed to widespread reductions in sleep duration, exacerbated by aging and sleep disorders [2–4]. Such deprivation has been linked to an increased risk of cardiovascular disease, metabolic dysfunction, immune alterations, cognitive impairment, and psychological distress (see Table 1).

Table 1. Health impacts of sleep restriction and circadian disruption [1,2,5,6].

System	Main Effects
Metabolic	• Insulin resistance and increased risk of type 2 diabetes • Impaired glucose metabolism and adipocyte dysfunction • Growth hormone suppression and reduced muscle repair • Altered secretion of cortisol and appetite-regulating hormones (ghrelin ↑ / leptin ↓)
Cardiovascular	• Elevated sympathetic tone and reduced parasympathetic activity • Increased blood pressure (hypertension) • Endothelial dysfunction and arterial stiffness • Higher risk of arrhythmia and acute cardiovascular events
Immune	• Decreased antibody production and immune surveillance • Increased pro-inflammatory cytokine release (e.g., interleukin-6, tumor necrosis factor α) • Greater susceptibility to infections and inflammation
Neurological	• Impaired glymphatic clearance of neurotoxins • Disruption in memory consolidation and cognitive function • Potential contribution to neurodegenerative disease progression
Psychological	• Increased risk of mood disorders (e.g., depression, anxiety) • Acute effects on mood, energy levels, irritability, and sense of well-being • Disrupted sleep architecture contributing to emotional instability

As stated, sleep is critical for good health, and its restriction is increasingly prevalent worldwide. Alongside this increase, the prevalence of metabolic diseases, particularly T2DM, has also risen in recent decades. Given that sleep restriction increases the risk of developing diabetes, further investigation of its effects on insulin resistance is important. Insulin resistance is a key metabolic marker, and it can be measured using methods such as the hyperinsulinemic–euglycemic clamp (HEC) [7], HOMA-IR (Homeostasis Model Assessment of Insulin Resistance), Matsuda index, and QUICKI (Quantitative Insulin Sensitivity Check Index) [8,9]. In this sense and considering the growing evidence that links sleep deprivation to impaired glucose metabolism and insulin sensitivity, the present review

aims to investigate the effects of sleep deprivation on insulin resistance in healthy adults, with particular attention to the physiological mechanisms involved in this relationship.

2. Materials and Methods

A comprehensive literature search was conducted across three major databases of published articles: PubMed, Web of Science, and Scopus. The Boolean operators AND and OR were used, along with the following keywords: “Sleep Deprivation” and “Insulin Resistance”. Given that the terms “sleep deprivation”, “sleep restriction” and “sleep loss” are considered synonyms, the Boolean operator OR was employed between these terms, for a broader search. Furthermore, a combination of the keywords “Diabetes” and “Insulin” was also used as an alternative strategy to identify studies addressing Insulin Resistance. Therefore, the search strategy was designed to address topics related to the intervention (sleep deprivation) and the primary outcome (insulin resistance).

The present study analyses the impact of sleep deprivation on insulin resistance and the underlying mechanisms involved, specifically in healthy adult individuals. A comprehensive review of the existing literature revealed numerous studies conducted on both human and animal subjects, focusing on the parameters of sleep deprivation. The specific parameters under scrutiny included, but were not limited to, insulin, leptin, adiponectin, resistin, lipids, blood glucose, cortisol, adrenaline and noradrenaline, glucagon, glucagon-like peptide-1 (GLP-1), and peptide YY (PYY).

The inclusion criteria were as follows: (1) articles published within the last 10 years; (2) clinical trials and cohort studies; (3) studies directly analyzing the effect of sleep deprivation on hormonal response (insulin) and blood glucose levels. The exclusion criteria were: (1) articles published more than 10 years ago; (2) reviews, meta-analyses, and systematic reviews; (3) studies involving non-adult populations (in human studies); (4) studies that did not assess relevant metabolites or hormones; (5) studies involving techniques, substances, or microorganisms aimed at mitigating the effects of sleep deprivation; (6) studies including variables outside the scope of this review, such as caffeine; (7) studies involving populations with existing pathologies; (8) unrelated, inaccessible and duplicate articles.

After applying all inclusion and exclusion criteria, a total of 24 studies were retained for analysis, 5 of which were conducted in animal models, as stated in Figure 1.

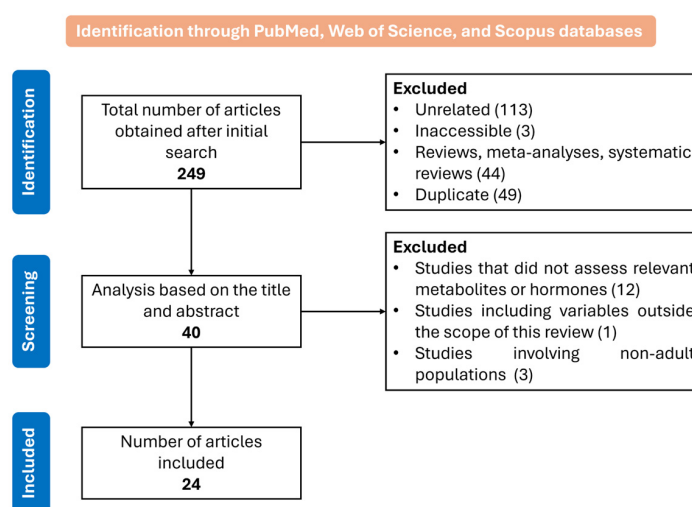


Figure 1. Flowchart of the literature review process.

3. Human Evidence on the Impact of Sleep Deprivation on Insulin Sensitivity and Metabolic Regulation

A total of 19 studies were analyzed in terms of the results obtained in humans. Eight of these studies were carried out in the United States of America [10–17], two in China [18,19], two in Thailand [18,20], two in Sweden [21,22], two in the Netherlands [23,24], two in the United Kingdom [25,26] and two in Germany [27,28]. The study population consisted of healthy adult men and women who were not obese, according to their body mass index (BMI), with ages ranging from 20 to 80, although one study included a population with type 1 diabetes mellitus (T1DM) [23]. All of the analyzed studies investigated the metabolic response to sleep deprivation in different ways. Most of the studies assessed the insulin response to glucose administration or measured fasting blood glucose after sleep deprivation. However, other studies evaluated metabolites such as fatty acids, cholesterol, cortisol, glucagon, acylcarnitines, GLP-1, ghrelin and fibroblast growth factor 21 (FGF-21).

3.1. Effects of Sleep Deprivation on Insulin Sensitivity and Glucose Metabolism

Of the results analyzed, four were cohort studies. In 2014 the study carried out by Deng et al. [18] examined populations from China and Thailand, resorting to a total of 162,121 individuals aged between 20 and 80 years. Participants were recruited in 1996 and monitored until 2014. Questionnaires were used to assess symptoms of insomnia and sleep duration, and participants were categorized into three groups according to their sleep duration: short (less than 6 h), normal (6–8 h) and long (more than 8 h). During the follow-up period, participants attended regular clinical assessments for diagnosis of obesity, alterations in fasting glycaemia, diabetes, dyslipidemia, hypertension and other cardiovascular conditions. These diagnoses were based on different measurements, including blood samples collected after a 12-h overnight fast to assess fasting glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total cholesterol. The authors found that a sleep of less than 6 h per night was significantly associated with an increased risk of developing hypertension, prediabetes, diabetes, low HDL levels, hypertriglyceridemia and metabolic syndrome. Conversely, sleep durations of more than eight hours were associated with a reduced risk of hypertriglyceridemia and metabolic syndrome [18]. In a different cohort study, performed by Li X. et al. in 2015 [19] in China, included 4774 participants aged 30–65 years without metabolic syndrome. Upon recruitment, the participants underwent physical assessments and completed questionnaires and were followed over a period of 4.4 years. Sleep duration was self-reported through a questionnaire, and participants were categorized into five groups: <6 h, 6–7 h, 7–8 h, 8–9 h and >9 h. At the end of the follow-up period, it was determined whether metabolic syndrome had developed. Results indicated that participants who slept 6 h or less showed higher fasting glucose levels, while BMI and waist circumference did not vary significantly with sleep duration. Interestingly, participants with longer sleep durations also demonstrated an increased risk of elevated fasting glucose, suggesting a U-shaped relationship [19]. In 2018, Dijk et al. [24] conducted a study in the Netherlands using data from the EGIR-RISC cohort. This cohort included 1002 participants from 14 European countries: 46% were men and 54% were women, and all were aged between 30 and 60 years. Participants self-reported their sleep duration in a follow-up period of three years. Insulin sensitivity was evaluated via blood samples collected before and at 30-min intervals during a two-hour oral glucose tolerance test (OGTT), which assessed plasma glucose and insulin levels. Insulin sensitivity was calculated using different indices, including OGIS (Oral Glucose Insulin Sensitivity, that estimates insulin sensitivity), MCR (Metabolic Clearance Rate, that reflects the rate at which insulin is removed from the bloodstream), ISI (Insulin Sensitivity Index, that quantifies the body's responsiveness to insulin) and HOMA-IR. Insulin secretion was derived from OGTT data based on three

indices: β -cell glucose sensitivity, β -cell glucose rate sensitivity and the potentiation factor ratio. The study established that both short and long sleep durations were associated with reduced insulin sensitivity, with BMI mediating most of these associations. No significant associations were found between sleep duration and insulin secretion parameters or oral glucose sensitivity [24]. Most recently, Kanagasabai et al. [16] analyzed data from the US National Health and Nutrition Examination Survey (NHANES) in the United States of America (USA). The study aimed to quantify the contribution of gamma-glutamyl transferase (GGT), C-reactive protein (CRP), bilirubin, carotenoids, uric acid and vitamins to fasting insulin concentrations and glycemic control measures in order to determine whether inflammation, oxidative stress and micronutrient antioxidants mediate these relationships. Data were drawn from the 2005–2006 survey with 10,348 participants. Those under 20 years of age, pregnant women and individuals lacking sleep or biochemical data were excluded, resulting in a final sample of 1946 individuals. Sleep quantity and quality were assessed using a validated sleep disturbance questionnaire. Fasting blood samples were analyzed to quantify CRP, GGT, bilirubin, carotenoids, uric acid and vitamins A, C, D and E, as well as insulin and HbA1c concentrations. A mediation model was employed to explore the relationship between sleep variables and insulin concentrations. The contribution of each mediator was categorized as large, moderate, modest, or weak. The results showed that GGT, carotenoids, uric acid and vitamins C and D significantly mediated the relationship between sleep duration and fasting insulin levels, while CRP, bilirubin and vitamin C significantly mediated the relationship between sleep quality and fasting insulin levels. While these factors were statistically significant, they were considered moderate mediators of the sleep–glycemic control relationship. These findings suggest that poor sleep quality and/or altered sleep duration may influence biochemical markers of oxidative stress and inflammation, thereby potentially promoting systemic insulin resistance [16].

Concerning clinical trials, the analyzed studies demonstrated an association between sleep deprivation and increased insulin levels and decreased insulin sensitivity. In 2014, Leproult et al. [10] conducted a randomized clinical trial involving 26 American healthy adults with normal BMI, aged between 21 and 39 years, to assess sleep restriction and circadian misalignment. The participants had no history of endocrine, psychiatric or sleep disorders, were not shift workers and had not travelled across time zones in the two months prior to the study. They also did not report habitual sleep durations of less than 7.5 h or more than 8.5 h. In the week prior to the intervention, participants were instructed to maintain a regular sleep schedule, which was verified using actigraphy. The intervention consisted of three days with a 10-h sleep opportunity, followed by eight days with a 5-h sleep opportunity. Participants were assigned to either the circadian alignment group (going to bed at 3 a.m.) or the circadian misalignment group (going to bed 8.5 h later at 9 a.m.). An intravenous glucose tolerance test (IVGTT) was performed after an overnight fast on days 2 and 10 of the study. Additionally, seven measurements of high-sensitivity C-reactive protein (hsCRP) were taken at four-hour intervals at baseline and after sleep restriction. For the purposes of this review, the group of interest is the one in which only sleep restriction was tested (i.e., circadian alignment was maintained). In this group, a decrease in insulin sensitivity was observed, which was not offset by an increase in β -cell responsiveness. The disposition index (DI), a marker of diabetes risk, was also reduced, indicating increased risk of diabetes. Furthermore, the group exposed to circadian misalignment exhibited elevated hsCRP levels, indicating increased inflammation [10].

