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Sleep Debt and Insulin Resistance: What's Worse, Sleep Deprivation or Sleep Restriction?

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Abstract

Objective To evaluate which condition of sleep debt has a greater negative impact on insulin resistance: sleep deprivation for 24 hours or 4 hours of sleep restriction for 4 nights.

Materials and Methods In total, 28 healthy male subjects aged 18 to 40 years were recruited and randomly allocated to two groups: sleep deprivation (SD) and sleep restriction (SR). Each group underwent two conditions: regular sleep (11 PM to 7 AM) and total sleep deprivation for 24 hours (SD); regular sleep (11 PM to 7 AM) and 4 nights of sleep restriction (SR) (1 AM to 5 AM). The oral glucose tolerance test (OGTT) was performed, and baseline glucose, insulin, free fatty acids (FFAs), and cortisol were measured. In addition, the area under the curve (AUC) for glucose and insulin, the homeostasis model assessment of insulin resistance (HOMA-IR), and the Matsuda Index (Insulin Sensitivity Index, ISI) were calculated.

Results Glucose and insulin had a similar pattern between groups, except at the baseline, when insulin was higher in the sleep debt condition of the SR when compared with the SD ($p < 0.01$). In the comparison between regular sleep and sleep debt, the SD had a higher insulin AUC ($p < 0.01$) and FFAs ($p = 0.03$) after sleep deprivation, and insulin and the insulin AUC increased ($p < 0.01$ for both), while the ISI decreased ($p = 0.02$) after sleep restriction in the SR. In baseline parameters covariate by the condition of regular sleep, insulin ($p = 0.02$) and the HOMA-IR ($p < 0.01$) were higher, and cortisol ($p = 0.04$) was lower after sleep restriction when compared with sleep deprivation.

Conclusion Sleep restriction for 4 consecutive nights is more detrimental to energy metabolism because of the higher insulin values and insulin resistance compared with an acute period of sleep deprivation of 24 hours.

Keywords
- sleep deprivation
- sleep restriction
- metabolism
- insulin resistance
- glucose

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Introduction

Sleep plays a fundamental role in maintaining physical and mental health, due to its ability to influence various physiological systems of our organism.[1] It can be divided into two phases: non-rapid eye movement (NREM) and rapid eye movement (REM); NREM sleep has 3 stages (N1, N2, and N3) characterized by muscle hypotonia, cortical synchronization, and slow eye movement; the REM stage is characterized by rapid eye movement, muscle atony, cortical desynchronization, genital swelling, and dream activity.[2] Its importance is such that, in approximately 1/3 of our life, we are sleeping and, for a healthy life, 7 to 9 hours of sleep per night is recommended.[3] However, taking into account the current moment that we live in due to a pandemic, on the one hand, we have the recommendation for a night of sleep with good quality and quantity for the good of our immune system,[4] and, on the other hand, it is observed that the total sleep time has been decreasing in large urban centers, accompanied by an increase in the number of complaints and poor sleep quality and sleep disorders.[5] Within this scenario, energy metabolism is one of the factors most affected by sleep debt.[6] Considering the routine of a healthy person, blood glucose is expected to be higher during waking, with intermediate levels during REM sleep and lower levels during NREM sleep.[7–9] Regarding fatty acids, it is expected that this energy source will be used during the day, and at night its concentrations will be even higher due to prolonged fasting during sleep.[7] However, sleep output protocols have shown that the concentrations these energetic substrates are altered over 24 hours, leading to insulin resistance.[10,11]

There is still no explanation for the relationship between lack of sleep and insulin resistance. It is known that high glucose concentrations further stimulate the production and secretion of insulin by pancreatic β cells, and, in the long run, it can lead to the death of these cells.[12,13] Furthermore, high levels of fatty acids appear to influence the insulin pathway, increasing the serine phosphorylation of insulin receptor substrates, PI3K (Phosphoinositide 3-kinase) and Akt (Protein kinase B), blocking insulin signaling, and preventing the translocation of the glucose transporter to the membrane of the cell.[14] In addition, the Randle cycle (which explains the competition between glucose and fatty acids for the same receptor) should be considered. Finally, it is essential to note that both sleep deprivation and sleep restriction are stressful conditions that increase cortisol secretion, which may explain the damage to insulin action and glucose uptake.[15]

