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Impact of Sleep Deprivation on Thyroid and Pancreatic Function in Adult Male Albino Rat

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Abstract

Sleep deprivation (SD) is primarily defined as the quantitative or qualitative disruption of natural sleep. SD is responsible for a variety of adverse health consequences, including daytime sleepiness and an association with multiple chronic conditions. The goal of the investigation is to assess impact of SD on thyroid and pancreatic function in adult male albino rat. This study was conducted on 40 adult male albino rats of local strain. Rats were separated into four equal groups; Group (1): Control group was allowed to sleep normally, group (2): Intermittent SD group for 24 hours, and then rats were returned to home cage and allowed undisturbed for recovery for 12 hours, group (3): Intermittent SD group for 48 hours, and then rats were returned to home cage and allowed undisturbed for recovery for 12 hours, and group (4) was sleep deprived for 1 week (168 hours) continuously. Serum insulin level, fasting blood sugar (FBS), Oral glucose tolerance test (OGTT), and thyroid tissue were assessed. Serum insulin levels were significantly lower in group 2, 3, and 4 compared to group 1 (control group), while FBS levels were significantly higher in group 2, 3, and 4 compared to group 1 (control group) (P1, 2, and 3 <0.001). At 0, 30, 60, 90 and 120 minute, OGTT had significantly greater levels in group 3 and 4 compared to group 1 (control group) (P2, and P3 < 0.001). T3 and TSH levels were significantly greater in group 3 and 4 compared to group 1 (control group) (P2, and P3 < 0.001). T4 levels were insignificantly different among the four studied groups. SD stress disturbed many metabolic functions on adult male albino rats.

Keywords: Sleep Deprivation; Thyroid Function; Pancreatic Function; Albino Rat

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1. Introduction

In the animal kingdom, sleep is a fundamental aspect that is highly conserved and plays a critical role in the maintenance of homeostasis [1]. SD primarily relates to qualitative or quantitative modifications to the normal sleep cycle. The modern technological world and lifestyle appear to be intrinsically linked to SD. Several of variations are established by a multitude of factors, and all age groups can experience reductions in sleep duration or quality [2]. SD is certainly prevalent; however, there is currently no consensus regarding the extent of this phenomenon to epidemic levels. SD is responsible for a variety of adverse health effects in humans, including daily sleepiness and an association with numerous chronic conditions, including mental health disorders, obesity, cardiovascular disease, neurodegenerative disorders and diabetes [3]. In mammals, the two physiological states of sleep and wakefulness can be identified by electroencephalographic (EEG) patterns that are influenced by homeostatic processes and circadian cycles [4]. Non-REM sleep (NREM) and the rapid eye movement (REM) are the two stages of sleep that alternate cyclically during sleeping hours [5]. The information that was acquired during wakefulness is revised and integrated into the existing neural templates during REM sleep.

This sleep phase has been significantly reduced by modern lifestyles [6]. In humans, Spiegel et al. [7] By adhering to a sleep-restriction protocol of four hours per night for six consecutive nights, he exhibited an increase in serum cortisol levels and sympathetic hyperactivity. Additional homeostatic disturbances, including hypothermia and reduced serum gonadal hormone levels, were observed in animals after paradoxical SD for 96 hours [8]. An imbalance between antioxidants and oxidants in favor of oxidants results in oxidative stress, which defined as a disruption of redox signaling and control and/or molecular damage [9]. Reactive oxygen species (ROS) distributed across a range of functions contingent upon their concentration. ROS play a critical role in a diversity of physiological processes, including cell death, immune function, and redox signaling, when present at low levels (oxidative eustress). Nevertheless, ROS can cause

injury (oxidative distress) at higher concentrations [10]. In general, redox homeostasis is preserved by a variety of oxidative stress responses that are initiated by numerous molecular redox switches [11].

A variety of factors, including increased ROS production, inactivation of antioxidant enzymes, or increased antioxidant consumption, can be responsible for imbalance between antioxidants and oxidants that is identified in oxidative stress [12]. Antioxidants, both enzymatic (including superoxide dismutase, transferase, and glutathione peroxidase) and nonenzymatic (such as glutathione, micronutrients, etc.), reduce the excess of ROS generated by oxidative stress [13]. The functions and methods of determination of the primary antioxidants are relatively well-known and have been previously examined [14]. The accumulation of damage can result from the unbalanced increased oxidant load, which activates multiple programs, including mitophagy, apoptosis, autophagy, necroptosis, and ferroptosis [15]. Additionally, the production of ROS may lead to modifications in DNA structure, the activation of transcription factors, alterations in proteins and lipids, the synthesis of inflammatory cytokines, and the regulation of signal transduction pathways [16]. A wide variety of toxic compounds, including malonaldehyde (MDA), lipid hydroperoxides, and 4-hydroxynonenal (4-HNE), are produced as a result of oxidative injury to lipids [17].

These products can further induce protein and DNA degradation through denaturation or cross-linking [18]. Nitric oxide (NO) is capable of performing a diverse array of intricate physiological and pathological functions, such as oxidative damage, inflammation, signaling, vascular regulation, and sleep–wake cycles. Inducible NO synthase (iNOS), endothelial NO synthase (eNOS), and neuronal NO synthase (nNOS), are the three enzyme isoforms that mediate NO synthesis. Each isoform is specific in its localization and plays a unique role [19]. NO provides a complex role in the context of oxidative stress. Although the availability of NO can be reduced by increased ROS through NO scavenging, this is particularly true in the cardiovascular system [20], Oxidative/nitrosative stress can be exacerbated by dysregulated NO, which may cause oxidative damage in lipids, proteins, and DNA [21]. In addition to being impacted by other endocrine signals and chemicals like gonadal hormones and cortisol, thyroid hormones (THs) operate in almost every tissue, regulating metabolism and sympathetic activity [22]. Thyroxine, or 3, 5, 3′-triiodothyronine, is the principal end product of the thyroid gland.

It is converted from 3,5,3′-tetra iodothyronine, a precursor molecule, into 3,5,3′-triiodothyronine, an active molecule that adheres to nuclear thyroid hormone receptors and may either activate or inhibit transcriptional responses that are dependent on thyroid hormone [23]. During an experimental research that included eleven healthy individuals, Kessler et al. [24] exhibited that partial sleep restriction was associated with statistically significant decreases in free T4 and TSH, which were primarily noticed among female participants. It is important to mention that thyroid function in sleep-deprivation models has only been examined in two studies, in spite of the widely recognized physiological significance of THs and the effect of the circadian cycle on pulsatile TSH release. Everson & Novack [25] suggested that serum T4 levels were decreased and TRH mRNA expression was increased in rodents after exposure to SD for 15 or 21 days, while serum TSH was unaffected. Utilizing the gyratory platform method, Balzano et al. [26] noted significant raises in D2 activity and decreases in plasma T4 concentrations in rats brown adipose tissue (BAT). The objective of the investigation is to assess the influence of SD on thyroid and pancreatic functions of adult male albino rats.

2. Materials and Methods

The investigation performed on 40 adult male albino rats of local strain, with a mean weight of 135g and a weight range of 120-150g, at the age of 3 months. Rats purchased from Nile Pharmaceutical Company. Animals kept on normal light-dark cycle on cages (30cm×25cm×25cm) 3 rats in each cage at room temperature for two weeks before starting experiment for adaptation. Food and water were available.