Also, within this group of studies, in 2015 Eckel et al. [17] conducted a clinical trial in the USA, involving 8 women and 8 men with a mean age of 22.4 years, a normal BMI, no medical or psychiatric conditions, typical sleep durations (between 7 and 9.25 h per night), low to moderate caffeine consumption and no recent travel across time zones. One week

before the study began, the participants stopped consuming caffeine and maintained a sleep schedule of approximately nine hours per night. Upon admission to the research center, participants underwent three nights of sleep opportunity lasting 9 h, followed by two experimental conditions: adequate sleep and a sleep opportunity lasting 5 h for five consecutive nights, to mimic a typical working week. Sleep restriction was achieved by delaying bedtime and wake time by 2 h. OGTT was conducted on days 7 and 12 (after three and five nights of 9 and 5 h of sleep, respectively), while IVGTT were performed on days 9 and 14. In this study, insulin sensitivity, as measured by the Matsuda index, decreased by 21%, in line with previous findings. Furthermore, melatonin levels were also assessed, showing a prolonged elevation of its levels to be associated with poorer insulin sensitivity. Unlike the previous study, the authors reported a compensatory increase in insulin secretion by β -cells. This adaptive response suggests a physiological attempt to maintain normoglycemia during sleep deprivation [17]. In 2019, the same research group [14], performed a randomized clinical trial involving 36 participants (18 men and 18 women) with an average age of 25.5 years and a BMI of 22.4 kg/m². The aim of the study was to determine whether ad libitum recovery sleep during the weekend could prevent metabolic dysregulation caused by recurrent insufficient sleep. Participants were excluded if they had chronic medical or psychiatric disorders, were pregnant, worked shifts, had lived below an altitude of 1600 m in the previous year, had travelled across time zones within the three weeks prior to the onset of the lab protocol, had a BMI greater than 27.5 kg/m², had experienced recent weight loss, had an eating disorder or had abnormal eating patterns. The volunteers were initially divided into three groups to implement the protocol: control group (CON) that maintained a sleep opportunity of 9 h per night throughout the study; sleep restriction group (SR); and weekend recovery (WR). These two groups underwent sleep manipulation: sleep restriction for the SR group and a recovery sleep period following restriction for the WR group, to simulate what occurs during weekends. The protocol began with seven days of sleep at home, without sleep deprivation, following a diet prescribed by a clinical research center nutritionist to ensure that participants started the protocol without sleep debt. Then, during study days 1–3, the participants stayed at the center, where they completed three nights of normal sleep. On days 4–13, they followed different sleep protocols according to their group assignment (CON, SR or WR). While in the laboratory, they underwent numerous assessments, including polysomnography, blood sampling for melatonin analysis, an assessment of insulin sensitivity, and evaluations of hunger and physical exhaustion. Insulin sensitivity was measured on day 4 of the protocol, before sleep deprivation, and again on day 12. This was achieved through a HEC using glucose and glycerol isotopic tracers to evaluate insulin sensitivity in the liver and adipose tissue. This assessment was conducted across all participant groups. On study days 5 and 11, blood samples were collected to analyze melatonin levels. The results showed that weekend ad libitum sleep is insufficient to compensate for sleep loss during the working week, with insulin sensitivity being decreased in both sleep-restricted groups. The weight gain seen in the WR group may have contributed to this reduction, suggesting that insulin sensitivity is not fully restored following recovery sleep. Regarding adipose tissue insulin sensitivity, the values of both the SR and WR groups were similar to those of the CON group by day 12. For hepatic sensitivity, the values remained stable between days 0 and 12 in the SR group, but a significant reduction was observed in the WR group. Muscular insulin sensitivity values were similar in the CON and SR groups between days 0 and 12 but decreased in the WR group. Thus, the study suggests that changes in insulin sensitivity and glucose uptake in other tissues, such as the kidneys and brain, may contribute to the overall reduction in insulin sensitivity during insufficient sleep [14].

In line with previous studies, Wang X et al. [12] conducted a randomized clinical trial in the USA in 2015. Fifteen men participated in the study, with a mean BMI of 24.5 kg/m², an average age of 20.6 years, and no sleep disorders. The participants had self-reported sleep durations of 6.5 to 10 h and had not crossed time zones in the month prior to the study. Nine participants initially followed a protocol in which they were allowed to sleep ad libitum for three days, after which an OGTT was performed the following morning. The other six participants began with three days of sleep restriction, followed by an OGTT. The participants then switched protocols and the OGTT was repeated under the same conditions, always after a 12-h overnight fast. In addition, fasting plasma cortisol and glucagon concentrations were measured. The study demonstrated that insulin concentrations before and after glucose administration were significantly increased in the sleep-restricted group (5 h/night) compared to the control group (approximately 6.7 h/night). Furthermore, as in the study by Eckel et al., indices of insulin sensitivity and resistance (Matsuda, HOMA-IR and QUICKI) indicated a decrease in sensitivity subsequent to sleep restriction. This group also showed an increase in glucagon levels, which may reflect compensatory mechanisms aimed at maintaining glucose homeostasis [12].

However, it is pertinent to question whether this variation also occurs in groups exposed to shorter durations of sleep deprivation. To explore this possibility, in 2015 Cedernaes et al. [21] conducted a randomized clinical trial in Sweden to assess the effect of a single night of sleep deprivation on insulin sensitivity and the cephalic phase insulin response. Sixteen healthy male participants with a mean age of 22.88 years, a mean BMI of 22.88 kg/m², regular sleep habits, and no history of metabolic, neurological, psychiatric, or sleep disorders were enrolled. An OGTT was performed to confirm normal glucose regulation. Participants were assigned to two experimental conditions: the control group was allowed to sleep from 10:30 p.m. to 7:00 a.m., while the sleep-deprived group's sleep was restricted to 2:45 a.m. to 7:00 a.m. The following morning, at 8:30 a.m., the participants ingested a glucose-rich solution, after which blood samples were collected to assess glucose and insulin levels before and after ingestion. The results showed elevated insulin levels in the sleep-deprived group compared to the control group, besides HOMA-IR values also increased following sleep restriction, indicating decreased insulin sensitivity. However, no changes were observed in glucose levels or the cephalic phase insulin response between the two groups. These findings suggest that even a single night of sleep restriction is sufficient to impair insulin sensitivity [21].

To determine the effect of sub-chronic sleep restriction on hepatic insulin sensitivity, substrate uptake and peripheral insulin sensitivity, Rao et al. (2015) [11] conducted a randomized crossover clinical trial involving 14 healthy men and women aged 18–45 years, in the USA. Participants were excluded if they had a history of chronic medical or psychiatric illness, were taking medication, were obese, had used tobacco or illicit drugs in the past year, had a history of alcoholism, had first-degree relatives with type 2 diabetes mellitus, worked shifts, or had sleep disturbances. Each participant was admitted to the research center twice for one-week periods, with a washout phase in between. During this time, their diet, physical activity and sleep–wake patterns were strictly controlled. On day 7 of each protocol, an OGTT was performed, followed by a HEC with stable isotope tracers on day 8. In addition, two consecutive 24-h urine collections began on day 6 for hormonal analyses. Seven participants began with the normal sleep protocol, comprising two acclimation nights followed by five experimental nights. During acclimation, participants had the opportunity to sleep for 9 h; during the normal sleep protocol, this was reduced to 8 h and to 4 h during the sleep-restriction protocol. Despite similar fasting glucose and insulin levels between conditions, post-OGTT glucose levels, glucose area under the curve (AUC), and insulin levels did not differ significantly. However, the insulin AUC was 20% higher

in the sleep-restricted group, indicating increased integrated insulin secretion. The clamp study revealed a 25% decrease in overall insulin sensitivity and a 29% reduction in peripheral insulin sensitivity under sleep-restricted conditions, with no sex differences observed. Endogenous glucose production (EGP) did not differ in fasting states nor was it impaired during hyperinsulinemia. During the clamp, EGP was modestly reduced under sleep restriction, indicating decreased glycogenolysis. In contrast, gluconeogenesis contributed more to EGP in the sleep-restricted group than in the normal sleep condition [11].

3.2. Effects of Sleep Deprivation on Lipolysis, Non-Esterified Fatty Acids, and Insulin Sensitivity

Sleep restriction has emerged as a critical factor affecting metabolic regulation, particularly by modulating lipolytic hormone activity, circulating non-esterified fatty acids (NEFA), and insulin sensitivity. In 2015, Broussard et al. [13] proposed that insufficient sleep may alter these metabolic pathways, leading to impaired glucose homeostasis, which prompted further investigation through controlled clinical trials. To investigate this theory, the authors assessed the impact of sleep restriction on insulin sensitivity, through a randomized clinical trial involving 19 healthy men aged 18–30. Participants were excluded if they had chronic or acute illness, worked shifts, had recently travelled across time zones, had depressive symptoms, were taking medications or supplements that affect glucose metabolism, smoked, consumed excessive amounts of alcohol or caffeine, or had abnormal findings in physical or laboratory examinations. Then, the included participants underwent two experimental conditions, separated by a four-week interval: four consecutive nights of an 8.5-h sleep opportunity (normal sleep) or a 4.5-h sleep opportunity (sleep restriction). Throughout the study, participants remained in the laboratory under sedentary conditions, with caloric intake strictly controlled and standardized across protocols. Polysomnography was used to monitor sleep each night and blood samples were collected every 15–30 min over 24 h (starting on the evening before the third night) to measure NEFA, growth hormone, norepinephrine, cortisol, glucose and insulin. Body fat percentage was also assessed and an IVGTT was performed at 10:00 a.m. after the fourth night. The results showed that, despite similar fasting glucose levels, fasting insulin levels were elevated after sleep restriction compared to normal sleep, indicating insulin resistance. Sleep restriction also resulted in a greater glucose AUC trend and significantly increased insulin AUC, consistent with reduced insulin sensitivity. Furthermore, IVGTT-derived insulin sensitivity decreased by 23% under sleep restriction. The inability to compensate for this insensitivity with increased insulin secretion led to a reduced DI, indicating an increased risk of diabetes [13].

On the other hand, the association between specific metabolic pathways and sleep restriction was also analyzed. Berg et al. [23] were the first authors to investigate this hypothetical relationship. In this context, a randomized clinical trial was conducted in the Netherlands in 2015 involving 16 participants—nine healthy individuals and seven with T1DM. Of these participants, eight were female and the mean BMI was 23.7 kg/m². Exclusion criteria included: BMI >26 kg/m², a history of sleep disorders or psychiatric illness, and the use of sleep medication, beta-blockers or prokinetic agents. All participants maintained a stable weight over the preceding three months and exhibited regular, non-extreme sleep patterns. In the three days prior to the study, they were instructed to maintain their usual diet, physical activity and sleep routines. Participants with T1DM were advised to maintain stable insulin levels throughout the study. Subjects were admitted to the hospital for three days. On the first day, baseline measurements were collected, and the participants were acclimatized to the hospital setting. All individuals underwent one night of normal sleep (at least 8 h) and one night of sleep restriction (limited to 4 h). On both nights, fasting began at 10:00 p.m. During the sleep-restricted night, participants were permitted to sleep only between 01:00 and 05:00 a.m. Fasting blood glucose was measured

at 08:30 a.m. following each night. A continuous glucose infusion via catheter was then initiated to assess peripheral insulin sensitivity, endogenous insulin production and hepatic insulin sensitivity. Fasting blood samples were also collected to quantify free fatty acid (FFA) and metabolite analysis. The findings demonstrated that a single night of sleep deprivation resulted in increased peripheral insulin resistance, as evidenced by a reduced glucose disposal and infusion rate. Furthermore, an increase in endogenous glucose production by the liver was observed following sleep restriction. Notably, the increase in peripheral insulin resistance occurred independently of baseline insulin sensitivity values. These results suggest that sleep deprivation induces insulin resistance via a common pathway affecting both healthy individuals and those with T1DM [23].