Several studies have shown that sleep debt results in changes in the glycemic and insulin response in several groups: diabetics,[16] the elderly,[17] adolescents,[18] shift workers,[19] healthy individuals with a family history of diseases,[20] and healthy and physically-active individuals.[21]

However, it is not known what is most detrimental to the metabolism: sleep deprivation for 24 hours or restricting sleep by 1 half for several days. Currently, it is common for people to experience acute situations of sleep deprivation (be it to work shifts during the night or even for social commitments or health reasons) and sleep restriction (especially in large urban centers, people are involved in professional activities and extensive commuting involving the workplace, the place where they study and their homes during the week, and take advantage of the weekend to make up for this sleep debt). Therefore, it is pertinent to evaluate the different responses in both conditions, since there are no data in the literature comparing the two situations. Thus, the objective of the present study is to verify, in young, healthy, and physically-active individuals without a family history of diabetes mellitus, which situation has the greatest negative impact on insulin resistance: sleep deprivation for 24 consecutive hours or sleep restriction of 4 hours for 4 consecutive days). We hypothesize that sleep restriction, as it is a situation of chronic sleep debt that can be repeated more frequently, would present more relevant changes compared with total sleep deprivation, which is an acute and less common situation among the population.

Materials and Methods

In the present randomized clinical trial, 28 healthy, physically-active male subjects aged 18 to 40 years were recruited. The volunteers should have a usual sleep duration of 7 to 8 hours/night and maintain regular eating habits (breakfast, lunch, and dinner). Obese individuals (Body Mass Index $> 30.0\ kg/m^2$) with diabetes mellitus or impaired glucose tolerance (and with a family history of this disease) who had sleep disorders and/or were chronic users of drugs, alcohol, and tobacco were not included.

The volunteers were recruited through advertisements at the university and on social networks. Before starting the protocols, the volunteers who met the inclusion criteria received all information about the procedures to be performed and the risks and discomforts that could happen. Those who agreed to participate signed the free and informed consent form. The study was approved by the Research Ethics Committee of Universidade Federal de São Paulo (#0579/2016) and followed the normative recommendations established by Brazilian Legislation in Resolution no. 466/12 of the Brazilian National Health Council.

Preliminary Assessments

Initially, the volunteers were submitted to the preliminary assessments (first visit) for proper verification of the inclusion criteria and evaluation of relevant data for the beginning of the protocol. The first visit was conducted to assess the volunteers' general health status, and it consisted of clinical examinations (resting electrocardiogram and exercise test) and an assessment of body composition. The volunteers answered four questionnaires that assessed the sleep pattern and the presence of possible disorders.

At the end of all these procedures, the volunteers were randomly allocated to two groups: sleep deprivation (SD) and sleep restriction (SR) (►**Fig. 1**).

Experimental Protocols

Experiment 1–SD Group

A total of 14 volunteers started the first experiment, but 4 were not included in the final analysis (2 did not complete all

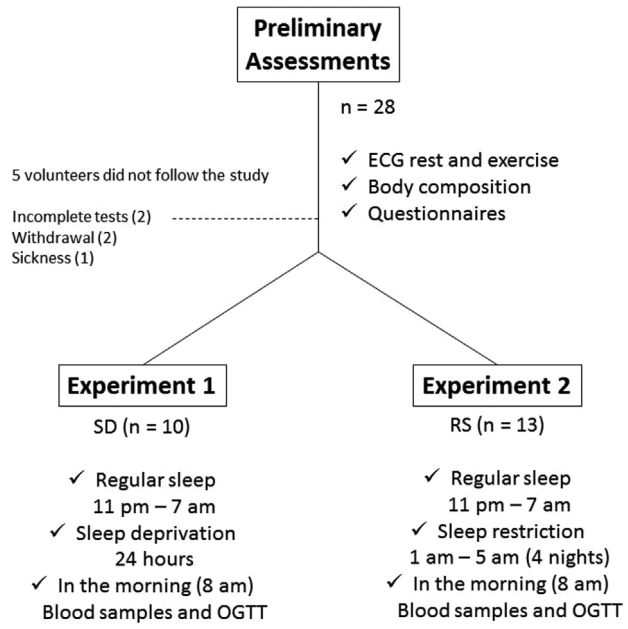

Fig. 1 Experimental design.