Rats were separated into four equal groups**:** Group (1) (n=10): Control group was allowed to sleep normally, Group (2) (n=10): Intermittent SD group (SD for 24 hours): This group was sleep-deprived for 24 hours, and then returned to home cage and allowed undisturbed for recovery for 12 hours, Group (3) (n=10): Intermittent SD group,(SD for 48 hours): This group was sleep deprived for 48 hours, and then returned to home cage and allowed undisturbed for recovery for 12 hours, and Group (4) (n=10): This group was sleep deprived for 1 week (168 hours) continuously.

Equipment used: -ACCU-CHEK glucometer, -Centrifuge (Harvard Biosystems), automated Microtome: Leica Biosystems, light microscope: Olympus BHS Trinocular Polarizing Microscope.

Chemicals: Dextrose (D-glucose) solution: Dextrose (50g) was weighed out and heated and stirred with 50ml of distilled water to produce a 50% dextrose solution. Stirring and heating until dextrose dissolved in solution. Solution was poured into a graduated cylinder and diluted up to 100mL and allowed to be cool at room temperature. Kits for glucose oxidase method (ACCU-CHEK kits). Kits for estimation of serum insulin. (Abcam's Insulin ELISA "Enzyme- Linked Immunosorbent Assay" kits). Hematoxylin and Eosin stains.

2.1. Procedures

Induction of sleep deprivation: To conduct total sleep deprivation (TSD), the disc-on-water (DOW) approach was used [27]. The approach was selected because it successfully induced TSD in a single animal without requiring severe physical exertion. In contrast, the control group received the same stimulation but still managed to get an adequate quantity of sleep [28]. To accomplish SD in mice, a modified multiple platform technique was utilized, which employs a REM strategy to manipulate SD. Rat cages (40 × 40×30 cm) with 4 discs (platforms, 5× 3 cm) was soaked with little of water. In each tank, four mice were placed for 24 hours, 48 hours, and 1 week with food and water. The mice were all from the same cage. They woke awake when they touched the water, which was caused by the SD-related decrease of muscular tone. There are no limitations on movement or social isolation in this approach [29].

Anesthesia: Ethyl ether was employed to anesthetize the rats by placing them in an anesthetic box that was filled with ether vapor. Vapor could persist by intermittently applying liquid ether to a piece of cotton wool located at base of box [30].

Blood samples: Blood samples were obtained from retro orbital venous plexus of the rat by retro orbital bleeding technique [31]. 2ml of blood were collected in graduated

tube, centrifugated and left for clotting at room temperature for 15 minutes. The supernatant was collected in dry tube and kept at -60ºC until its use for determination of:

Measurement of Serum insulin level [32]: A sandwich test, an immunoradiometric method that uses two monoclonal anti-insulin antibodies, was used to assess the serum insulin level. There was a 125-I-labeled antibody and one that was adsorbed on the tube walls. We used too much of both antibodies when we incubated the samples. The cross-reactions (with all concentrations expressed in molar units) with C-peptide, proinsulin and split-fragments have been fully assessed. An insignificant cross-reaction occurred with intact proinsulin. The lowest detectable level was 0.2 mIU/l (1.4 pmol/l), and inter- and intra-assay coefficients of variation (CV) were 8.0% and 3.8%, respectively. OGTT was performed in accordance with standard method [33]. OGT tested after starving for 16 hours. The normal glucose level determined using a glucometer (ACCU-CHEK glucometer). Each animal's body weight should be monitored in rats that fed glucose at a rate of 2 grams per kg of body weight, with a daily dosage of 150 milligrams per kilogram of body weight. A glucometer employed to estimate serum glucose at 0, 30, 60, 90, & 120 minutes after blood sample taken from tail vein.

2.2. Serum Biochemical and Immunoassay Analysis

Centrifugation at 3,000 × g for 10 minutes was employed to capture serum samples. Thyroid-stimulating hormone (TSH), total T3 (TT3) and total T4 (TT4) were detected in serum using a Dxl 800 automatic immunoassay analyzer (Brea, CA, Beckman Coulter) in accordance with the appropriate kit protocol.

2.3. Histological techniques

Rats were sacrificed the thyroid glands were immediately dissected out, trimmed of connective tissue and placed into ice-cold isolation medium (ice-cold Krebs-Ringeir phosphate buffer, pH 7.4 (KRP). Then pancreas was obtained. Then specimens were cut and placed in 10 % formalin, fixed in neutral buffered formol saline, then dehydrated in ascending grades of ethyl alcohol and cleared in benzene. The specimens were blocked in hard paraffin wax. The blocks were cut at (4 um) thick, using a rotatory microtome. The sections stained with H&E [34]. Under a microscope, thyroid and pancreatic tissue sections examined.

2.4. Statistical analysis

We used SPSS version 25 (IBM Inc., NY, and ARMONK, USA) to do the statistical analysis. In order to determine if the statistical tests were parametric or nonparametric, we utilized histograms and the Shapiro-Wilks normality test to examine the distribution of quantitative data. Using analysis of variance (ANOVA) and a post hoc (Tukey) test for each group, we compared the three categories. We used the standard deviation (SD) and mean to represent the parametric variables. Categorical variables, represented as percentages and frequencies, were statistically analyzed using the Chi-square test. A two-tailed P value of less than 0.05 was determined to be significant for statistical purposes.

3. Results and discussion

3.1. Results

Serum insulin levels were significantly lower in group 2, 3, and 4 compared to group 1 (control group), while FBS levels were significantly greater in group 2, 3, and 4 compared to group 1 (control group) (P1, 2, and 3 <0.001) Table 1, Figure 1. At 0, 30, 60, 90 and 120 minute, OGTT was insignificantly different between group 1 (control group) and 2. At 0, 30, 60, 90 and 120 minute, OGTT had significantly greater levels in group 3 and 4 compared to group 1 (control group) (P2, and P3 < 0.001) Table 2, Figure 2. T3 and TSH levels were insignificantly different between group 1 (control group) and group 2. T3 and TSH levels were significantly greater in group 3 and 4 compared to group 1 (control group) (P2, and P3 < 0.001). T4 levels insignificantly different among the four studied groups Table 3, Figure 3.

3.2. Discussion

The findings of the current investigation indicated that at 0, 30, 60, 90 and 120 minute, OGTT was insignificantly different between group 1 (control group) and 2. At 0, 30, 60, 90 and 120 minute, OGTT had significantly greater levels in group 3 and 4 compared to group 1 (control group) (P2, and P3 < 0.001). These findings are in agreement with Babu et al. [35], Yaggi et al. [36], Baud et al. [37] and Nedeltcheva & Scheer [38] who observed that decrease in sleep duration or in sleep quality have been shown to adversely affect glucose regulation resulting to decrease in glucose tolerance that degrade GTT evaluated by intravenous glucose tolerance test (IVGTT) or by OGTT. This could be explained by the fact that sleep restriction led to an elevated in endogenous glucose production, which suggests that the hepatic insulin system is resistant. Additionally, rate of glucose disposal was decreased by sleep restriction, which was indicative of a decrease in peripheral insulin sensitivity. This achieved by modifying the activity of the autonomic nervous system. In a healthy individual, a single night of shortened sleep is sufficient to decrease insulin sensitivity [39]. The slower glucose clearance indicates presence of insulin insensitivity [40-41]. Also, partial SD induces an increase in 24-h epinephrine and night time norepinephrine levels [42]. Plasma level of epinephrine elevated along with nocturnal awakening.