The following year, in 2016, Wang et al. [12] conducted a randomized clinical trial in the USA to investigate the impact of three consecutive nights of sleep restriction on insulin, glucose and glucagon concentrations. A total of 15 young adults (eight women and seven men) were enrolled in the study, with an average age of 20.6 years and an average BMI of 24.5 kg/m². Exclusion criteria included self-reported major health problems, use of sleep medication, diagnosed sleep disorders, a usual self-reported sleep duration of less than 6.5 or more than 10 h, and recent travel across time zones in the month before the study visit. Participants underwent two OGTTs: one following three nights of restricted sleep (1–3 h less time in bed per night) and one after three nights of unrestricted sleep. The order of conditions was randomized: six participants completed the sleep restriction phase first, while the remaining nine began with the ad libitum sleep phase. During the sleep restriction phase, participants were instructed to delay their bedtime or advance their wake-up time by 1–3 h to reduce their total time in bed. During the ad libitum phase, participants could sleep as much as they wanted for three consecutive nights. The morning after the third night of each condition, after fasting for 12 h, participants came to the laboratory for anthropometric measurements (weight and height), underwent an OGTT and blood samples were collected to assess insulin and glucagon levels. The results were partially consistent with previous findings: fasting and post-OGTT insulin concentrations were higher in the sleep restriction condition. The Matsuda index, HOMA-IR and QUICKI were calculated, all of which indicated reduced insulin sensitivity following sleep restriction. Glucagon levels were also significantly elevated post-sleep restriction. However, no significant differences were observed in fasting or post-OGTT glucose concentrations between the sleep-restricted and ad libitum sleep conditions [12].

Also exploring this relationship, but in a slightly smaller sample, Sweeney et al. [26] conducted a randomized clinical trial in the United Kingdom in 2017, involving ten participants, to compare plasma insulin responses following sleep restriction versus control sleep. The inclusion criteria comprised healthy males aged 18–40 years who were non-smokers with regular sleep patterns of 7–9 h per night. Those excluded from the study included individuals who had travelled across time zones or engaged in shift work within the past four months, had sleep disorders, metabolic or inflammatory diseases, or used medications known to interfere with metabolic processes. Prior to each study phase, participants underwent a one-week training period at home, during which they adhered to fixed bedtimes and wake times. Afterwards, they received specific instructions regarding sleep and wake times for the experimental phase. The study protocol involved two consecutive nights of either control sleep or sleep restriction, the latter being defined as a 50% reduction in each individual's usual sleep duration. After a three-week washout period, participants crossed over and completed the alternate protocol. Following the second night of each condition, height, BMI, blood pressure and heart rate were measured in a fast state. Consistent with previous findings, no differences were observed in fasting or plasma glucose responses to the OGTT performed between the two conditions. However, plasma insulin responses

during the OGTT were elevated following sleep restriction and the Matsuda index was lower, indicating reduced whole-body insulin sensitivity. Additionally, skeletal muscle biopsies were analyzed to determine whether the reduction in insulin sensitivity observed was associated with changes in the activity of protein kinase B (PKB/Akt), which is a key enzyme in the insulin signaling pathway that is responsible for GLUT4 translocation and glucose uptake. Although no significant differences in PKB activity were observed between the different conditions, there was a trend towards reduced PKB activation in response to glucose intake after sleep restriction [26].

In a different perspective, in 2019, Wilms et al. [27] aimed to investigate the effects of acute sleep deprivation on the circadian regulation of the white adipose tissue (WAT) transcriptome. The authors conducted a randomized clinical trial in Germany involving 15 male participants aged 18–30 years with a mean BMI of 22.9 kg/m². Using a randomized crossover design, the participants underwent three separate sleep conditions: normal sleep (8 h from 11 p.m. to 7 a.m.), sleep restriction (4 h from 3 a.m. to 7 a.m.), and total sleep deprivation. Each sleep condition was separated by a washout period of at least two weeks. Subcutaneous WAT biopsies were collected at 9:00 p.m. and 07:00 a.m. to assess diurnal variations. Additionally, glucose homeostasis was characterized by measuring plasma glucose, insulin and C-peptide concentrations, and a mathematical model was used to estimate β -cell function and insulin resistance. Triglycerides (TG), FFA, resistin, interleukin-8 (IL-8) and retinol-binding protein 4 (RBP4) were also measured. Regarding glucose homeostasis, fasting C-peptide secretion was reduced the morning after sleep restriction; however, this was not accompanied by changes in fasting insulin levels. Similarly, plasma glucose concentrations did not differ between conditions. HOMA-%B (an index of β -cell function) and HOMA-IR (an index of insulin resistance) were calculated, revealing a reduction in HOMA-%B after sleep restriction, whereas HOMA-IR remained unchanged. Thus, this study demonstrated that sleep restriction for a single night is sufficient to impair β -cell secretory capacity without inducing an increase in insulin resistance [27]. In addition, the same authors [28] also investigated the effects of early versus late sleep deprivation on glucose homeostasis. For this study, 15 healthy male participants aged between 20 and 30 years (mean age 24.6 years) and with a BMI ranging from 20 to 24.9 kg/m² (mean 23.3 kg/m²) were recruited. Participants were excluded if they had acute or chronic illnesses, took regular medication, smoked, consumed more than 50 g of alcohol or 300 mg of caffeine per day, had first-degree relatives with diabetes, worked shifts, had travelled across time zones within the past 4 weeks, habitually slept for less than 6 h per day or had abnormal findings on physical examination or laboratory analysis. Participants underwent one adaptation night in the laboratory and were subsequently tested in a randomized order under three different conditions, each separated by a minimum of three weeks. Two of these conditions involved sleep restriction (4 h of sleep during either the first or second half of the night), while the third condition involved 8 h of sleep and served as a control. The following morning, glucose homeostasis was assessed using the Botnia clamp, which combines an IVGTT with a HEC to evaluate both β -cell function and peripheral insulin sensitivity. In addition, the cortisol and glucagon concentrations were also measured. The study revealed that sleep deprivation predominantly affected REM sleep. Insulin sensitivity was found to be reduced by 16% under both sleep restriction conditions, with no significant difference in peripheral insulin sensitivity between early and late sleep deprivation. This suggests that insulin sensitivity is not dependent on the timing of sleep restriction. Furthermore, there was a tendency towards a reduced β -cell secretory response following both forms of sleep restriction. Regarding glucagon, no significant differences were observed between sleep-restricted and control groups. However, glucagon concentrations decreased when

sleep restriction occurred during the latter part of the night, indicating that α -cell activity may be dependent on the timing of sleep loss [28].

All the previously described studies demonstrated that sleep deprivation reduces insulin sensitivity, although differences were observed in across metabolic parameters. Thus, an interesting question rose: could extending the sleep of chronically sleep-deprived individuals improve insulin resistance? This was precisely the focus of the randomized clinical trial conducted by So-ngern et al. [20] in Thailand, in 2019. The study included 21 healthy participants (19 women and 2 men) aged between 20 and 55 years. Participants had to meet the following eligibility criteria: usual sleep duration of ≤ 6 h on weekdays; a self-reported desire for ≥ 7 h of sleep at weekends; the belief that time spent in bed could be increased by at least 1 h per night over two weeks; absence of diabetes; low risk of obstructive sleep apnea syndrome (OSAS); and usual bedtime before 3:00 a.m. Then, they were assigned to either maintain their usual sleep pattern or extend their sleep by at least 1 h per night, for a period of two weeks. A washout period of at least two weeks was implemented before crossover. During the sleep extension phase, participants progressively advanced their bedtime by 15–20 min each day until they had increased it by 1 h compared to their usual schedule. This new schedule was then maintained for the two-week intervention. Following an overnight fast, participants underwent an OGTT at the end of each sleep condition, with multiple blood samples collected for glucose and insulin analysis. Additionally, the HOMA-IR was used alongside calculating the Insulinogenic Index (an estimate of early-phase insulin secretion) and the DI. The results showed that participants who successfully extended their sleep beyond six hours exhibited significant improvements in glycemic parameters—specifically, a reduction in fasting insulin resistance, an increase in insulin secretion and enhanced β -cell function—when compared to those who maintained their usual sleep pattern. These results prove the need for an optimal amount of sleep to achieve metabolic beneficial effects [20].

As sleep deprivation impairs insulin sensitivity, in 2021 Mateus Brandao et al. [22] performed a randomized crossover trial in Sweden to examine the impact of complete sleep restriction on the levels of circulating FGF-21. Fifteen healthy participants (mean age: 22.3 years; mean BMI: 22.6 kg/m²) were subjected to two conditions: one night of total sleep deprivation and one night of usual sleep time. Participants were pre-screened to ensure their good health (consuming less than 5 units of alcohol per week, not using nicotine, having normal fasting glucose levels and normal blood counts), and ensure they had not worked shifts recently nor travelled across time zones within the previous three weeks. All participants consumed low-sugar, low-carbohydrate meals in the days preceding the intervention. During the control condition, sleep was permitted from 10:30 p.m. to 07:00 a.m., while during sleep deprivation, participants remained awake in bed and were not permitted to eat. Following each condition, fasting blood samples were collected, along with subcutaneous adipose tissue and skeletal muscle biopsies, after which an OGTT was performed. Although insulin sensitivity was not the primary outcome, the AUC for plasma glucose was significantly higher after sleep deprivation compared to the control condition [22].

In the same year, Radcliffe et al. [15] conducted a randomized crossover clinical trial in the USA to investigate how short-term severe sleep restriction influences appetite, energy intake, appetite-regulating hormones, and food preferences. To address this hypothesis, they recruited 18 men with a mean BMI of 24.4 kg/m² and aged between 17 and 45 years (mean age: 20 years). Exclusion criteria included abnormal blood biochemistry, failure to a regular sleep of 7–9 h per night, a Pittsburgh Sleep Quality Index score greater than 5, a history of sleep disorders, sleep apnea or psychiatric disorders, as well as a history of gastrointestinal, cardiovascular or metabolic disease. Frequent use of nonsteroidal anti-

inflammatory drugs (NSAIDs), corticosteroids, psychiatric medications or lipid-lowering drugs was also grounds for exclusion. The study comprised two 3-day phases: one with adequate sleep (7–9 h per night) and one with sleep restriction (2 h per night). During both phases, participants remained in a sleep laboratory under continuous supervision. On the third day of each phase, participants were offered buffet-style meals to assess their food selection behavior. Throughout both phases, participants received prescribed meals and completed a standardized, low-intensity physical activity program. On the fourth day, blood levels of ghrelin, PYY, GLP-1, insulin and glucose were measured in the fasting state and then at 20- and 60-min intervals over a four-hour postprandial period following the buffet meal. The results revealed that, after sleep restriction, fasting PYY concentrations were lower and glucose levels were higher, while insulin, ghrelin and GLP-1 concentrations did not differ significantly. During the postprandial period, PYY and GLP-1 concentrations were significantly lower, and glucose levels were higher in the sleep-restricted condition than in the control condition. Postprandial insulin and ghrelin responses remained unchanged. However, these postprandial findings should be interpreted with caution, since the composition and quantity of food consumed in the buffet meal following the sleep-restricted condition varied between participants, which could have influenced glycemic responses. In contrast, fasting glycemic values aligned with previously reported data, though fasting insulin levels did not differ significantly between conditions [15].