the assessments, and 2 dropped out). The 10 remaining volunteers had a mean age of 23.7 ± 1 years, mean body mass of 72.5 ± 8.8 kg, mean height of 1.74 ± 0.02 m, and mean BMI of 23.74 ± 3.18 kg/m^2. The volunteers were submitted to two different conditions and separated by at least one week: regular sleep and sleep deprivation. In the condition of regular sleep, the volunteers slept for 1 night (11 PM to 7 AM) and, upon waking up, they were submitted to blood collections and the oral glucose tolerance test (OGTT). In the condition of sleep deprivation, the volunteers spent 24 consecutive hours deprived of sleep and fasting from 11 PM to 7 AM (during the period, they remained in the laboratory and were constantly monitored by the researcher; meals were not allowed, and they had access to television, music, and videogames), and, in the morning, they were submitted to blood collections and the OGTT. The volunteers were instructed to maintain the same eating habits in both conditions, and blood collection was performed at 8 AM.

Experiment 2–RS Group

A total of 14 volunteers started the second experiment, and 1 was not included in the final analysis for health reasons. The 13 remaining volunteers had a mean age of 28.23 ± 4.51 years, mean body mass of 81.11 ± 11.13 kg, mean height of 1.76 ± 0.04 m, and mean BMI of 25.90 ± 2.73 kg/m^2. The volunteers were submitted to two distinct conditions and separated by at least one week: regular sleep and sleep restriction. In the condition of regular sleep, the volunteers slept for 1 night (11 PM to 7 AM) and, upon waking up, they were submitted to blood collections and the OGTT. In the condition of sleep restriction, the volunteers had 4 hours of sleep (1 AM to 5 AM) for 4 consecutive nights. They were supposed to fast from 11 PM to 7 AM and, the morning after the last night, they were subjected to blood collections and the OGTT. The volunteers were instructed to maintain the same eating habits in both conditions, and blood collection was performed at 8 AM. During the four nights of restriction, the volunteers slept in their own residences, maintained their normal activities, and were monitored remotely by the researchers (through telephone contact and instant messages via cell phone app) regarding the time to sleep and wake up, as well as the impossibility of taking naps in the daytime.

Blood Samples

Blood collection was performed early in the morning after a period of fasting by superficial puncture of the forearm vein, with the volunteers in a sitting position. The samples were centrifuged to obtain plasma and serum and stored in a biofreezer at -80°C until the time of analysis. Insulin and cortisol were determined by an immunoassay system (Unicel DxI800 Acess, Beckman Coulter, Brea, CA, Unites States), glycemia was analyzed by colorimetric/enzymatic assay (Unicel DxI 800 Acess, Beckman Coulter), and free fatty acids (FFAs), by spectrophotometry.

OGTT, HOMA-IR and ISI

The OGTT was performed with at least 8 hours of fasting, and it consisted of the oral administration of a standard dose of 75 g of anhydrous glucose dissolved in water (dextrose) in a 300-mL bottle (Gluc Up 75, lemon flavor, New Prov Produtos Para Laboratório, Pinhais, PR, Brazil), followed by blood collections of glucose and insulin at baseline (state before glucose administration) and 30, 60, 90, and 120 minutes after ingesting the solution.

The calculation of the homeostasis model assessment of insulin resistance (HOMA-IR), which verifies the degree of insulin resistance, was performed using the formula described by Matthews et al.[22] (1985), using the following equation: glycemia fasting $\times$ 0.0555 $\times$ fasting insulin/22.5.

The calculation of the Matsuda Index (Insulin Sensitivity Index, ISI), which verifies the degree of sensitivity to insulin, was performed using the formula described by Matsuda and Defronzo[23] (1999), from the expressed equation of the division of 10,000 by the square root of the fasting blood glucose and insulin product, multiplied by the product of the mean blood glucose and insulin at 0, 30, 60, 90 and 120 minutes.

Questionnaires

a) A self-applicable instrument, initially proposed by the World Health Organization (WHO) in 1998, and validated in Brazil.[24] This instrument consists of eight questions regarding the frequency (days per week) and the duration (minutes per day) of physical activities at the following intensities: vigorous, moderate, and walking. High extremes (over 120 minutes per session) will be recorded, while low extremes (under 10 minutes) will be eliminated. By estimating the total weekly energy expenditure according to the score measured in metabolic equivalents of task (MET) minutes/week or by combining the different forms of physical activity proposed in the instrument, there is a final classification of the volunteers as "insufficiently active," "sufficiently active," or "highly active." For

the present study, volunteers with a minimum "sufficiently active" rating will be considered.