Consequently, the relationship between glucose tolerance and endocrine homeostasis is unclear, despite the fact that sequential nights of partial SD stimulate changes in these parameters [43]. Moreover, changes in sympathovagal balance and elevated cortisol levels are two possible pathways by which SD may affect glucose metabolism. Serum insulin levels, hepatic gluconeogenesis, and insulin secretion can all be negatively impacted by elevated cortisol levels, even when these levels are within the normal physiological range [44]. Even brief arousals from sleep or sustained awakenings can abruptly elevate circulating cortisol levels and adrenocortical activity. [45]. The sympathetic nervous system activation is also associated with abnormalities in glucose metabolism and promotes insulin resistance, according to substantial evidence [46]. Insulin-mediated glucose transport is reduced, pancreatic insulin secretion is inhibited, serum glucose is reduced, and hepatic glucose release stimulated by increased sympathetic activity [47]. Alterations in level of circulating adipokines, which may be linked to type 2 diabetes and insulin resistance, would also be related to SD. This is correlated with the results in present work as insulin decreased [48-49]. Hyperphagia can increase metabolic rate which increases glucose metabolism in presence of stressful condition, including SD, leading to impairment of glucose tolerance.

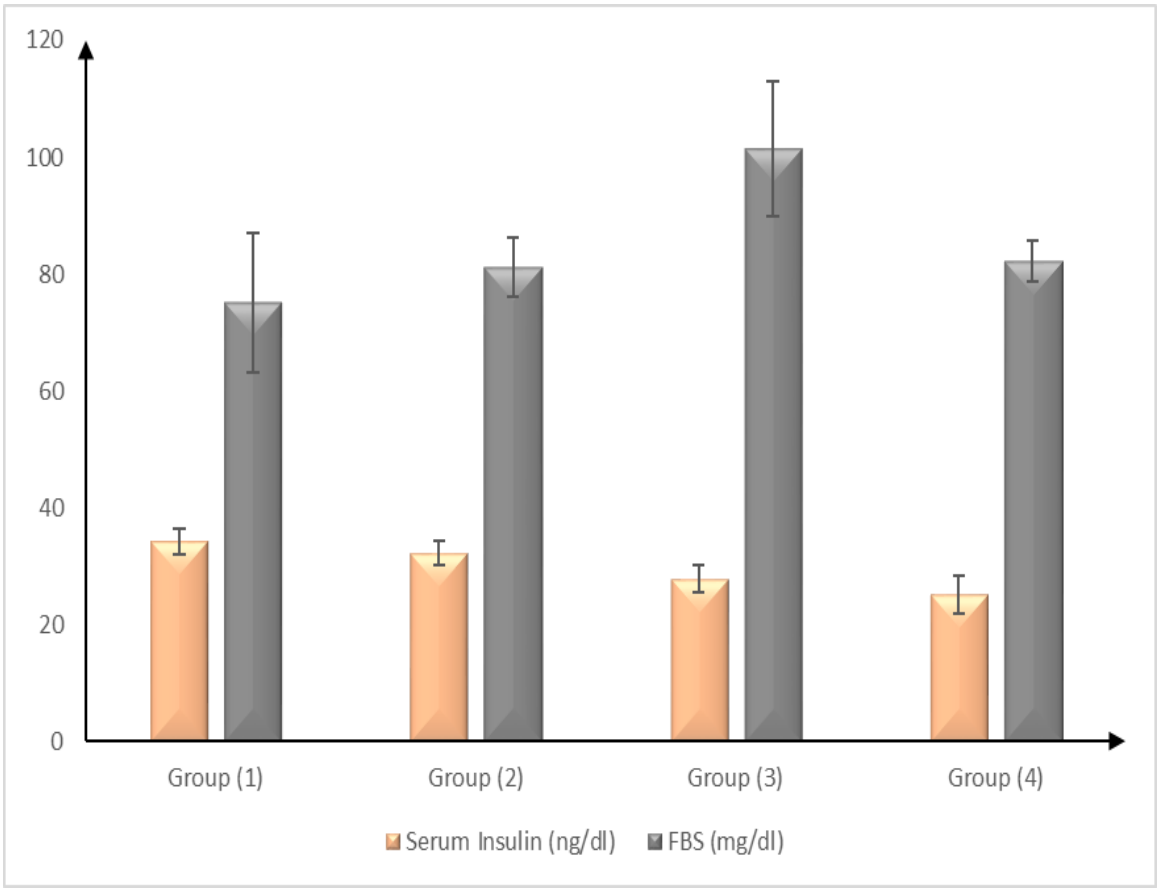

Figure 1: Changes in serum insulin and FBS levels among different groups

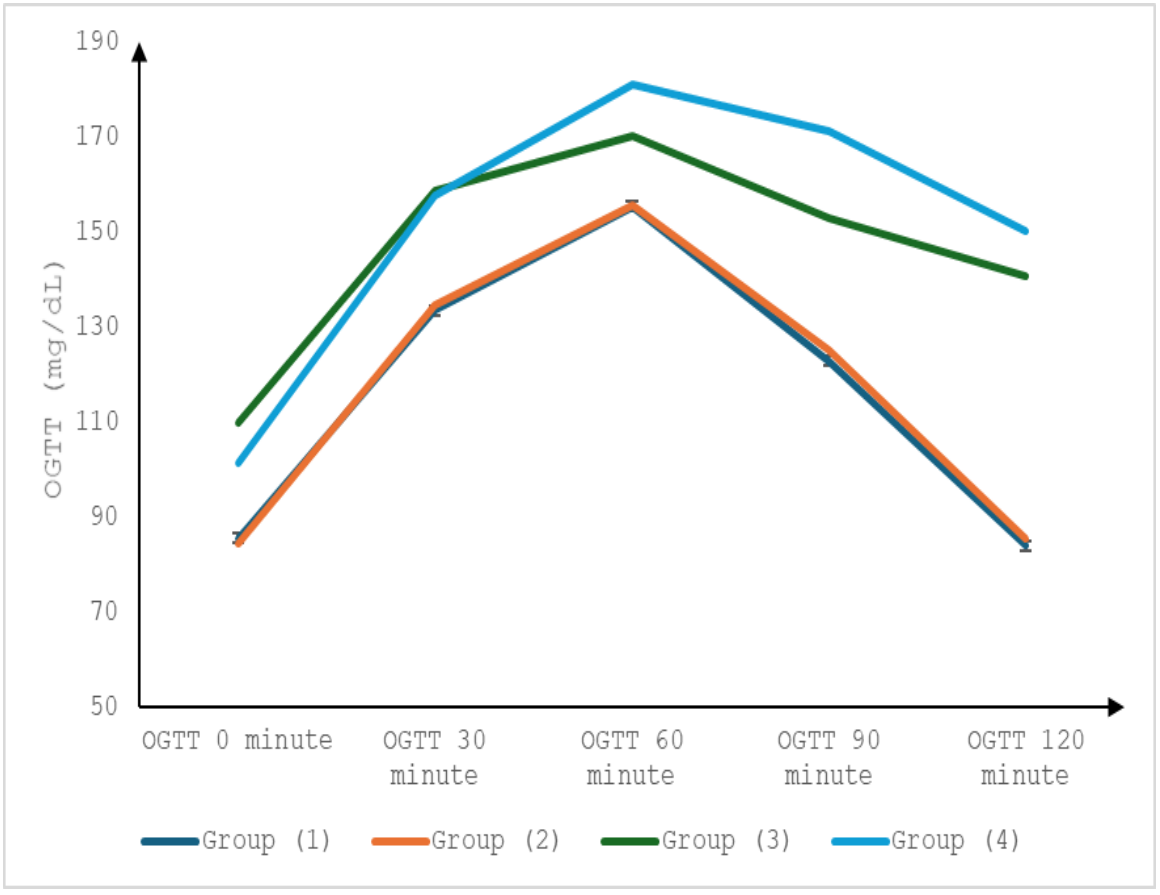

Figure 2: Changes in oral glucose tolerance level among different groups

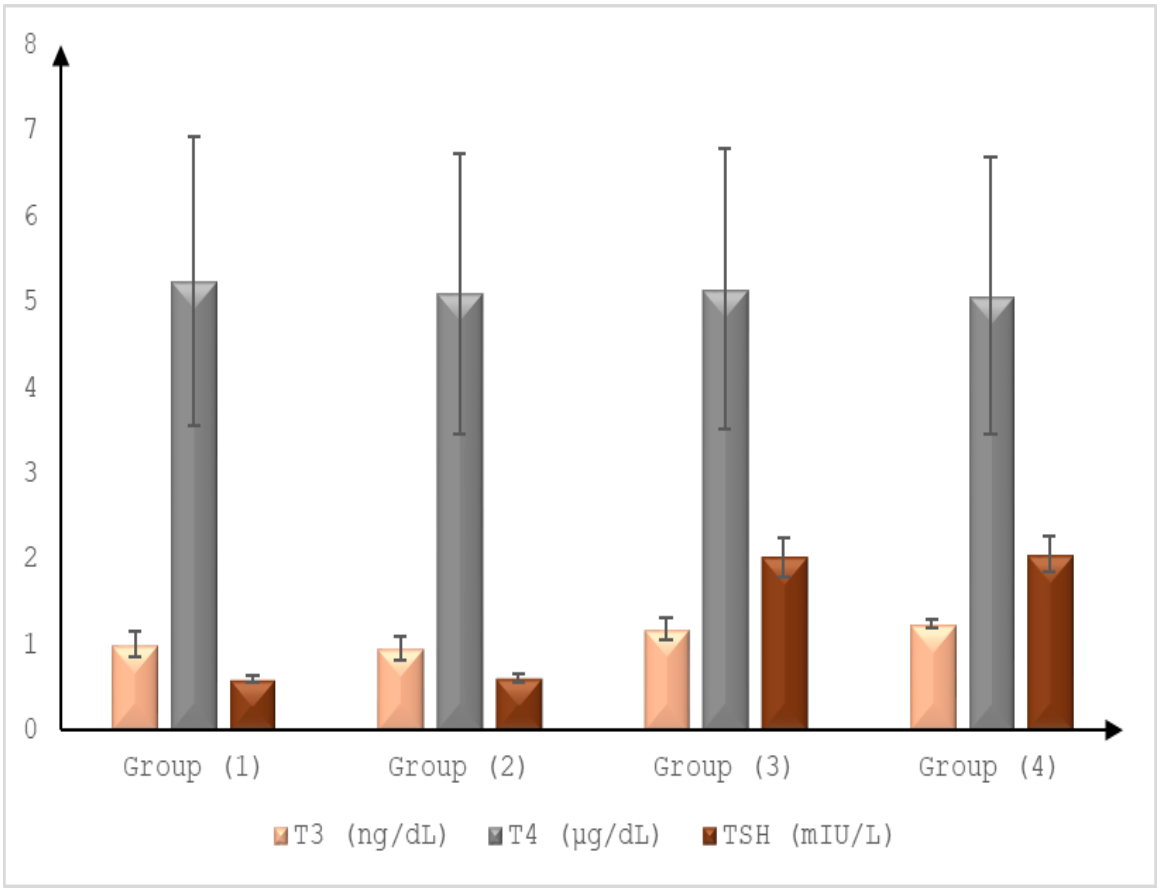

Figure 3: Changes in T3, T4, and TSH levels among different groups

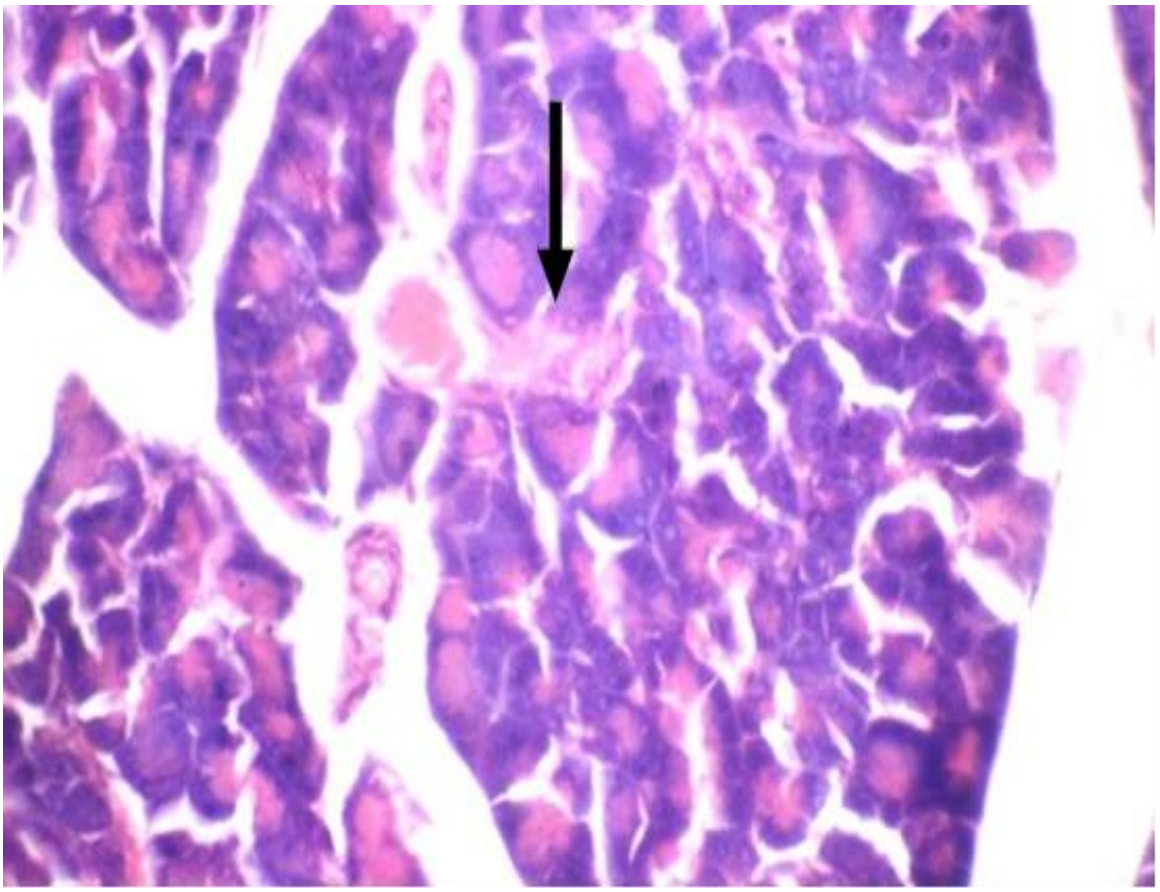

Figure 8: (1week sleep deprivation): pancreatic tissue showing average exocrine areas with mildly edematous interstitium (black arrow) (H&E x 360).