3.3. Impact of Sleep Deprivation on Fatty Acid and Acylcarnitine Metabolism

Another relevant issue concerns the impact of sleep deprivation on fatty acid metabolism. Several studies have addressed this topic in recent years. In this context, the randomized clinical trial by Rao et al. [11], previously mentioned, investigated substrate uptake under conditions of sleep restriction. Regarding fatty acid metabolism, the study reported a 62% increase in fatty acid uptake during sleep deprivation. Concurrently, the respiratory quotient decreased while resting energy expenditure remained unchanged, indicating an overall increase in whole-body fat oxidation. Furthermore, the levels of β -hydroxybutyrate, which is a marker of hepatic fat oxidation, increased by 55% during sleep restriction [11]. Similarly, Broussard et al. [13] found that there was a circadian variation in FFA concentrations in both experimental groups mentioned previously. However, under conditions of sleep deprivation, the nocturnal elevation in FFA levels was prolonged by approximately 50 min. Furthermore, during the sleep restriction protocol, morning FFA levels plateaued rather than declining continuously as would typically be observed under normal sleep conditions. A significant average increase in nocturnal and morning FFA concentrations (from 15% to 30%) was observed under sleep-deprived conditions compared to normal sleep. Notably, the observed reduction in insulin sensitivity correlated with the increase in mean nocturnal FFA levels [13]. Indeed, these studies provide important insight into the effects of sleep restriction on fatty acid metabolism. Consistently, the 2018 study by Wilms et al. [27], previously cited, aimed to determine the effect of sleep restriction on adipose tissue metabolism. The findings revealed that pathways involved in carbohydrate and lipid metabolism were more sensitive to sleep restriction during the day. Specifically, genes associated with carbohydrate metabolism lost their circadian rhythm [27].

Some of the studies discussed aimed to evaluate the impact of sleep deprivation on insulin sensitivity and to identify the specific metabolic pathways affected by such conditions. To this end, a broad range of metabolites were assessed, including acylcarnitines. In 2014, Davies et al. [25] investigated the effects of acute sleep deprivation on the human metabolome by quantifying 171 plasma metabolites, including acylcarnitines, in the United Kingdom. This randomized clinical trial enrolled 12 healthy young men, aged 18–35 years

and with a mean BMI of 24.9 kg/m². Exclusion criteria included regular medication use, pre-existing medical conditions, smoking, self-reported sleep disturbances or depression, and irregular sleep habits. The participants remained in a controlled laboratory setting for 48 h. Initially, they proceeded with a normal sleep–wake cycle for 24 h, followed by 24 h of total sleep deprivation. Two blood samples were collected during the 48-h period for metabolomic analysis. The majority of quantified metabolites remained unchanged; however, 16% of the samples showed significant alterations. These included eight acylcarnitines, serotonin, taurine and tryptophan, as well as thirteen glycerophospholipids and three sphingolipids, all of which increased [25]. Similarly, the study by van den Berg et al. [23] reported an increase in acylcarnitines. In this investigation, 163 plasma metabolites were analyzed and thirteen were found to be increased across both study subgroups, specifically acylcarnitines [23].

3.4. Role of Cortisol, Catecholamines, and Growth Hormone in Sleep Deprivation

In addition to assessing whether sleep deprivation induces insulin resistance, some studies also measured different metabolic and neuroendocrine markers, including metanephrine, normetanephrine, cortisol and growth hormone (GH), in order to investigate potential mechanistic pathways. These complementary parameters are addressed briefly below.

In the study by Rao et al. [11], urinary levels of free cortisol, metanephrines and normetanephrines were assessed to investigate potential underlying mechanisms and tissue-specific roles in the development of insulin resistance. The authors observed a 21% increase in urinary free cortisol concentrations during sleep restriction. Additionally, urinary metanephrine and normetanephrine levels increased by 8% and 18%, respectively, under the same conditions [11]. Similar findings were reported by Broussard et al. [13], who observed a two-hour phase advance in the cortisol peak in participants exposed to sleep restriction. Furthermore, cortisol levels were 23% higher during the late afternoon and early evening in the extended wakefulness condition. The authors also found that noradrenaline concentrations were elevated in participants subjected to sleep restriction. A significant correlation was identified between elevated morning noradrenaline levels and increased circulating NEFA levels during this period. Regarding GH, alterations in its secretion pattern were observed under sleep-deprived conditions. Specifically, a biphasic secretion profile emerged, contributing to an overall increase in total GH secretion. This rise in GH levels was strongly associated with nocturnal increases in NEFA concentrations [13].

In contrast to the findings reported in the previously mentioned studies, no increase in cortisol levels was observed in the study by Wang et al. [12]. The study by Wilms et al. [27] in 2019 found that cortisol levels depend on specific sleep conditions, i.e., not only sleep restriction, but also the sleep phase during which it occurs. Sleep loss occurring during the late-night period resulted in lower cortisol concentrations than sleep loss during the early night or normal sleep. Furthermore, cortisol levels increased following late-night sleep deprivation but subsequently returned to levels observed during normal sleep and early-night sleep restriction [27]. Lastly, Mateus Brandão et al. [22] examined how total sleep deprivation affected circulating FGF-21 levels and also assessed cortisol concentrations in their study. Their results showed that the normal cortisol response to the transition from night to morning was attenuated in individuals subjected to total sleep deprivation compared with those who experienced a normal sleep [22].

In conclusion, a reduction in insulin sensitivity was observed under conditions of sleep deprivation across all the analyzed studies. Although the protocols varied in several aspects, including the duration of sleep restriction, the use of a crossover design, the presence or absence of an acclimatization period and other conditions associated with the experimental

phase, this outcome remained consistent. A similar consensus was found regarding the measurement of FFA levels, which increased across studies that assessed this parameter. In contrast, such consistency was not observed for other parameters, where results varied between studies. As previously mentioned, for example, this lack of agreement was evident in the measurements of cortisol, metanephrines and normetanephrines. Furthermore, certain studies also reported an increase in specific acylcarnitines. Overall, the results align with theoretical expectations, at least regarding the association between sleep deprivation and the development of insulin resistance. However, the mechanisms involved are multiple and complex, which may explain why several other parameters did not yield the expected results and should therefore be investigated further. Table 2 summarizes the analyzed findings for humans.

Table 2. Overview of the key human studies on sleep and glucose metabolism cited.

Author and Year	Sample	Analyzed Markers	Results
Leproult et al., 2014 [10]	26 healthy adults	Glucose, hsCRP	SR reduced insulin sensitivity without compensatory insulin increase, and inflammation increased. Mean hsCRP levels did not vary significantly in the SR group.
Davies et al., 2014 [25]	12 healthy men	171 metabolites (acylcarnitines)	Most metabolites remained unchanged; only 16% were significantly increased, including 8 acylcarnitines, serotonin, taurine, tryptophan, 13 glycerophospholipids, and 3 sphingolipids.
Deng et al., 2014 [18]	162,121 individuals	Fasting glucose, HDL, LDL, Cholesterol	<6 h sleep/day significantly increased risk of hypertension, prediabetes, diabetes, low HDL-C, hypertriglyceridemia, and MetS. >8 h sleep/day lowered risk of hypertriglyceridemia and MetS.
Li et al., 2015 [19]	4774 participants without MetS	Fasting glucose, BMI, waist circumference	<6 h sleep led to increased fasting glucose; BMI and waist circumference did not vary. Long sleep led to increased risk of elevated fasting glucose.
Eckel et al., 2015 [17]	8 women and 8 men	OGTT, IVGTT, Melatonin	21% decrease in insulin sensitivity. Longer elevated melatonin levels associated with worse sensitivity. Compensatory insulin secretion increased.
Rao et al., 2015 [11]	14 healthy men and women	OGTT, NEFA, β -hydroxybutyrate	No changes in fasting glucose/insulin. Glucose AUC and insulin levels unchanged, but insulin AUC increased 20% after SR. 25% decrease in whole-body insulin sensitivity and 29% decrease in peripheral sensitivity. SR increased NEFA use by 62%, β -hydroxybutyrate by 55%, urinary cortisol by 21%, urinary metanephrines by 8%, and normetanephrines by 18%.
Wang et al., 2015 [12]	15 non-obese men	OGTT, Cortisol, Glucagon	Insulin levels significantly increased pre- and post-glucose. Insulin sensitivity indices (Matsuda, HOMA-IR, QUICKI) indicated reduced sensitivity. Glucagon increased after SR; cortisol unchanged.
Cedernaes et al., 2015 [21]	16 men	OGTT, Glucose, Insulin	Elevated insulin in the morning after SR; HOMA-IR increased, suggesting insulin resistance. Glucose and cephalic insulin responses unchanged. One night of SR sufficient to impair insulin sensitivity.
Broussard et al., 2015 [13]	19 healthy men	NEFA, GH, Noradrenaline, Cortisol, Glucose, Insulin, IVGTT	SR raised nocturnal/morning NEFA (15–30%), contributing to insulin resistance. Insulin sensitivity via IVGTT dropped 23%. NEFA plateaued in SR vs. normal decline. Cortisol peaked 2 h earlier, increased 23%. Noradrenaline and GH increased.
Van den Berg et al., 2015 [23]	18 individuals (9 healthy, 7 T1DM; 2 excluded)	Glucose, FFA, Acylcarnitines	One night of SR increased peripheral insulin resistance and hepatic endogenous glucose production. Increased acylcarnitines.
Sweeney et al., 2017 [26]	10 healthy male participants	OGTT, Muscle tissue	2 nights of SR altered glucose regulation via whole-body insulin sensitivity reduction. PKB activity results were inconclusive.
Dijk et al., 2018 [24]	1002 participants	OGTT, Glucose, Insulin	SR duration linked to lower insulin sensitivity. Insulin secretion remained unchanged. Sleep influences insulin resistance.

Table 2. Cont.

Author and Year	Sample	Analyzed Markers	Results
Wilms et al., 2018 [27]	15 men	Glucose, Insulin, C-peptide, TG, FFA, Resistin, IL-8, RBP4	SR reduced β -cell secretory capacity without increasing insulin resistance. No changes in TG and FFA. RBP4 increased; IL-8 and resistin unchanged.
Depner et al., 2019 [14]	36 participants (18 men, 18 women)	Melatonin, Glucose, Insulin	SR decreased total insulin sensitivity (possibly brain/kidney-mediated). Weekend recovery reduced total, hepatic, and muscular insulin sensitivity.
Wilms et al., 2019 [28]	15 men	IVGTT (insulin & glucose), Cortisol, Glucagon	16% reduction in insulin sensitivity in both early/late SR. No differences in peripheral sensitivity. β -cell response reduced in both SR types. Glucagon levels unchanged overall but decreased with late-night SR. Cortisol levels varied by sleep phase.
So-ngern et al., 2019 [20]	21 healthy participants (19 women, 2 men)	OGTT (glucose & insulin)	Sleep extension improved glycemic parameters: reduced fasting insulin resistance, increased insulin secretion, and improved β -cell function.
Radcliffe et al., 2021 [15]	18 healthy men	Ghrelin, PYY, GLP-1, Insulin, Glucose	Lower postprandial PYY and GLP-1, higher glucose in SR vs. control. Fasting glucose stable; insulin unchanged. Postprandial ghrelin and insulin unaffected.
Mateus Brandão et al., 2021 [22]	15 participants	FGF-21, Adipose & skeletal muscle tissue, OGTT, Cortisol	SR increased glucose AUC. Circulating FGF-21 increased post-SR; no tissue-specific production/response changes. Attenuated cortisol shift from night to morning.
Kanagasabai et al., 2022 [16]	10,348 participants	CRP, GGT, Bilirubin, Carotenoids, Uric Acid, Vitamins A, C, D, E, Insulin, HbA1c	Poor sleep quality/duration affected oxidative stress and inflammation markers, potentially promoting systemic insulin resistance.

Abbreviations: AUC: area under the curve; BMI: body mass index; CRP: C-reactive protein; FFA: free fatty acids; FGF-21: fibroblast growth factor 21; GGT: gamma-glutamyl transferase; GH: growth hormone; GLP-1: glucagon-like peptide-1; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; hsCRP: high-sensitivity C-reactive protein; IL-8: interleukin-8; IVGTT: intravenous glucose tolerance test; LDL: low-density lipoprotein; MetS: metabolic syndrome; NEFA: non-esterified fatty acids; OGTT: oral glucose tolerance test; PKB: protein kinase B; PYY: peptide YY; RBP4: retinol binding protein 4; SR: sleep restriction; TG: triglycerides.