b) Epworth Sleepiness Scale: A self-administered questionnaire that assesses the level of daytime sleepiness; it refers to the ease of napping in 8 everyday situations, grading the possibility of napping on a scale from 0 to 3, in which 0 means none, and 3, a high possibility of napping. Scores $\geq$ 10 indicate a high possibility of daytime sleepiness, and scores $>$ 16 indicate severe sleepiness. The lowest scores indicate that the subject has a small propensity to sleep, even when they are awake but relaxed.[25–27]

c) Pittsburgh Sleep Quality Index: A questionnaire that evaluates sleep in general aspects, highlighting the subjective sleep quality in the last month, based on numerical and qualitative information. The questionnaire consists of 19 self-administered questions and 5 questions answered by your roommate (the latter being used only for clinical application). The 19 questions are grouped into 7 components (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of sleeping medications, and daytime dysfunction) with distributed weights on a scale from 0 to 3. These component scores are added to produce a global score, which ranges from 0 to 21. A global score above 5 indicates that the individual has great difficulty in at least 2 components or moderate difficulty in more than 3 components.[27–29]

d) Sleep Questionnaire: A questionnaire originally developed by Del Giglio[57] that enables the identification of the volunteer's sleep profile.[30]

e) Mini-Sleep Questionnaire: A questionnaire that assesses sleep and reported disorders. This instrument is divided into 10 questions, with 7 alternatives that quantify the occurrence of sleep disorders, with scores from 1 to 7 points. The total score is of 70 points, with scores $>$ 30 representing very impaired sleep.[31–33]

Statistical Analysis

The statistical analyses were performed using the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States) software, version 21.0, and the Origin (Origin Lab Corporation, Northampton, MA, United States) software, version 6.0, to calculate the area under the curve (AUC) for glucose and insulin. For the comparison between the groups, the generalized linear model (GLM) with normal distribution was used, determined by the Akaike information criterion (AIC), with the Sidak post hoc test. In the comparisons between sleep deprivation and sleep restriction, the model was covariate due to the condition of regular sleep. For repeated measures, the generalized estimation equations (GEE) with gamma distribution, determined by the quasi-likelihood under independence model criterion (QIC), with the Sidak post-hoc test, were used. Data were presented as mean $\pm$ standard error of the mean (SEM) values, with a significance level of $p \leq 0.05$.

Results

►**Table 1** shows the descriptive data of the study sample. The 23 volunteers who completed the entire protocol were young, eutrophic, physically active, and normally slept for more than 7 hours a night, with good sleep quality and normal daytime sleepiness.

The glycemic curve after the OGTT showed a similar pattern between the groups. When analyzing the interaction between time and group (Wald = 1463.46; df = 19; $p < 0.01$), in the SD group, we observed that blood glucose increased at 30 minutes in regular sleep ($p < 0.01$) and in sleep debt ($p < 0.01$), and started to fall at 60 minutes in the sleep condition ($p = 0.04$) and at 90 minutes in sleep debt ($p < 0.01$). In the SR group, in both conditions (regular sleep and sleep debt), blood glucose increased at 30 minutes ($p < 0.01$ for both) and decreased at 90 minutes ($p < 0.01$ for both); at 30 minutes, the glycemia was higher when the subjects were restricted from sleep when compared with the night they slept regularly ($p < 0.01$) (►**Table 2**, ►**Fig. 2a**).

The insulin curve also showed similar patterns between the groups. When analyzing the interaction between time and group (Wald = 1141.72; df = 19; $p < 0.01$), we observed

Table 1 Characteristics of the study sample

	Total ($n = 23$)	SD ($n = 10$)	SR ($n = 13$)
Age (in years)	26.2 ± 4.1	23.7 ± 1.0	28.2 ± 4.5
Body Mass (in kg)	77.2 ± 10.8	72.5 ± 8.8	81.1 ± 11.1
Height (in m)	1.75 ± 0.03	1.74 ± 0.02	1.76 ± 0.04
BMI (in kg/m^2)	24.9 ± 3.1	23.7 ± 3.1	25.9 ± 2.7
IPAQ-SF (in MET)	2,457.0 ± 1,285.7	1,773.3 ± 1,000.8	2,728.8 ± 1,441.3
Total sleep time (in hours)	7.4 ± 0.8	7.5 ± 0.7	7.3 ± 0.8
PSQI (score)	5.0 ± 3.0	4.4 ± 3.1	5.2 ± 2.3
ESS (score)	7.0 ± 3.0	7.5 ± 3.8	6.3 ± 1.7
Sleep questionnaire (score)	25.0 ± 4.0	23.8 ± 4.9	26.0 ± 3.4
MSQ (score)	22.0 ± 6.0	25.3 ± 7.5	20.4 ± 4.5