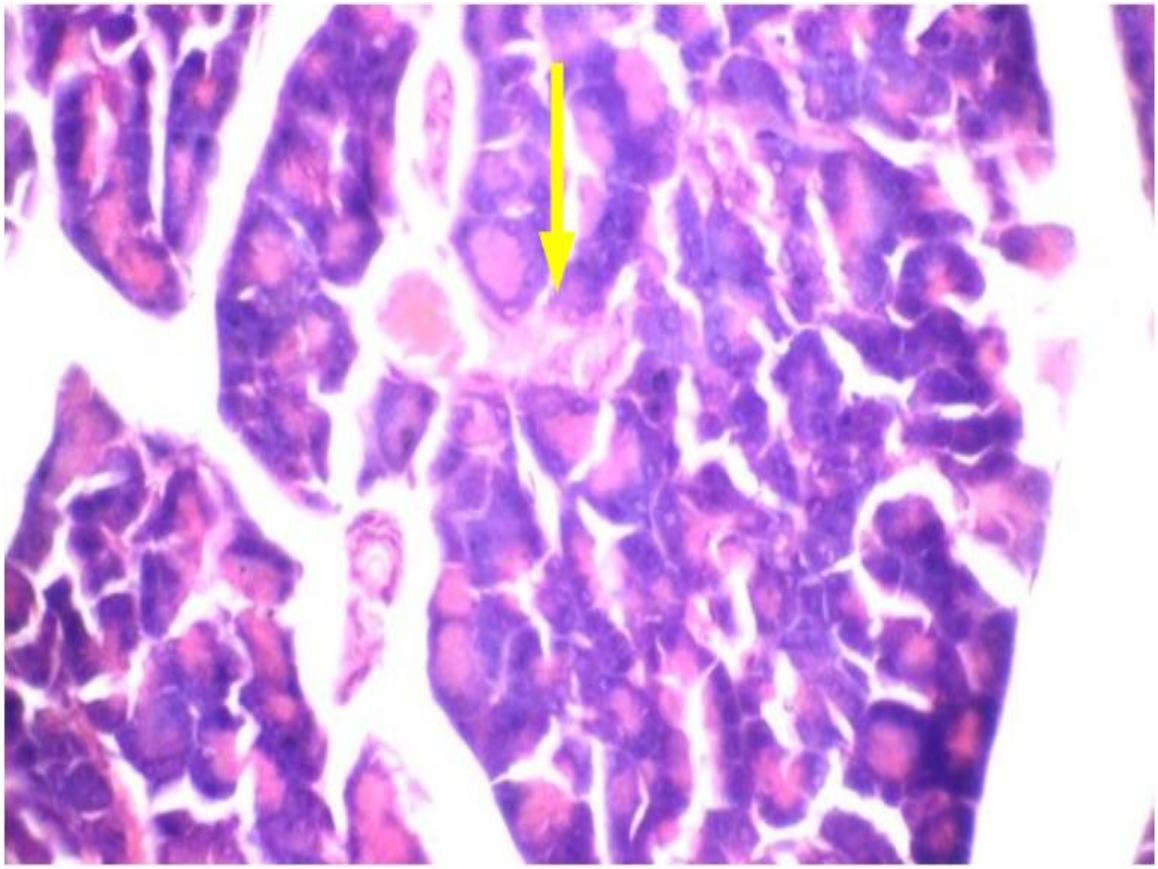

Figure 9: (1week sleep deprivation): pancreatic tissue showing average exocrine areas with mildly edematous interstitium (yellow arrow) (H&E x 360)

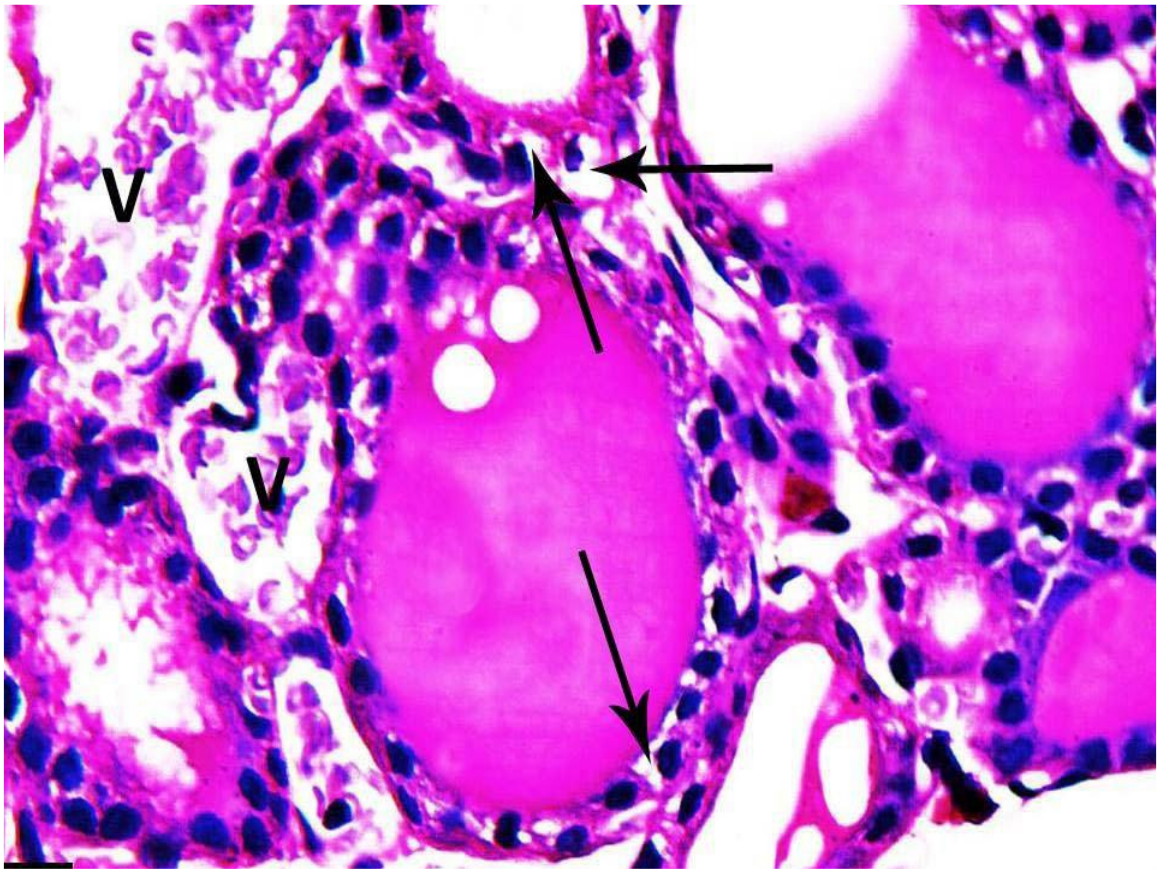

Figure 10: (1week sleep deprivation): thyroid tissue showing vacuolated cytoplasm and deeply stained nuclei in some follicular cells (black arrows) and congested dilated blood vessels (V) in thyroid parenchyma (H&E 400X).