4. Animal Evidence on the Impact of Sleep Deprivation on Insulin Sensitivity and Metabolic Function

A total of five in vivo animal studies were identified in the literature search. Most were conducted in rodents [29–32], except for one study carried out in the USA which used dogs as the animal model.

Venancio et al. [29] conducted a study in 2014 involving 34 90-day-old male Wistar rats, of which 16 were subjected to REM sleep restriction (SR21) for 21 days. For this, the animals were placed on platforms immersed in water 1 cm above the top edge, every day from 4 p.m. to 10 a.m. and then returned to their normal cages, resulting in sleep restriction of 18 h. This method suppressed REM sleep and induced a 25% reduction in slow-wave sleep. The control group comprised 18 rats kept in the same cages as the SR21 rats. Body weight and food intake were measured daily, as were plasma leptin, Toll-like receptor 4 (TLR4), phosphorylated nuclear factor kappa B (pNFkB), phosphorylated insulin receptor substrate-1 (pIRS-1), the hypothalamic leptin receptor, interleukin-6 and -10 (IL-6, IL-10), tumor necrosis factor alpha (TNF- α), circulating levels of endotoxin, and intraperitoneal glucose tolerance test (IPGTT). Regarding the results of IPGTT, it was found that glycemia returned to baseline values more slowly in the SR21 group after glucose administration, and glycemia values were higher in this group at 30 min. Leptin, IL-10 and TLR4 expression levels did not vary significantly, while IL-6 and TNF- α levels increased. Furthermore, pNFkB expression and plasma endotoxin levels increased in the SR21 group. This indicates that pro-inflammatory cytokine production occurs in adipose tissue. Furthermore, SR21 rats were found to have reduced IRS-1 phosphorylation in skeletal muscle. In summary, SR21

induced changes similar to those observed in MetS, possibly mediated by inflammation of the retroperitoneal adipose tissue [29].

In 2015, Oliveira et al. [30] conducted a study involving 3-month-old male C57BL/6 mice. As before, the sleep restriction method was adapted from the multiplatform method. The SR group was subjected to sleep deprivation for 21 h per day with 3 h of sleep, for 15 days. Glucose and insulin tolerance tests were performed, and fasting glycemia, leptin, insulin, adiponectin, resistin and free glycerol were measured. The study included two groups of mice: one group subjected only to sleep restriction and another group subjected to sleep restriction followed by a high-fat diet. Due to the scope of the work, only the results of the first group were considered. Comparing serum insulin levels at the beginning and end of the sleep restriction period there was an increase of approximately 50%. Leptin levels did not vary significantly, while TNF and IL-6 levels increased, as in the aforementioned study. Additionally, free glycerol had a 20% decrease, with no changes observed in serum adiponectin levels. To assess the impact of SR on adipose tissue, real-time PCR of adipokines, adipogenic markers, and proinflammatory cytokines was carried out. This highlighted that resistin levels were markedly elevated in the epididymal fat of SR rats [30].

In a different study, Xu et al. [31] resorted to 24 five-month-old female Sprague-Dawley rats, which were randomly divided into control group (CON) and chronic sleep deprivation group (PCS). All groups underwent a 1-week adaptation period to laboratory conditions and the following were measured: IPGTT, insulin tolerance test (ITT), glucose, aspartate transaminase (AST), alanine aminotransferase (ALT), creatinine, total cholesterol, LDL cholesterol, HDL cholesterol and body weight. The IPGTT and ITT tests were performed after three months of PCS, with samples taken at 08:00 and 10:00. The PCS group was subjected to the modified multiple platform method (MMPM), whereby the water tank contained 12 platforms with up to 1 cm of water covering their surface. This allowed the animals to move around the tank by jumping between the platforms, and when they started to fall asleep, their faces would touch the water, which kept them awake. After a week of adaptation, the rats were placed in the MMPM for 18 h every day, after which they were placed in cages to sleep for 6 h. The control group was placed in similar conditions, but with a grid covering the platforms to allow the rats to lie without falling into the water. The results of IPGTT showed that plasma glucose levels were found to be higher in the PCS group than in the control group. After the ITT, a marked increase was observed, indicating a decrease in insulin sensitivity. Regarding the blood tests, the fasting glycaemia of the PCS group was significantly higher than that of the CON group. Additionally, the HOMA-IR calculation was increased among the rats in the PCS group. However, there were no significant differences between the groups in terms of ALT, AST, creatinine, LDL, HDL and TG levels [31].

Aiming to investigate the mechanisms by which sleep restriction leads to insulin resistance, but focusing on the liver, Shigiyama et al. [32] conducted an experiment on male C57BL/6J mice. The animals were placed in cages under a 12-hour light/12-h dark cycle with a controlled room temperature and were given access to food and water ad libitum. The sleep restriction protocol consisted of gently touching the animals when they began to close their eyes, for 6 h. The animals in the single 6 h sleep restriction (SR) group and the respective control group were kept fasting and after the restriction time, IPGTT and pyruvate tests were performed. In the chronic sleep restriction group, the above conditions were maintained for five consecutive days, and the tests were performed at the end of the protocol. Finally, a group was included in which sleep recovery was performed after a night of 6 hours' sleep restriction. In addition to the aforementioned tests, glucagon, corticosterone, adrenocorticotrophic hormone (ACTH), triglyceride and hepatic

metabolite measurements were also performed. Regarding the results related to acute sleep deprivation, there was a significant increase in blood glucose concentration in the SR group after only one night of deprivation. In addition, the plasma glucose AUC after IPGTT was significantly higher in the SR group. However, there was no difference in plasma insulin levels 60 min after IPGTT between the SR and the control groups. Regarding chronic sleep deprivation, blood glucose concentrations were significantly lower at 0 and 60 min after IPGTT in the SR group. The plasma glucose AUC was comparable in both groups. The effect of sleep recovery on glucose tolerance was also evaluated, revealing that a 24-h recovery period improved insulin tolerance. As previously mentioned, the pyruvate test was performed in this study to examine the liver's gluconeogenic capacity, which reflects hepatic insulin sensitivity. Sleep deprivation was found to be associated with a significant increase in glucose levels after the pyruvate test compared to the control group. In the SR group, hepatic expression of glucose-6-phosphatase mRNA (a gluconeogenic enzymes) also increased [32].

More recently, in 2020, Brouwer et al. [33] conducted a study comparing the impact of sleep deprivation and a high-fat diet on insulin sensitivity and β -cell function. To achieve this, the authors gathered 24 adult (>1 year old) mixed-breed dogs of normal weight, which were subjected to two different conditions in a randomized method: normal sleep and sleep deprivation, with at least a four-day interval between each condition. Additionally, two weeks after completing the normal diet protocol, eight of the dogs were fed a high-fat diet for nine months to study the effect of sleep deprivation after this type of diet. This consisted of standard feed mixed with pork fat to achieve a fat content of 52%. During the sleep restriction protocol, the dogs were deprived of sleep for 24 h through constant physical contact to prevent them from falling asleep. After the sleep deprivation period, the dogs were given the opportunity to recover with a normal night's sleep. This protocol was repeated at different times during the study, including after the high-fat diet period. TTGIV tests were performed, and glucose sensitivity (AIRG), glucose effectiveness (SG) and glucose tolerance (KG) were subsequently calculated. Additionally, NEFA levels, as well as cortisol, norepinephrine, epinephrine, insulin and glucose levels, were measured. The results of this study showed that one night of experimental sleep deprivation significantly reduced insulin sensitivity by $21 \pm 6\%$, without β -cell compensation. Additionally, there was no increase in the acute response to glucose. On the other hand, KG was reduced, but not statistically significant. No differences were found in fasting NEFA glucose, glucose effectiveness, or adipose tissue-specific insulin sensitivity. As for cortisol and catecholamine values, both metabolites that were not studied in any of the other studies mentioned, it was found that both fasting cortisol concentration and catecholamines did not vary between the control group and the sleep restriction group [33].

In conclusion, studies in several animal models consistently showed that sleep deprivation, both acute and chronic, led to impaired glucose metabolism, insulin resistance and pro-inflammatory changes, particularly in adipose tissue. Although the magnitude and mechanisms varied depending on the study design and species, inflammation and altered hepatic or muscular insulin signaling emerged as common features. These results support the hypothesis that sleep loss contributes to metabolic dysfunction via multiple interrelated pathways. A summary of these findings is provided in Table 3.

Table 3. Overview of the key animal studies on sleep and glucose metabolism cited.

Author and Year	Sample	Analyzed Markers	Results
Venancio et al., 2014 [29]	34 male Wistar rats	Leptin; TLR4 and pNFκB; pIRS-1 and hypothalamic leptin receptor; IL-6, IL-10 and TNF-α; Endotoxin; IPGTT	Expression of pro-inflammatory cytokines increased in the SR21 group. Elevated pNFκB in adipose tissue suggests it is the source of cytokine production. Higher glycemia at 30 min and delayed return to baseline glucose levels in the SR21 group. Elevated endotoxin levels in the SR21 group.
de Oliveira et al., 2015 [30]	Male C57BL mice	Glucose and insulin tolerance tests; Glycemia; Fasting leptin, insulin and adiponectin; Resistin and free glycerol	Metabolic alterations during sleep restriction appear to primarily affect adipose tissue, exacerbating the detrimental effects of diet-induced obesity.
Xu et al., 2016 [31]	24 female Sprague-Dawley rats	IPGTT; ITT; Blood: glucose, AST, ALT, creatinine, triglycerides, total cholesterol, LDL and HDL; Body weight	Glucose intolerance developed in CSD rats after 3 months of sleep deprivation (via IPGTT). CSD rats showed marked increases in HOMA-IR and ITT, indicating reduced insulin sensitivity.
Shigiyama et al., 2018 [32]	Male C57BL/6J mice	Blood glucose; Plasma insulin; Glucagon; Corticosterone; ACTH; Hepatic triglycerides; Hepatic metabolites	Sleep restriction-induced hepatic steatosis and hepatic insulin resistance appear to be mediated by upregulation of lipogenic hepatic enzymes.
Brouwer et al., 2020 [33]	24 adult mixed-breed dogs (>1 year old, normal weight)	Glucose tolerance test; NEFA; Cortisol; Epinephrine and norepinephrine; Insulin and glucose	A single night of experimental sleep deprivation impairs insulin sensitivity without compensatory β-cell response. Sleep deprivation impaired insulin sensitivity similar to that observed after 9 months of chronic high-fat diet. No evidence of adipose tissue insulin resistance observed in response to sleep deprivation.

Abbreviations: ACTH: Adrenocorticotrophic hormone; ALT: Alanine transaminase; AST: Aspartate transaminase; CSD: Chronically sleep deprived; HDL: High-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; IL: Interleukin; IPGTT: Intraperitoneal glucose tolerance test; ITT: Insulin tolerance test; LDL: Low-density lipoprotein; NEFA: Non-esterified fatty acids; pIRS-1: Phosphorylated insulin receptor substrate 1; pNFκB: Phosphorylated nuclear factor kappa B; TLR4: Toll-like receptor 4; TNF-α: Tumor necrosis factor alpha; SR21: 21-day sleep restriction.

5. Discussion

The studies consistently investigated how sleep deprivation affected insulin sensitivity in different ways. In order to achieve this goal, a number of studies conducted measured blood glucose levels, while others employed indices as a means of data collection. The clinical trials analyzed demonstrated an association between sleep restriction and increased insulin resistance, with evidence of changes in hormone levels, such as increased fasting insulin and variations in glucagon, indicating metabolic dysfunction. Conversely, the extension of sleep in individuals with chronic sleep deprivation has been shown to have the potential to improve insulin sensitivity and β-cell function, as demonstrated in the study by So-ngern et al. [20].