Abbreviations: BMI, Body Mass Index; ESS, Epworth Sleepiness Scale; IPAQ-SF, International Physical Activity Questionnaire-Short Form; MET, metabolic equivalents of task; MSQ, Mini-Sleep Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SD, sleep deprivation; SR, sleep restriction.
Note: Data presented as mean ± standard deviation values.

Table 2 Glucose and insulin during the OGTT

		Baseline		30 minutes		60 minutes		90 minutes		120 minutes	
		SD	SR	SD	SR	SD	SR	SD	SR	SD	SR
Glucose (mg/dL)	Regular sleep	84.0 ± 1.8	90.3 ± 1.9	112.2 ± 4.6[a]	128.6 ± 6.8[a]	93.6 ± 6.0[b]	115.5 ± 10.4	85.7 ± 7.2[b]	95.6 ± 3.9[b]	83.1 ± 3.8[b]	85.2 ± 6.7[b]
	Sleep debt	86.5 ± 2.0	92.0 ± 2.0	138.3 ± 7.0[a]	152.5 ± 7.3[a#]	120.0 ± 11.3	118.8 ± 10.4	90.3 ± 9.3[bc]	102.6 ± 7.5[b]	80.7 ± 7.5[bc]	84.1 ± 8.2[bcd]
Insulin (uIU/mL)	Regular sleep	4.9 ± 0.6	8.0 ± 0.9	33.0 ± 4.1[a]	60.3 ± 6.2[a]	27.6 ± 5.1[a]	52.8 ± 12.0[a]	40.8 ± 7.7[a]	32.7 ± 4.7[ab]	14.4 ± 2.7[b]	18.4 ± 4.3[b]
	Sleep debt	4.3 ± 0.6	9.2 ± 0.8[*]	41.7 ± 6.1[a]	70.6 ± 7.4[a]	46.0 ± 8.2[a]	55.3 ± 8.7[a]	31.4 ± 6.7[a]	42.8 ± 7.9[a]	21.3 ± 5.1[ac]	24.4 ± 5.5[bcd]

Abbreviations: OGTT, oral glucose tolerance test; SD, sleep deprivation; SR, sleep restriction.
Notes: Generalized estimation equations with the Sidak post-hoc test. Data presented as mean ± standard error of the mean values.
[#]Different from regular sleep in the same moment and group.
[*]Different from SD in the same moment.
[a]Different from baseline in the same condition.
[b]Different from 30 minutes in the same condition.
[c]Different from 60 minutes in the same condition.
[d]Different from 90 minutes in the same condition.

that insulin at baseline in the SR was higher in comparison with the SD ($p < 0.01$). In the SD, the insulin concentrations increased at 30, 60, and 90 minutes ($p < 0.01$ for all) and decreased after 120 minutes ($p < 0.01$) in the condition of regular sleep. In the condition of sleep debt, insulin was above the baseline value throughout the period of the OGTT ($p < 0.01$ at 30, 60, and 90 minutes; and $p = 0.04$ at 120 minutes), and it started to decrease at 120 minutes (when compared with the value at 90 minutes; $p < 0.01$). In the SR, in regular sleep and sleep debt, insulin increased at 30 minutes ($p < 0.01$ for both), and this lasted up to 90 minutes ($p < 0.01$); at 120 minutes, it was lower than at 30 minutes ($p < 0.01$ for both) (►**Table 2**, ►**Fig. 2b**).

When analyzing the baseline parameters (glucose, insulin, glucose and insulin AUC, ISI, HOMA-IR, FFAs, and cortisol), in the comparison between regular night's sleep and the period of sleep debt, an increase in the insulin AUC (Wald = 30.5; df = 3; $p < 0.01$) and FFA concentrations (Wald = 10.4; df = 3; $p = 0.03$) after sleep deprivation were observed. Furthermore, after sleep restriction, insulin (Wald = 18.7; df = 3; $p < 0.01$) and the insulin AUC increased (Wald = 30.5; df = 3; $p < 0.01$), while the ISI decreased (Wald = 20.7. df = 3; $p = 0.02$) (►**Table 3**).