Table 1: Changes in serum insulin and FBS levels among different groups

	Group (1)	Group (2)	Group (3)	Group (4)	P-value	
Serum insulin (ng/dl)	34.2±2.2	32.3±2	27.9±2.4	25.2±3.2	<0.001*	P1<0.001*
						P2<0.001*
						P3<0.001*
FBS (mg/dl)	75.1±11.9	81.1±5.1	101.4±11.6	82.2±3.5	<0.001*	P1<0.001*
						P2<0.001*
						P3<0.001*

FBG: Fasting blood glucose. Data is presented as mean ± SD. *statistically significant as P-value ≤ 0.05.

Table 2: Changes in oral glucose tolerance level among different groups.

	Group (1)	Group (2)	Group (3)	Group (4)	P-value	
OGTT 0 min	85.5±5.9	84.5±4.5	109.9±8.1	101.4±5.9	P<0.001*	P1= 0.507
						P2<0.001*
						P3<0.001*
OGTT 30 min	133.5±2.8	134.6±3.4	158.7±4.4	157.6±6.2	P<0.001*	P1= 0.44
						P2<0.001*
						P3<0.001*
OGTT 60 min	155.4±2.9	155.7±3.1	170.2±4.8	181.1±5.6	P<0.001*	P1= 0.79
						P2<0.001*
						P3<0.001*
OGTT 90 min	122.9±2.2	125.1±3.5	152.8±5.6	171.2±6.9	P<0.001*	P1= 0.109
						P2<0.001*
						P3<0.001*
OGTT 120 min	84±2.1	85.5±1.1	140.8±2.4	150.4±5.3	P<0.001*	P1= 0.067
						P2<0.001*
						P3<0.001*

OGTT: Oral glucose tolerance test. *statistically significant as P-value ≤ 0.05. Data is presented as mean ± SD.

Table 3: Changes in Total T3, Total T4, and TSH levels among different groups

	Group (1)	Group (2)	Group (3)	Group (4)	P-value	
Total T3 (ng/dL)	1.01 ± 0.14	0.96 ± 0.14	1.18 ± 0.13	1.25 ± 0.06	<0.001*	P1=0.493
						P2<0.001*
						P3<0.001*
Total T4 (µg/dL)	5.24 ± 1.68	5.1 ± 1.64	5.16 ± 1.64	5.08 ± 1.62	0.522	
TSH (mIU/L)	0.6 ± 0.05	0.62 ± 0.05	2.03 ± 0.23	2.06 ± 0.21	<0.001*	P1=0.461
						P2<0.001*
						P3<0.001*

TSH: Thyroid stimulating hormone. Data is presented as mean ± SD. T3: Triiodothyronine, T4: Thyroxine, *statistically significant as P-value ≤ 0.05.

Frequently, sleep loss associated with hyperphagia [50]. Because hyperphagia persists throughout experiment despite a reduction in sleeping time, it proposes that not only sleep quantity but also sleep quality are important for food intake regulation. Furthermore, hyperphagia was not associated with any weight gain, which indicates these sleep disturbances likely lead to a rise in energy expenditure. The metabolic rate of animals is elevated as a result of SD [51]. It is unclear what molecular pathways connect sleep disruption with appetite regulation; nevertheless, it is possible that circulating hormones like leptin and ghrelin, as well as neuropeptides like orexin and neuropeptide Y, have a role [52]. The glucose tolerance test in 24 hours sleep-deprived group was normal indicating that either SD period was not enough to impair glucose tolerance or recovery period is enough to restore homeostasis. These changes also correlate with other parameters as FBS and serum insulin in this group. As regards to FBS, FBS levels were significantly greater in group 2, 3, and 4 compared to group 1 (control group). These findings were disagreement with Nedeltcheva et al. [42], Donga et al. [39], and Wehrens et al. [53], who did not detect any differences in fasting glucose levels b/w partial sleep restriction and baseline sleep in contrast Klingenberg et al. [54] observed no changes in blood glucose level.

The fasting glucose and insulin concentrations were not reported in other partial SD investigations [7-55]. The significant increase of FBS is due to insulin sensitivity by altering the activity of the autonomic nervous system [39], increasing circulating catecholamines [42] and increase secretion of cortisone hormone [56] as SD is a sort of stress. The results of one-week sleep deprived group seems to be confusing as FBS decreased although OGTT impaired and

insulin level decrease. This could be explained by edematous interstitium of pancreas which may impair insulin secretion ans disturbed homeostasis due to prolonged period of SD without recovery. Papale et al. [57] it found that certain chronic stressors induce various alterations & compensatory mechanisms. As regards to insulin level; serum insulin levels were significantly lower in group 2, 3, & 4 compared to group 1 (control group). Nedeltcheva [42], Donga [39] and Wehrens [53] did not detect any difference in insulin levels. Klingenberg et al. [54] observed increase insulin level. This disagree with the results of this research. The autonomic nerve system exerts strict control over the generation and metabolism of glucose and insulin [58], It has been proposed that a change in equilibrium b/w parasympathetic and sympathetic neural systems could be cause of insulin insensitivity following SD.

In particular, the hypothalamus—and more especially the wake-promoting substance orexin—may play a role in this [59]. Neurons from the hypothalamus project to the liver, the fat tissue, and the pancreas [60], and orexin has been shown to enhance sympathetic neurons innervating these tissues [61], which could lead to, raised glucose mobilization and altered insulin sensitivity [62-63]. Orexin increase in cerebrospinal fluid after SD [64-65]. Therefore, sustained wakefulness may induce an overstimulation of the sympathetic nervous system and an increase in glucose mobilization as a consequence of increased exposure to orexin. The circadian rhythm is a key regulator of body's total energy metabolism. It affects every cell, tissue, and organ's metabolic rate [66]. Energy metabolism significantly influenced by thyroid gland. Sleep patterns undoubtedly linked to thyroid function [67]. Our study reported that T3 and TSH levels were insignificantly different b/w group 1 (control group) and group 2. T3 and TSH levels were significantly greater in group 3 and 4 compared to group 1 (control group). T4 levels were insignificantly different among the four studied groups.

This results indicated that the thyroid gland exhibited unusual alterations in weight, cell structure, and numerous biochemical markers following SD. Thyroid epithelial cells exhibited vacuolar degeneration, which indicates cell injury, potentially accompanied by apoptosis. Additionally, the thyroid's weight index decreased. This was verified by TUNEL staining of chromatin. TG is regarded as a unique indicator of thyroid integrity. The injury to the thyroid results in a decrease in TG levels, which in turn enhances the levels of TSH through a feedback mechanism and further promotes the increase of TPO. In conjunction with a comprehensive peroxidation initiation system, TPO is a critical enzyme in the synthesis of THs, catalyzing the iodination and coupling of TG tyrosine residues [68-69]. Thyroid cells secrete T4 and T3 in response to an increase in TSH, and synthesis of THs is also facilitated by an increase in TPO. THs are primary regulators of metabolism, growth, and development. The catabolism of proteins, carbohydrates, and lipids is directly induced by an increase in thyroid hormone serum levels, which leads to weight loss [70]. Balzano et al. [26], who additionally showed decreases in serum T4 levels in sleep-deprived animals, but NOT in TSH.