There seems to be no consistency among cohort studies on the role of long sleep duration and insulin resistance, considering that Deng et al. [18] found no association between sleeping longer than 8 h and increased risk of MetS, a finding that was confirmed in the cohorts conducted by Li et al. [19] and Dijk et al. [24]. The study by Kanagasabi et al. [16] differs from the others in that it was the first to study the mediating effect of inflammation, oxidative stress and antioxidant micronutrients on glycemic control, finding

that low sleep quality and/or duration can affect several biochemical analytes associated with oxidative stress and inflammation, which in turn can promote insulin resistance [16].

Establishing a comparison with animal studies [29,31,32], there were similar results to those conducted on humans. The findings of these studies indicated that chronic REM sleep deprivation resulted in elevated blood glucose levels, insulin resistance, and inflammatory responses, characterized by increased pro-inflammatory cytokines (TNF and IL-6), and pNFkB. Specifically, the findings indicated that sleep deprivation induced metabolic alterations comparable to those observed in MetS, including elevated glucose levels post-tolerance testing and modifications in adipose and hepatic tissues. These findings suggest a substantial impact on glycemic and inflammatory regulation.

Insulin is produced in the β -cells of the pancreas; thus, one of the variables to be studied in cases of insulin resistance is β -cell function. Theoretically, in the case of insulin resistance and at an early stage, β -cells secrete elevated levels of insulin in order to maintain glucose tolerance. Consequently, an increase in glucose levels only occurs when β -cells are unable to produce sufficient insulin, thereby preventing glucose from entering the cells, remaining in the bloodstream. Therefore, from a sequential standpoint, insulin resistance occurs prior to the alteration in blood glucose levels that is concomitant with β -cell dysfunction [34]. In this sense, a large number of studies have also investigated how β -cell function varies with sleep restriction. Leproult et al. [10] and Broussard et al. [13] found that decreased insulin sensitivity did not cause a sufficient increase in β -cell function, which resulted in an increased risk of diabetes, which was in line with the expected outcomes. On the other hand, the studies conducted by Eckel et al. [17], Cedernaes et al. [21] and Wang et al. [12] demonstrated a compensatory response from β -cells, resulting in increased insulin secretion. This finding was also observed in the study by Songer et al. [20], who extended sleep beyond 6 h. As demonstrated by Wilms research group [27,28], sleep deprivation has been shown to reduce the secretion capacity of β -cells. Sleep restriction has been demonstrated to exert a multifaceted effect on β -cells, encompassing the potential to enhance, diminish, or maintain function. To understand the reason for this discrepancy, it is possible that this effect is due to the duration of sleep deprivation. While the hypothesis may be relevant, it is insufficient to explain the observed effects, particularly in the context of intermediate sleep deprivation (3–5 nights). The results showed a significant increase in function, but this was insufficient to compensate for the observed insulin resistance. Conversely, in scenarios of acute deprivation (lasting a single night), there were instances of both an increase and a decrease in β -cell function. Consequently, there are other variables that appear to have an effect on β -cell function, such as circadian dysregulation, or even the effect of REM sleep loss.

Conversely, there are also variations in the protocols that may affect the relationship between sleep loss and the metabolic consequences mentioned in this review. A number of studies that were analyzed examined sleep-related variables such as the effect of sleep deprivation on REM sleep and the existence of circadian dysregulation—a condition that is particularly prevalent among shift workers—which appear to be relevant and may explain some of the variations that emerged between studies. In this sense, the study by Leproult et al. [10] suggested that sleep deprivation can cause a decrease in insulin sensitivity, a fact that was also verified in the study by Wilms et al. [28]. However, it was found that circadian dysregulation more significantly affected both insulin action and release, which was not the case in the study by Wilms et al. [28], where disposition index was affected by sleep deprivation and not by the phase in which it occurred. In the study by Leproult et al. [10], a higher increase in inflammatory markers was also recorded in the group with circadian misalignment, suggesting an exacerbation of the mechanisms behind the development of insulin resistance. The findings of Eckel et al. [17] provide further support for this

conclusion, highlighting that elevated melatonin levels in this group appear to enhance the impact of circadian misalignment on reducing insulin sensitivity. Conversely, the study by Wilms [27] revealed that sleep deprivation during the late-night phase predominantly led to a reduction in glucagon levels and a transient increase in cortisol. The findings of these studies indicate that alterations in sleep timing do not possess sufficient potency to exert an effect on insulin sensitivity. However, it has been demonstrated that there is a substantial impact, given that circadian dysregulation, or sleep deprivation in later stages, serves to potentiate the effect of sleep deprivation. Conversely, the present study's findings indicate that this variable does not appear to exert a substantial influence on β -cell function, at least in the acute setting, as the results obtained were not consistent.

Another variable among the study protocols that should be considered is the duration of sleep deprivation, as there was a wide dispersion in this parameter, ranging from a single night of sleep deprivation [21,23,27] to years of inadequate sleep patterns [16,18,19,24]. Consequently, it was observed that a single night of acute sleep deprivation can have detrimental effects on insulin sensitivity [21,23,27]. This suggests that even sporadic poor sleep practices can have metabolic consequences. Conversely, three prospective studies [18,19,24] and a retrospective one [16] have also demonstrated that prolonged exposure to sleep deprivation may be associated with the development of MetS. However, it should be noted that a causal relationship cannot be assumed, as there may be other variables contributing to this effect besides sleep deprivation. Nevertheless, from the studies analyzed, it seems that sleep deprivation, whether brief or prolonged, exerts an influence on insulin sensitivity.

In addition to parameters directly associated with changes in insulin sensitivity, given the existence of numerous hypotheses concerning the development of insulin resistance and sleep deprivation, a variety of other parameters indirectly related were also analyzed throughout the studies. In general, the postulated mechanisms involve changes in energy consumption and expenditure, as well as hormonal changes resulting from reduced sleep periods. Specifically, reduced sleep has been demonstrated to exert an influence on metabolic health, with changes observed in the neuroendocrine and autonomic nervous systems, in addition to alterations in eating behavior and physical activity. Furthermore, sleep deprivation has been demonstrated to be associated with the activation of inflammatory signaling pathways such as TNF- α , as well as increased food intake and hormonal changes such as ghrelin and leptin that affect appetite [35]. In consideration of the dynamics of energy consumption and expenditure, it has been hypothesized that sleep deprivation may promote an increase in energy consumption and appetite, concomitant with a decrease in energy expenditure. The systematic review by Zhu et al. [36] confirms that sleep deprivation is indeed associated with increased hunger and appetite, and also with increased caloric intake. However, the findings of Radcliffe et al. [15] contradict these results, as their study demonstrated that severe sleep restriction led to a suppression of appetite and energy intake. Nevertheless, in this same study by Zhu et al. [36], the second hypothesis was not verified, as it was found that sleep restriction did not affect energy expenditure.

As previously discussed, the mechanisms responsible for this phenomenon may be associated with hormonal changes, but also with the fact that sleeping less ultimately increases the number of hours people are awake, leading to increased caloric intake. It is evident that sleep restriction exerts a considerable influence on hormonal equilibrium. It is widely accepted that sleep restriction is associated with a decrease in leptin levels and an increase in ghrelin levels, an orexigenic hormone [37,38], resulting in an increase in the ghrelin/leptin ratio [35]. In the review conducted by Zhu et al. [36], it was concluded that sleep restriction did not result in alterations to leptin or ghrelin levels, nor did it affect

energy expenditure. Similarly, the studies analyzed in this review lack measurement of ghrelin levels, only Radcliffe et al. [15] did so, and the results indicated that they remained constant.

From a hormonal perspective, sleep restriction has been hypothesized to induce the suppression of anorexigenic hormones that regulate appetite, including PYY and GLP-1. This hypothesis was not entirely verified in Radcliffe's study, where GLP-1 levels remained constant, but PYY levels did decrease. However, the results are not universally applicable, as Benedict et al. [39] found a decrease in GLP-1 levels.

On the other hand, cortisol has been hypothesized to play a pivotal role in the onset of insulin resistance. The hypothalamic–pituitary–adrenal (HPA) axis is involved in the stress response, which is triggered in situations of sleep deprivation. Upon activation, the hypothalamus triggers the synthesis of corticotropin-releasing hormone (CRH), which subsequently stimulates the synthesis of ACTH in the pituitary gland. ACTH exerts its effects on the adrenal glands, where glucocorticoids such as cortisol are synthesized. However, this axis is controlled by a negative feedback loop, which means that cortisol has an inhibitory effect on CRH and ACTH synthesis [40]. Consequently, in circumstances of sleep deprivation, it is hypothesized that chronic sleep restriction results in elevated night-time cortisol levels and diminished cortisol rhythm amplitudes over a 24-h period. As indicated by the extant literature, the mechanisms through which fluctuations in cortisol levels may be associated with the onset of glucose tolerance are related to the functions of cortisol. These include, but are not limited to, hepatic gluconeogenesis, which controls blood glucose levels, and lipolysis, by promoting the release of FFA and the accumulation of triglycerides in adipose tissue. Conversely, cortisol has been observed to activate glucocorticoid receptors in pancreatic β -cells, resulting in a reduction in insulin sensitivity. However, the results of the present review did not align with the existing consensus, as cortisol levels were found to be increased in two of the studies [11,13], while no variation was observed in the study performed by Wang et al. [12]. In the study conducted by Wilms et al. [27], it was determined that the variation in cortisol levels is contingent on the restricted phase of sleep. Specifically, an increase in cortisol levels was observed in response to sleep restriction in the subsequent phases. A thorough analysis of existing studies was conducted in an attempt to formulate hypotheses to explain the results, which revealed several similarities between the studies, namely the fact that the same participants were subjected to both protocols (normal sleep and sleep deprivation) in all studies. This factor contributes to greater uniformity of results. However, in the study by Wang et al. [12], the sleep opportunity is slightly longer—5 h, compared to 4 h and 4.5 h in the studies by Broussard et al. [13], and Rao et al. [11], respectively. Furthermore, greater control over food intake was observed in the studies by Broussard et al. [13] and Rao et al. [11] in comparison to the study by Wang et al. [12].

However, a crucial factor that must be taken into consideration is the phase of sleep restriction. As demonstrated in the study by Wilms et al. [27], the phase in which sleep restriction occurs appears to exert an influence on cortisol variation. In the study by Rao et al. [11], bedtime was between 1 a.m. and 5 a.m. In the study by Broussard et al. [13], bedtime was at a similar timeframe, from 1 a.m. to 5:30 a.m. Finally, in the study by Wang et al. [12], participants were required to reach a specific number of hours in bed, with the freedom to choose whether sleep restriction occurred at night or in the morning. Consequently, studies that imposed sleep restriction at analogous times yielded analogous results, in contrast to the study that lacked uniformity. It is acknowledged that there are other variables that can be taken into account in order to enhance the reliability of the results. These include the method of cortisol collection and the moment of the protocol in which the collection occurs. It is recognized that these variables can also interfere with the results, given that maintaining uniformity between studies becomes challenging. In this

regard, further investigation into the role of the HPA axis, as evidenced by cortisol levels, in the development of insulin resistance appears warranted.

Sleep restriction has been demonstrated to induce stress in the body, which can ultimately result in inflammation [41]. This association can be verified by the quantification of systemic inflammation markers, such as CRP and IL-6. However, there are numerous other metabolites that can be measured, including TNF, IL-8, resistin and RBP4, which are also associated with inflammation levels. Resistin, a hormone secreted by mononuclear cells in peripheral blood, exerts its effects on these cells by promoting inflammation and inducing insulin resistance through the activation of nuclear factor κ B [42]. RBP4, another factor of interest, has been associated with endothelial inflammation by promoting monocyte adhesion and leukostasis [43]. Given the importance of these inflammatory markers, several studies have analyzed these parameters associated with inflammation. Wilms et al. [27] observed that RBP4 levels increased, while IL-8 and resistin levels remained unchanged, as would be expected. In the study by Kanagasabai et al. [16], the level of CRP was found to be increased and to have an effect on fasting insulin concentration. Furthermore, the study by Leproult et al. [10] measured hSPCR levels and found them to be increased, especially in the group subjected to circadian misalignment, suggesting the importance that this factor may have in the role of inflammation in sleep restriction. Consequently, as expected, the levels of PCR and RBP4 increased; however, as sleep deprivation in the study by Wilms et al. [27] occurred during only one night, it may not have been sufficient to cause changes in the other parameters. To elucidate this relationship, it is imperative to recognize the different mechanisms involved, including the well-documented effect on the HPA and the sympathetic nervous system. These systems act in a synergistic manner to promote the expression of pro-inflammatory genes.