In the analysis of baseline parameters covariate by regular sleep condition, we could observe differences between sleep restriction and sleep deprivation. Insulin concentrations (Wald = 5.1; df = 1; $p = 0.02$) and the HOMA-IR (Wald = 8.4; df = 1; $p < 0.01$) were higher in sleep restriction, accompanied by lower cortisol values (Wald = 4.2; df = 1; $p = 0.04$) (►**Table 4**) (for the data analysis see ►**Supplementary Material**).

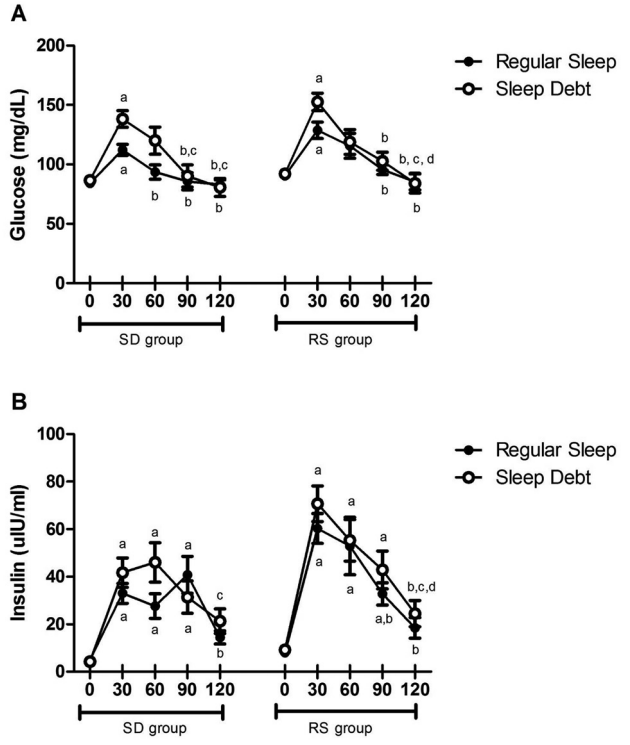

Fig. 2 Glucose and insulin after OGT. GEE with Sidak's posthoc. Data presented as mean ± sem. Legend: a - different to baseline in the same condition; b - different to 30 min in the same condition; c - different to 60 min in the same condition; d - different to 90 min in the same condition.

Table 3 Baseline parameters (sleep regular and sleep debt)

	SD			SR		
	Regular	Debt	*p*	Regular	Debt	*p*
Glucose (mg/dL)	84.8 ± 1.9	86.5 ± 2.0	0.99	88.8 ± 1.4	90.6 ± 1.6	0.74
Glucose AUC	376.7 ± 16.7	431.8 ± 26.3	0.39	409.7 ± 22.1	466.6 ± 22.3	0.38
Insulin (ulU/mL)	5.1 ± 0.6	5.2 ± 0.7	1.00	7.2 ± 0.6	9.2 ± 0.8	< 0.01*
Insulin AUC	88.0 ± 14.1	134.0 ± 18.3	< 0.01*	143.0 ± 15.2	187.4 ± 19.9	< 0.01*
ISI	9.8 ± 1.3	9.5 ± 1.3	1.00	7.1 ± 0.9	5.6 ± 0.6	0.02*
HOMA-IR	1.0 ± 0.1	0.9 ± 0.1	0.92	1.8 ± 0.2	2.1 ± 0.2	0.77
FFAs (umol/L)	285.4 ± 31.4	525.3 ± 70.5	0.03*	310.3 ± 41.4	418.3 ± 54.5	0.39
Cortisol (ug/dL)	10.2 ± 0.8	12.1 ± 0.8	0.15	11.7 ± 1.7	8.8 ± 2.5	0.73

Abbreviations: AUC, Area Under the Curve; FFAs, free fatty acids; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, Insulin Sensitivity Index; SD, sleep deprivation; SR, sleep restriction.
Notes: Generalized estimation equations with the Sidak post-hoc test. Data presented as mean ± standard error of the mean values.
*Different from regular sleep in the same group.