In an investigation conducted by Everson & Nowak [25], the central hypothyroidism caused by TSD was attributed to a deficiency of TRH secretion, which influenced the TSH response to hypothyroxinemia. Rodrigues et al. [71] discovered that the thyroid gland adjusts to sleep deprivation-induced central hypothyroidism by enhancing the T4 to T3 activation peripherally (in BAT and potentially other tissues), thereby increasing circulating T3. The absence of a hypothyroxinemia-induced the large levels of T3 seen in their procedure may help explain the TSH response and inhibit the HPT axis separately. The protocol they used included an increase in T3. Results showed that systemic fractional conversion of T4 to T3 was enhanced by increased D2 activity in BAT, which may have played a role in the observed increase in serum T3 and decrease in serum T4 levels. In SD settings, body goes into an oxidative stress state, as shown by many studies [72]. The thyroid possesses robust compensatory and antioxidative stress mechanisms, as well as elevated concentrations of variety of antioxidant enzymes. To help reduce ROS to less harmful compounds, the thyroid enhances antioxidant system activity, which in turn produces GPx, SOD, and other antioxidant chemicals [70].

4. Conclusions

Twenty-four hours- sleep deprived group revealed no significant changes. One week sleep-deprived group revealed significant changes in all parameters, So, SD stress disturbed many metabolic functions on adult male albino rats.

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Conflict of Interest: Nil

References

[1] H. Bringmann. (2019). Genetic sleep deprivation: using sleep mutants to study sleep functions. EMBO reports. 20(3): e46807.

[2] A. Bandyopadhyay, N.L. Sigua. (2019). What is sleep deprivation? Am. J. Respir. Crit. Care Med. 199(6): P11-P12.

[3] J. Owens. (2014). Insufficient sleep in adolescents and young adults: an update on causes and consequences. Pediatrics. 134(3): e921-32.

[4] A. Borbély. (2022). The two-process model of sleep regulation: Beginnings and outlook. J Sleep Res. 31(4): e13598.

[5] O. Le Bon. (2020). Relationships between REM and NREM in the NREM-REM sleep cycle: a review on competing concepts. Sleep Medicine. 70: 6-16.

[6] C.E. Okechukwu. (2022). The neurophysiologic basis of the human sleep–wake cycle and the physiopathology of the circadian clock: a narrative review. Egypt J Neurol Psychiatry Neurosurg. 58(1): 34.

[7] K. Spiegel, R. Leproult, E. Van Cauter. (1999). Impact of sleep debt on metabolic and endocrine function. Lancet. 354(9188): 1435-9.

[8] A.C.D. Scoralick, A.d.C.V. Júnior, A.L. Cavalcanti, A.P.C. dos Santos, D.D. Neves, M.H.A. Melo. (2021). Evaluation of Erectile Dysfunction in Nonobese, Nondiabetic Men with Obstructive Sleep Apnea. Open Urol Nephrol J. 14(1).

[9] H. Sies. (2020). Oxidative Stress: Concept and Some Practical Aspects. Antioxidants (Basel). 9(9).

[10] S.K. Bardaweel, M. Gul, M. Alzweiri, A. Ishaqat, A.L. HA, R.M. Bashatwah. (2018). Reactive Oxygen Species: the Dual Role in Physiological and

Pathological Conditions of the Human Body. Eurasian J Med. 50(3): 193-201.
[11] F. Ursini, M. Maiorino, H.J. Forman. (2016). Redox homeostasis: The Golden Mean of healthy living. Redox Biology. 8: 205-215.
[12] R. Vona, L. Pallotta, M. Cappelletti, C. Severi, P. Matarrese. (2021). The Impact of Oxidative Stress in Human Pathology: Focus on Gastrointestinal Disorders. Antioxidants. 10(2): 201.
[13] S. Demirci-Çekiç, G. Özkan, A.N. Avan, S. Uzunboy, E. Çapanoğlu, R. Apak. (2022). Biomarkers of Oxidative Stress and Antioxidant Defense. JPBA Open. 209: 114477.
[14] İ. Gulcin. (2020). Antioxidants and antioxidant methods: an updated overview. Arch Toxicol. 94(3): 651-715.
[15] L. Lin, M.-X. Zhang, L. Zhang, D. Zhang, C. Li, Y.-l. Li. (2022). Autophagy, Pyroptosis, and Ferroptosis: New Regulatory Mechanisms for Atherosclerosis. Front Cell Dev Biol. 9.
[16] M. Mittal, M.R. Siddiqui, K. Tran, S.P. Reddy, A.B. Malik. (2014). Reactive oxygen species in inflammation and tissue injury. Antioxid Redox Signal. 20(7): 1126-67.
[17] G. Barrera, S. Pizzimenti, M. Daga, C. Dianzani, A. Arcaro, G.P. Cetrangolo, G. Giordano, M.A. Cucci, M. Graf, F. Gentile. (2018). Lipid Peroxidation-Derived Aldehydes, 4-Hydroxynonenal and Malondialdehyde in Aging-Related Disorders. Antioxidants (Basel). 7(8).
[18] G. Martemucci, C. Costagliola, M. Mariano, L. D'andrea, P. Napolitano, A.G. D'Alessandro. (2022). Free radical properties, source and targets, antioxidant consumption and health. Oxygen. 2(2): 48-78.
[19] E. Goshi, G. Zhou, Q. He. (2019). Nitric oxide detection methods in vitro and in vivo. Med Gas Res. 9(4): 192-207.
[20] J. Tejero, S. Shiva, M.T. Gladwin. (2019). Sources of vascular nitric oxide and reactive oxygen species and their regulation. Physiol Rev. 99(1): 311-379.
[21] F. Wang, Q. Yuan, F. Chen, J. Pang, C. Pan, F. Xu, Y. Chen. (2021). Fundamental Mechanisms of the Cell Death Caused by Nitrosative Stress. Front Cell Dev Biol. 9: 742483.
[22] N.C. Rodrigues, N.S. da Cruz, C. de Paula Nascimento, R.R. da Conceição, A.C.M. da Silva, E.L. Olivares, M.P. Marassi. (2015). Sleep deprivation alters thyroid hormone economy in rats. Exp Physiol. 100(2): 193-202.
[23] D. Zhang, A.P. Heaney. (2020). Nuclear Receptors as Regulators of Pituitary Corticotroph Pro-Opiomelanocortin Transcription. Cells. 9(4): 900.
[24] L. Kessler, A. Nedeltcheva, J. Imperial, P.D. Penev. (2010). Changes in serum TSH and free T4 during human sleep restriction. Sleep. 33(8): 1115-8.
[25] C.A. Everson, T.S. Nowak, Jr. (2002). Hypothalamic thyrotropin-releasing hormone mRNA responses to hypothyroxinemia induced by sleep deprivation. Am J Physiol Endocrinol Metab. 283(1): E85-93.
[26] S. Balzano, B.M. Bergmann, M.A. Gilliland, J.E. Silva, A. Rechtschaffen, S. Refetoff. (1990). Effect of total sleep deprivation on 5'-deiodinase activity of rat brown adipose tissue. Endocrinology. 127(2): 882-90.
[27] H.M. Chang, U.I. Wu, T.B. Lin, C.T. Lan, W.C. Chien, W.L. Huang, J.Y. Shieh. (2006). Total sleep deprivation inhibits the neuronal nitric oxide synthase and cytochrome oxidase reactivities in the nodose ganglion of adult rats. J Anat. 209(2): 239-50.
[28] B.M. Bergmann, C.A. Everson, C.A. Kushida, V.S. Fang, C.A. Leitch, D.A. Schoeller, S. Refetoff, A. Rechtschaffen. (1989). Sleep deprivation in the rat: V. Energy use and mediation. Sleep. 12(1): 31-41.
[29] C.L. Patti, K.A. Zanin, L. Sanday, S.R. Kameda, L. Fernandes-Santos, H.A. Fernandes, M.L. Andersen, S. Tufik, R. Frussa-Filho. (2010). Effects of sleep deprivation on memory in mice: role of state-dependent learning. Sleep. 33(12): 1669-79.
[30] J.B. Watkins, C.P. Siegers, C.D. Klaassen. (1984). Effect of diethyl ether on the biliary excretion of acetaminophen. Proc Soc Exp Biol Med. 177(1): 168-75.
[31] H. van Herck, V. Baumans, C.J. Brandt, A.P. Hesp, J.H. Sturkenboom, H.A. van Lith, G. van Tintelen, A.C. Beynen. (1998). Orbital sinus blood sampling in rats as performed by different animal technicians: the influence of technique and expertise. Lab Anim. 32(4): 377-86.
[32] D. Vezzosi, A. Bennet, J. Fauvel, C. Boulanger, O. Tazi, J.P. Louvet, P. Caron. (2003). Insulin levels measured with an insulin-specific assay in patients with fasting hypoglycaemia related to endogenous hyperinsulinism. Eur J Endocrinol. 149(5): 413-9.
[33] V. Du Vigneaud, W.G. Karr. (1926). Carbohydrate utilization. I. Rate of disappearance of d-glucose from the blood. J Biol Chem. 66: 281.
[34] A. Stevens, W. I., The haematoxylins and eosin. In *Theory and practice of histological techniques*, Bancroft D.,A., S., Eds. Pbl. Churchill Livingstone: New York, 1996; pp 47–67.
[35] A.R. Babu, J. Herdegen, L. Fogelfeld, S. Shott, T. Mazzone. (2005). Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. Arch Intern Med. 165(4): 447-52.
[36] H.K. Yaggi, A.B. Araujo, J.B. McKinlay. (2006). Sleep duration as a risk factor for the development of type 2 diabetes. Diabetes Care. 29(3): 657-61.
[37] M.O. Baud, P.J. Magistretti, J.M. Petit. (2013). Sustained sleep fragmentation affects brain temperature, food intake and glucose tolerance in mice. J Sleep Res. 22(1): 3-12.
[38] A.V. Nedeltcheva, F.A. Scheer. (2014). Metabolic effects of sleep disruption, links to obesity and diabetes. Curr Opin Endocrinol Diabetes Obes. 21(4): 293-8.
[39] E. Donga, M. van Dijk, J.G. van Dijk, N.R. Biermasz, G.J. Lammers, K.W. van Kralingen, E.P. Corssmit, J.A. Romijn. (2010). A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. J Clin Endocrinol Metab. 95(6): 2963-8.