Regarding the impact of sleep restriction on the sympathetic nervous system, it has been demonstrated to stimulate the production of inflammatory metabolites. Additionally, it may be indirectly associated with insulin resistance and alterations in energy homeostasis [35]. During normal sleep, there is a decrease in the activation of the sympathetic nervous system, which can be excessively activated in sleep deprivation [41]. The activation of the sympathetic nervous system is reflected in the levels of hormones it produces, namely adrenaline and noradrenaline. It is hypothesized that these increase in people who are subject to sleep restriction. In the study by Broussard et al. [13], noradrenaline levels were increased, and there was a correlation between its morning elevation and increased NEFA levels during this period. This allows an association to be established between the sympathetic nervous system and lipid metabolism. Indirectly, the levels of urinary metanephrine and normetanephrine, which are the result of the metabolism of adrenaline and noradrenaline, respectively, can also be measured [44]. The study by Rao et al. [11] demonstrated that the levels of these metabolites were, in fact, increased, thus corroborating the expectations.

Regarding lipid metabolism, sleep deprivation is thought to be associated with increased FFA [35], which appear to play a significant role in the pathogenesis of insulin resistance and the development of metabolic diseases [45,46]. The mechanisms through which sleep deprivation causes elevated FFA levels may be associated with activation of the sympathetic nervous system and increased levels of cortisol and GH, which, in this specific case, promote lipolysis, thereby increasing circulating FFA levels. In relation to the impact of GH, the study by Broussard et al. [13] is the only one to have examined this variable. The study observed a shift in the secretion pattern towards a biphasic one, which resulted in an increase in its secretion. Furthermore, a robust correlation was identified between the documented rise in GH and the escalation in nocturnal FFA secretion. These results are consistent with those of studies by other researchers, such as Spiegel et al. [47],

which lend support to the theory that GH has a partial effect on NEFA elevation. Given the significant correlation between NEFA increase and the development of insulin resistance, numerous studies have examined this variable in combination with insulin resistance. In the study by Rao et al. [11], it was concluded that sleep restriction led to an increase in fat oxidation throughout the body as well as hepatic fat, which supports the aforementioned theory. Furthermore, Broussard et al. [13] discovered that, in addition to elevated NEFA levels, sleep restriction prolonged the nocturnal increase in NEFA, a finding that was also anticipated. A notable finding was the identification of a substantial correlation between the observed increase in NEFA and a concomitant decrease in insulin sensitivity. This finding suggests a potential causal relationship between these two variables. Contrary, the study by Wilms et al. [27] did not identify a significant alteration in FFA levels. However, a change in the expression of genes associated with lipid metabolism was observed. This finding suggests that the impact of sleep restriction on FFA levels may be dose-dependent. In this particular condition, where sleep restriction was relatively brief, the anticipated effect was not observed.

Although the size of the studies' populations being very small [10,11,17,21,23,26], which may have a significant effect in the results, the cohort studies analyzed appear to corroborate the findings of the clinical trials, although there are some negative aspects that may limit their transposability to the scope of this study. Cohort studies do not specifically analyze insulin resistance, but rather its long-term consequence, i.e., diabetes mellitus. Furthermore, in the analyzed populations, no isolation of variables was observed. This indicates that sleep deprivation is not the only factor contributing to the onset of diabetes; other potential contributors include poor eating habits and a sedentary lifestyle, which are often associated with these populations. Furthermore, in these studies, sleep was self-reported, and there was no objective way to measure it [16,18,19,24]. A further potential limitation is the fact that these studies were conducted in specific populations, as evidenced by the study by Li et al. [19], which focused exclusively on the Chinese population. As stated in the study by Dijk et al. [24], difficulties in obtaining information about sleep patterns were also reported.

A further limitation is the population from which the study sample is selected, which frequently consists exclusively of healthy, normal-weight Caucasian males. This restriction limits the generalizability of the results to other populations [10,14,15,22,28]. More specific limitations are evident in the study by Rao et al. [11], which lacks measurement of GH or thyroid hormone, which are hormones known to affect metabolism and be affected by sleep deprivation. In the studies by Wang et al. [12] and Wilms et al. [28], the short duration of sleep deprivation was mentioned as a limitation in extrapolating results to situations of chronic sleep deprivation. As Wang et al. [12] also observed, the study's design lacked a comprehensive monitoring of both diet and physical activity, a factor that has the potential to influence the study's outcomes. Additionally, the study's flexibility in determining the sleep restriction period may have contributed to the observed results. In the study conducted by Berg et al. [23], the measurement of energy expenditure was not included in the research methodology. This may be considered a limitation of the study, given the established relationship between increased energy expenditure and prolonged periods of wakefulness, which can result in elevated acylcarnitine levels. A limitation identified in the study by Sweeney et al. [26] that may have a relevant effect is that insulin sensitivity is measured using OGTT and not IVGTT, which is the gold standard. Furthermore, the fact that the study was conducted in the home environment may have had a bearing on compliance with regard to diet, sleep and physical activity. In the study by Depner et al. [14], a cross-over study design was not employed, which may also limit the results. The study by So-ngern et al. [20] was conducted mainly on women, which may be considered a limitation,

given that the participants were not studied during the same phase of the menstrual cycle. It is hypothesized that this may be important, as insulin resistance may be higher during the luteal phase. As for the study by Mateus Brandão et al. [22], which reported a modest increase in FGF21 in response to sleep deprivation, the possibility of a flooring effect was pointed out, i.e., that the participants started from low baseline values.

6. Conclusions

This review provides a comprehensive analysis of the impact of sleep deprivation on insulin sensitivity and metabolic health, including type 2 diabetes mellitus. Moreover, short-term sleep deprivation seems to exert a considerable negative impact on insulin regulation, resulting in a decrease in insulin sensitivity and a consequent increase in resistance to this hormone.

The data analyzed also indicate that sleep deprivation induces increased cortisol levels and reduced anabolic hormones, including growth hormones. Furthermore, it has been demonstrated that prolonged sleep deprivation may be associated with increased appetite and caloric intake, promoting obesity.

Thus, the present study highlights the importance of adequate sleep in maintaining metabolic homeostasis and preventing insulin-related disorders. In addition, the study demonstrates that chronic sleep deprivation should not be overlooked as an independent risk factor for the development of metabolic diseases. In conclusion, it is recommended that future research explore the mechanisms underlying these interactions in more detail and that public health policies consider promoting healthy sleep habits as an integral part of strategies for preventing diabetes and other related conditions.

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Abbreviations

The following abbreviations are used in this manuscript:

ACTH	Adrenocorticotrophic hormone
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC	Area under the curve
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CSD	Chronically sleep deprived
DI	Disposition index
EGP	Endogenous glucose production
FFA	Free fatty acid

FGF-21	Fibroblast growth factor 21
GGT	Gamma-glutamyl transferase
GH	Growth hormone
GLP-1	Glucagon-like peptide-1
HDL	High-density lipoprotein
HEC	Hyperinsulinemic–euglycemic clamp
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HPA	Hypothalamic–pituitary–adrenal
hsCRP	High-sensitivity C-reactive protein
IL	Interleukin
IPGTT	Intraperitoneal glucose tolerance test
ISI	Insulin sensitivity index
ITT	Insulin tolerance test
IVGTT	Intravenous glucose tolerance test
LDL	Low-density lipoprotein
MCR	Metabolic clearance rate
MetS	Metabolic syndrome
MMPM	Modified multiple platform method
NEFA	Non-esterified fatty acids
NHANES	National Health and Nutrition Examination Survey
NREM	Non-rapid eye movement
NSAIDs	Nonsteroidal anti-inflammatory drugs
OGIS	Oral glucose insulin sensitivity
OGTT	Oral glucose tolerance test
pIRS-1	Phosphorylated insulin receptor substrate-1
PKB	Protein kinase B
pNFkB	Phosphorylated nuclear factor kappa B
PYY	Peptide YY
QUICKI	Quantitative insulin sensitivity check index
RBP4	Retinol-binding protein 4
REM	Rapid eye movement
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
TLR4	Toll-like receptor 4
TNF- α	Tumor necrosis factor alpha
WAT	White adipose tissue

References

1. Baranwal, N.; Yu, P.K.; Siegel, N.S. Sleep physiology, pathophysiology, and sleep hygiene. *Prog. Cardiovasc. Dis.* **2023**, *77*, 59–69. [\[CrossRef\]](#)
2. Liew, S.C.; Aung, T. Sleep deprivation and its association with diseases—A review. *Sleep Med.* **2021**, *77*, 192–204. [\[CrossRef\]](#)
3. Chaput, J.P.; McHill, A.W.; Cox, R.C.; Broussard, J.L.; Dutil, C.; da Costa, B.G.G.; Sampasa-Kanyinga, H.; Wright, K.P., Jr. The role of insufficient sleep and circadian misalignment in obesity. *Nat. Rev. Endocrinol.* **2023**, *19*, 82–97. [\[CrossRef\]](#)
4. Li, J.; Vitiello, M.V.; Gooneratne, N.S. Sleep in Normal Aging. *Sleep Med. Clin.* **2018**, *13*, 1–11. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Bishir, M.; Bhat, A.; Essa, M.M.; Ekpo, O.; Ihunwo, A.O.; Veeraraghavan, V.P.; Mohan, S.K.; Mahalakshmi, A.M.; Ray, B.; Tuladhar, S.; et al. Sleep Deprivation and Neurological Disorders. *BioMed Res. Int.* **2020**, *2020*, 5764017. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Arnaud, C.; Bochaton, T.; Pepin, J.L.; Belaidi, E. Obstructive sleep apnoea and cardiovascular consequences: Pathophysiological mechanisms. *Arch. Cardiovasc. Dis.* **2020**, *113*, 350–358. [\[CrossRef\]](#)
7. Tripathy, D.; Wessman, Y.; Gullstrom, M.; Tuomi, T.; Groop, L. Importance of obtaining independent measures of insulin secretion and insulin sensitivity during the same test: Results with the Botnia clamp. *Diabetes Care* **2003**, *26*, 1395–1401. [\[CrossRef\]](#)
8. Placzkowska, S.; Pawlik-Sobecka, L.; Kokot, I.; Piwowar, A. Indirect insulin resistance detection: Current clinical trends and laboratory limitations. *Biomed. Pap. Med. Fac. Univ. Palacky. Olomouc Czech Repub.* **2019**, *163*, 187–199. [\[CrossRef\]](#) [\[PubMed\]](#)