Table 4 Baseline parameters (SD versus SR)

	SD	SR	*p*
Glucose (mg/dL)	87.0 ± 1.9	90.2 ± 1.7	0.23
Glucose AUC	430.9 ± 24.4	469.9 ± 24.2	0.26
Insulin (ulU/mL)	6.3 ± 0.6	8.3 ± 0.5	0.02*
Insulin AUC	146.8 ± 18.1	169.7 ± 18.1	0.39
ISI	7.0 ± 0.5	6.1 ± 0.3	0.23
HOMA-IR	1.1 ± 0.2	1.9 ± 0.1	< 0.01*
FFAs (umol/L)	524.2 ± 64.9	419.2 ± 59.2	0.23
Cortisol (ug/dL)	12.7 ± 1.5	8.1 ± 1.6	0.04*

Abbreviations: AUC, Area Under the Curve; FFAs, free fatty acids; HOMA-IR, homeostasis model assessment of insulin resistance; ISI, Insulin Sensitivity Index; SD, sleep deprivation; SR, sleep restriction.
Notes: Generalized linear model with the Sidak post-hoc test. Data presented as mean ± standard error of the mean values.
*Different from SD.

Discussion

The present is the first study that sought to investigate differences in the response of energy metabolism in the face of 24-hour sleep deprivation or 4 nights of sleep restriction (for 4 hours). After the OGTT, we observed that the two conditions of sleep debt cause changes in the concentrations of glucose and insulin in the bloodstream, and before the administration of the glucose solution, insulin was higher in restriction when compared with sleep deprivation. Regarding the fasting assessments, insulin AUC and FFA concentration were higher in sleep deprivation compared with regular sleep (SD), and after sleep restriction, the insulin and insulin AUC values were higher, with a decrease in the ISI (SR). Finally, we observed differences between the two conditions of sleep debt concerning insulin concentrations, the HOMA-IR, and cortisol, indicating that sleep restriction increases insulin resistance even with lower cortisol concentrations.

It is well described in the literature that both total deprivation and sleep restriction harm energy metabolism, resulting in tissue resistance to insulin action. Total sleep deprivation protocols[21,34] with young, healthy adults corroborate our data, which showed an increase in the glucose and insulin AUC after 24 hours without sleep, and higher insulin levels after 60 consecutive hours without sleep. Regarding sleep restriction, protocols[11,35,36] of a single night, four nights, and a week (all samples with healthy young adults) resulted in a higher insulin AUC curve and endogenous glucose production, in addition to a decrease in the rate of glucose available after the euglycemic-hyperinsulinemic clamp test.

Following changes in glucose and insulin concentrations and the AUC of these same parameters after the OGTT, changes in the HOMA-IR and ISI were also observed in other studies involving healthy subjects. Sweeney et al.[37] (2017) restricted the sleep of healthy adults by 50% for 2 consecutive nights, causing an ISI decrease of 18.6% compared with 2 nights of usual sleep (7 to 9 hours of sleep). After 6 consecutive nights with 4 hours of sleep, Spiegel et al.[38] (2004) found an increase of more than 50% in the HOMA-IR in young and healthy adults. Klingenberg et al.[18] (2013) submitted 21 adolescents to 3 consecutive nights of sleep restriction (4 hours/night) or regular sleep (9 hours/night) and, having fewer hours of sleep resulted in a 65% increase in the HOMA-IR and a 28% decrease in the ISI. As these formulas use fasting glucose and insulin measures, insulin resistance may develop progressively with increased exposure to partial sleep loss,[6] and a 24-hour total sleep deprivation protocol may not be sufficient to change the HOMA-IR and ISI scores. Therefore, long-term sleep output can be a determining factor in decreasing sensitivity and increasing insulin resistance from these indexes.

Although the mechanism that induces an increase in FFAs during sleep debt has not been fully elucidated, it is believed that this energy component is one of the leading agents that cause insulin resistance. The accumulation of FFAs induces the activation of molecules responsible for the serine phosphorylation of the receptor substrates (such as JNK (c-Jun N-terminal

kinase), IKK (Inhibitor of nuclear factor-κB kinase), and PKC (Protein kinase C)), inhibiting the insulin signaling pathway.[14] When sleeping, the organism is subjected to prolonged fasting, and the FFAs are higher compared with waking, with a decrease in its concentrations in the morning (upon waking).[7] However, the sleep output causes this increase in FFAs to be prolonged, keeping their concentrations high even after the individual wakes up.[10] The present study has shown an increase in FFAs only after sleep deprivation; however, it is necessary to consider that, although it is not significant, sleep restriction was responsible for increasing the concentration of FFAs by ~ 35%, which may help explain the insulin changes. In total sleep deprivation and sleep restriction protocols,[11,21,39] an increase in FFAs was observed, accompanied by altered glycemic and insulinemic responses after the OGTT, the intravenous glucose tolerance test, and the euglycemic-hyperinsulinemic clamp. This increase in FFAs in response to a load of glucose and insulin may reflect a search for dynamic metabolism balance,[40,41] that is, a decrease or delay in lipolysis or an increase in FFA uptake and their use in peripheral tissues.[10] In addition, the increase in FFAs implies a decrease in glucose uptake by tissues by a competition mechanism,[15] which may help explain the concomitant increase in FFAs and glucose in the bloodstream.

Another potential mediator linked to sleep output and insulin resistance is cortisol. The stress imposed by the lack of a night's sleep or an incomplete nights sleep leads to greater activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, and these would be the two main counter-regulatory pathways responsible for increasing glucose levels in the bloodstream associated with reduced tissue tolerance to glucose.[42,43] Studies have shown that both sleep restriction[36,44] and sleep deprivation[45] can increase serum cortisol concentrations, which would imply the activation of enzymes responsible for the serine phosphorylation of the receptor substrates and proteins that participate in the transmission of the signal for the translocation of the transporter to the membrane, blocking the transmission of the insulin signal and preventing the uptake of glucose into the cell.[12,13] On the other hand, other studies[46,47] did not find changes in cortisol after situations of sleep debt; not even a decrease was observed. Cortisol is a hormone with circadian behavior whose concentrations change throughout the day.[48,49] The fact that we do not perform serial collections of this hormone and the time of this collection (early morning) may justify this answer.

The physiological and neurobehavioral responses to sleep deprivation and sleep restriction are similar, indicating that the mechanisms that lead to changes are also similar.[50] At first, sleep deprivation can be more harmful, especially if we analyze that an individual who remains without sleep for a long time does not have the opportunity to experience, even for a short time, the REM and NREM phases of sleep. In addition, we must consider that the organism does not support successive doses of total sleep deprivation,[51] making sleep restriction more common in people's routines. Nevertheless, even preserving a minimum amount of slow-wave sleep and REM sleep, sleep restriction implies an even greater sleep debt than sleep deprivation, as seen in the study by Van Dongen et al.[50] (2003), who evaluated participants who slept 4 hours/night for 14 nights and had a greater cumulative sleep than participants who were sleep-deprived for 88 hours. Moreover, to withstand the stress of consecutive days with a sleep duration shorter than the required amount, other physiological systems try to adapt (and may even overload) so that the organism remains in homeostasis.[52] Perhaps because of this fact, even with lower cortisol concentrations during sleep restriction, an increase in insulin response was observed with a concomitant increase in insulin resistance (HOMA-IR).

Despite the adjusted methodology – with a regular sleep control condition in each group and the maintenance of the same average sleep point (3 AM) in all conditions –, it should be noted that the present study has some limitations, such as the fact that the protocol is not a crossover, the absence of the FFA and cortisol curve, and the low number of participants (relying only on male young adults, which makes it impossible for us to extrapolate our findings to other populations). In addition, other parameters related to metabolism and sleep could be measured, such as catecholamines,[53] growth hormone (GH),[54] melatonin,[55] and microbiota.[56] On the other hand, the present study can lead to a critical reflection on what is observed in the daily life of the population, since a sample composed of healthy and physically-active young men, after an acute sleep debt protocol, showed significant changes in metabolism. Furthermore, what would be the metabolic response of people who are chronically restricted from sleep or who have some sleep disorder, who work in shifts, who have some chronic or family history, who do not eat properly, who have a high level of social jet lag, or who do not exercise regularly?

Thus, we can conclude that sleep deprivation and sleep restriction are conditions that result in changes in energy metabolism (glucose and FFAs) and hormones linked to metabolism (insulin and cortisol). However, sleep restriction for four consecutive nights is more dangerous to the organism due to the higher insulin values and insulin resistance. Since sleep debt is increasingly common in modern society, and, in the long run, this condition can cause even greater damage, further studies are needed to identify the mechanism that leads to sleep deprivation and sleep restriction causing these changes. Moreover, the results of the present study may assist the practice of all health professionals in search of better strategies that minimize these negative impacts.

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Conflict of Interests
The authors have no conflict of interests to declare.

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