9. Petrelli, A.; Cugnata, F.; Carnovale, D.; Bosi, E.; Libman, I.M.; Piemonti, L.; Cuthbertson, D.; Sosenko, J.M. HOMA-IR and the Matsuda Index as predictors of progression to type 1 diabetes in autoantibody-positive relatives. *Diabetologia* **2024**, *67*, 290–300. [\[CrossRef\]](#)
10. Leproult, R.; Holmback, U.; Van Cauter, E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. *Diabetes* **2014**, *63*, 1860–1869. [\[CrossRef\]](#)
11. Rao, M.N.; Neylan, T.C.; Grunfeld, C.; Mulligan, K.; Schambelan, M.; Schwarz, J.M. Subchronic sleep restriction causes tissue-specific insulin resistance. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 1664–1671. [\[CrossRef\]](#)
12. Wang, X.; Greer, J.; Porter, R.R.; Kaur, K.; Youngstedt, S.D. Short-Term Moderate Sleep Restriction Decreases Insulin Sensitivity in Young Healthy Adults. *Sleep Health* **2016**, *2*, 63–68. [\[CrossRef\]](#)
13. Broussard, J.L.; Chapotot, F.; Abraham, V.; Day, A.; Delebecque, F.; Whitmore, H.R.; Tasali, E. Sleep restriction increases free fatty acids in healthy men. *Diabetologia* **2015**, *58*, 791–798. [\[CrossRef\]](#)
14. Depner, C.M.; Melanson, E.L.; Eckel, R.H.; Snell-Bergeon, J.K.; Perreault, L.; Bergman, B.C.; Higgins, J.A.; Guerin, M.K.; Stothard, E.R.; Morton, S.J.; et al. Ad libitum Weekend Recovery Sleep Fails to Prevent Metabolic Dysregulation during a Repeating Pattern of Insufficient Sleep and Weekend Recovery Sleep. *Curr. Biol.* **2019**, *29*, 957–967.e954. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Radcliffe, P.N.; Whitney, C.C.; Fagnant, H.S.; Wilson, M.A.; Finlayson, G.; Smith, T.J.; Karl, J.P. Severe sleep restriction suppresses appetite independent of effects on appetite regulating hormones in healthy young men without obesity. *Physiol. Behav.* **2021**, *237*, 113438. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Kanagasabai, T.; Riddell, M.C.; Arden, C.I. Inflammation, Oxidative Stress, and Antioxidant Micronutrients as Mediators of the Relationship Between Sleep, Insulin Sensitivity, and Glycosylated Hemoglobin. *Front. Public Health* **2022**, *10*, 888331. [\[CrossRef\]](#)
17. Eckel, R.H.; Depner, C.M.; Perreault, L.; Markwald, R.R.; Smith, M.R.; McHill, A.W.; Higgins, J.; Melanson, E.L.; Wright, K.P., Jr. Morning Circadian Misalignment during Short Sleep Duration Impacts Insulin Sensitivity. *Curr. Biol.* **2015**, *25*, 3004–3010. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Deng, H.B.; Tam, T.; Zee, B.C.; Chung, R.Y.; Su, X.; Jin, L.; Chan, T.C.; Chang, L.Y.; Yeoh, E.K.; Lao, X.Q. Short Sleep Duration Increases Metabolic Impact in Healthy Adults: A Population-Based Cohort Study. *Sleep* **2017**, *40*, zsx130. [\[CrossRef\]](#)
19. Li, X.; Lin, L.; Lv, L.; Pang, X.; Du, S.; Zhang, W.; Na, G.; Ma, H.; Zhang, Q.; Jiang, S.; et al. U-shaped relationships between sleep duration and metabolic syndrome and metabolic syndrome components in males: A prospective cohort study. *Sleep Med.* **2015**, *16*, 949–954. [\[CrossRef\]](#)
20. So-Ngern, A.; Chirakalwasan, N.; Saetung, S.; Chanprasertyothin, S.; Thakkestian, A.; Reutrakul, S. Effects of Two-Week Sleep Extension on Glucose Metabolism in Chronically Sleep-Deprived Individuals. *J. Clin. Sleep Med.* **2019**, *15*, 711–718. [\[CrossRef\]](#)
21. Cedernaes, J.; Lampola, L.; Axelsson, E.K.; Liethof, L.; Hassanzadeh, S.; Yeganeh, A.; Broman, J.E.; Schioth, H.B.; Benedict, C. A single night of partial sleep loss impairs fasting insulin sensitivity but does not affect cephalic phase insulin release in young men. *J. Sleep Res.* **2016**, *25*, 5–10. [\[CrossRef\]](#)
22. Mateus Brandao, L.E.; Espes, D.; Westholm, J.O.; Martikainen, T.; Westerlund, N.; Lampola, L.; Popa, A.; Vogel, H.; Schurmann, A.; Dickson, S.L.; et al. Acute sleep loss alters circulating fibroblast growth factor 21 levels in humans: A randomised crossover trial. *J. Sleep Res.* **2022**, *31*, e13472. [\[CrossRef\]](#) [\[PubMed\]](#)
23. van den Berg, R.; Mook-Kanamori, D.O.; Donga, E.; van Dijk, M.; van Dijk, J.G.; Lammers, G.J.; van Kralingen, K.W.; Prehn, C.; Adamski, J.; Romijn, J.A.; et al. A single night of sleep curtailment increases plasma acylcarnitines: Novel insights in the relationship between sleep and insulin resistance. *Arch. Biochem. Biophys.* **2016**, *589*, 145–151. [\[CrossRef\]](#)
24. van Dijk, D.; Balkau, B.; Segrestin, B.; Gottsater, M.; Gabriel, R.; Hatunic, M.; Mari, A.; Dekker, J.M.; Rutters, F.; Group, E.-R.S. Associations between sleep duration and sleep debt with insulin sensitivity and insulin secretion in the EGIR-RISC Study. *Diabetes Metab.* **2019**, *45*, 375–381. [\[CrossRef\]](#)
25. Davies, S.K.; Ang, J.E.; Revell, V.L.; Holmes, B.; Mann, A.; Robertson, F.P.; Cui, N.; Middleton, B.; Ackermann, K.; Kayser, M.; et al. Effect of sleep deprivation on the human metabolome. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 10761–10766. [\[CrossRef\]](#)
26. Sweeney, E.L.; Jeromson, S.; Hamilton, D.L.; Brooks, N.E.; Walshe, I.H. Skeletal muscle insulin signaling and whole-body glucose metabolism following acute sleep restriction in healthy males. *Physiol. Rep.* **2017**, *5*, e13498. [\[CrossRef\]](#)
27. Wilms, B.; Leineweber, E.M.; Molle, M.; Chamorro, R.; Pommerenke, C.; Salinas-Riester, G.; Sina, C.; Lehnert, H.; Oster, H.; Schmid, S.M. Sleep Loss Disrupts Morning-to-Evening Differences in Human White Adipose Tissue Transcriptome. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 1687–1696. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Wilms, B.; Chamorro, R.; Hallschmid, M.; Trost, D.; Forck, N.; Schultes, B.; Molle, M.; Sayk, F.; Lehnert, H.; Schmid, S.M. Timing Modulates the Effect of Sleep Loss on Glucose Homeostasis. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 2801–2808. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Venancio, D.P.; Suchecki, D. Prolonged REM sleep restriction induces metabolic syndrome-related changes: Mediation by pro-inflammatory cytokines. *Brain Behav. Immun.* **2015**, *47*, 109–117. [\[CrossRef\]](#)
30. de Oliveira, E.M.; Visniauskas, B.; Sandri, S.; Migliorini, S.; Andersen, M.L.; Tufik, S.; Fock, R.A.; Chagas, J.R.; Campa, A. Late effects of sleep restriction: Potentiating weight gain and insulin resistance arising from a high-fat diet in mice. *Obesity* **2015**, *23*, 391–398. [\[CrossRef\]](#)

31. Xu, X.; Wang, L.; Zhang, Y.; Su, T.; Chen, L.; Zhang, Y.; Ma, W.; Xie, Y.; Wang, T.; Yang, F.; et al. Effects of chronic sleep deprivation on glucose homeostasis in rats. *Sleep Biol. Rhythms* **2016**, *14*, 321–328. [[CrossRef](#)]
32. Shigiyama, F.; Kumashiro, N.; Tsuneoka, Y.; Igarashi, H.; Yoshikawa, F.; Kakehi, S.; Funato, H.; Hirose, T. Mechanisms of sleep deprivation-induced hepatic steatosis and insulin resistance in mice. *Am. J. Physiol. Endocrinol. Metab.* **2018**, *315*, E848–E858. [[CrossRef](#)]
33. Brouwer, A.; Asare Bediako, I.; Paszkiewicz, R.L.; Kolka, C.M.; Bergman, R.N.; Broussard, J.L. Impact of sleep deprivation and high-fat feeding on insulin sensitivity and beta cell function in dogs. *Diabetologia* **2020**, *63*, 875–884. [[CrossRef](#)]
34. Kahn, S.E.; Cooper, M.E.; Del Prato, S. Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. *Lancet* **2014**, *383*, 1068–1083. [[CrossRef](#)]
35. Antza, C.; Kostopoulos, G.; Mostafa, S.; Nirantharakumar, K.; Tahrani, A. The links between sleep duration, obesity and type 2 diabetes mellitus. *J. Endocrinol.* **2021**, *252*, 125–141. [[CrossRef](#)]
36. Zhu, B.; Shi, C.; Park, C.G.; Zhao, X.; Reutrakul, S. Effects of sleep restriction on metabolism-related parameters in healthy adults: A comprehensive review and meta-analysis of randomized controlled trials. *Sleep Med. Rev.* **2019**, *45*, 18–30. [[CrossRef](#)] [[PubMed](#)]
37. Spiegel, K.; Tasali, E.; Penev, P.; Van Cauter, E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann. Intern. Med.* **2004**, *141*, 846–850. [[CrossRef](#)] [[PubMed](#)]
38. Cedernaes, J.; Fanelli, F.; Fazzini, A.; Pagotto, U.; Broman, J.E.; Vogel, H.; Dickson, S.L.; Schioth, H.B.; Benedict, C. Sleep restriction alters plasma endocannabinoids concentrations before but not after exercise in humans. *Psychoneuroendocrinology* **2016**, *74*, 258–268. [[CrossRef](#)] [[PubMed](#)]
39. Benedict, C.; Barclay, J.L.; Ott, V.; Oster, H.; Hallschmid, M. Acute sleep deprivation delays the glucagon-like peptide 1 peak response to breakfast in healthy men. *Nutr. Diabetes* **2013**, *3*, e78. [[CrossRef](#)]
40. Rao, R.; Somvanshi, P.; Klerman, E.B.; Marmar, C.; Doyle, F.J., 3rd. Modeling the Influence of Chronic Sleep Restriction on Cortisol Circadian Rhythms, with Implications for Metabolic Disorders. *Metabolites* **2021**, *11*, 483. [[CrossRef](#)]
41. Irwin, M.R.; Olmstead, R.; Carroll, J.E. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol. Psychiatry* **2016**, *80*, 40–52. [[CrossRef](#)] [[PubMed](#)]
42. Park, H.K.; Kwak, M.K.; Kim, H.J.; Ahima, R.S. Linking resistin, inflammation, and cardiometabolic diseases. *Korean J. Intern. Med.* **2017**, *32*, 239–247. [[CrossRef](#)] [[PubMed](#)]
43. Farjo, K.M.; Farjo, R.A.; Halsey, S.; Moiseyev, G.; Ma, J.X. Retinol-binding protein 4 induces inflammation in human endothelial cells by an NADPH oxidase- and nuclear factor kappa B-dependent and retinol-independent mechanism. *Mol. Cell Biol.* **2012**, *32*, 5103–5115. [[CrossRef](#)] [[PubMed](#)]
44. Oelmann, T.; Carson, R.; Shannon, J.R.; Ketch, T.; Robertson, D. Assessment of O-methylated catecholamine levels in plasma and urine for diagnosis of autonomic disorders. *Auton. Neurosci.* **2004**, *116*, 1–10. [[CrossRef](#)]
45. Donga, E.; van Dijk, M.; van Dijk, J.G.; Biermasz, N.R.; Lammers, G.J.; van Kralingen, K.W.; Corssmit, E.P.; Romijn, J.A. A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 2963–2968. [[CrossRef](#)]
46. DeFronzo, R.A. Dysfunctional fat cells, lipotoxicity and type 2 diabetes. *Int. J. Clin. Pract. Suppl.* **2004**, *58*, 9–21. [[CrossRef](#)]
47. Spiegel, K.; Leproult, R.; Colecchia, E.F.; L'Hermite-Baleriaux, M.; Nie, Z.; Copinschi, G.; Van Cauter, E. Adaptation of the 24-h growth hormone profile to a state of sleep debt. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2000**, *279*, R874–R883. [[CrossRef](#)]

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