[40] R.A. DeFronzo. (1988). Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes. 37(6): 667-87.

[41] G.M. Reaven, Insulin resistance, compensatory hyperinsulinemia, and coronary heart disease: syndrome X revisited. In *Handbook of Physiology, The Endocrine System, The Endocrine Pancreas and Regulation of Metabolism*, Jefferson LS, C. A., Ed. Oxford University Press: New York, NY, 2010; pp 1169-1197.

[42] A.V. Nedeltcheva, J.M. Kilkus, J. Imperial, K. Kasza, D.A. Schoeller, P.D. Penev. (2009). Sleep curtailment is accompanied by increased intake of calories from snacks. Am J Clin Nutr. 89(1): 126-33.

[43] M. Irwin, J. Thompson, C. Miller, J.C. Gillin, M. Ziegler. (1999). Effects of sleep and sleep deprivation on catecholamine and interleukin-2 levels in humans: clinical implications. J Clin Endocrinol Metab. 84(6): 1979-85.

[44] R.C. Andrews, B.R. Walker. (1999). Glucocorticoids and insulin resistance: old hormones, new targets. Clin Sci (Lond). 96(5): 513-23.

[45] M. Follenius, G. Brandenberger, J.J. Bandesapt, J.P. Libert, J. Ehrhart. (1992). Nocturnal cortisol release in relation to sleep structure. Sleep. 15(1): 21-7.

[46] K. Nonogaki. (2000). New insights into sympathetic regulation of glucose and fat metabolism. Diabetologia. 43(5): 533-49.

[47] A. Avogaro, G. Toffolo, A. Valerio, C. Cobelli. (1996). Epinephrine exerts opposite effects on peripheral glucose disposal and glucose-stimulated insulin secretion. A stable label intravenous glucose tolerance test minimal model study. Diabetes. 45(10): 1373-8.

[48] S.E. Shoelson, J. Lee, A.B. Goldfine. (2006). Inflammation and insulin resistance. J Clin Invest. 116(7): 1793-801.

[49] A. Sjöholm, T. Nyström. (2006). Inflammation and the etiology of type 2 diabetes. Diabetes Metab Res Rev. 22(1): 4-10.

[50] M. Koban, L.V. Sita, W.W. Le, G.E. Hoffman. (2008). Sleep deprivation of rats: the hyperphagic response is real. Sleep. 31(7): 927-33.

[51] M.H. Bonnet, R.B. Berry, D.L. Arand. (1991). Metabolism during normal, fragmented, and recovery sleep. J Appl Physiol (1985). 71(3): 1112-8.

[52] P.J. Martins, M.S. Marques, S. Tufik, V. D'Almeida. (2010). Orexin activation precedes increased NPY expression, hyperphagia, and metabolic changes in response to sleep deprivation. Am J Physiol Endocrinol Metab. 298(3): E726-34.

[53] S.M. Wehrens, S.M. Hampton, R.E. Finn, D.J. Skene. (2010). Effect of total sleep deprivation on postprandial metabolic and insulin responses in shift workers and non-shift workers. J Endocrinol. 206(2): 205-15.

[54] L. Klingenberg, J.P. Chaput, U. Holmbäck, T. Visby, P. Jennum, M. Nikolic, A. Astrup, A. Sjödin. (2013). Acute Sleep Restriction Reduces Insulin Sensitivity in Adolescent Boys. Sleep. 36(7): 1085-1090.

[55] E. Tasali, R. Leproult, D.A. Ehrmann, E. Van Cauter. (2008). Slow-wave sleep and the risk of type 2 diabetes in humans. Proc Natl Acad Sci U S A. 105(3): 1044-9.

[56] A. Omisade, O.M. Buxton, B. Rusak. (2010). Impact of acute sleep restriction on cortisol and leptin levels in young women. Physiol Behav. 99(5): 651-6.

[57] L.A. Papale, M.L. Andersen, I.B. Antunes, T.A. Alvarenga, S. Tufik. (2005). Sleep pattern in rats under different stress modalities. Brain Res. 1060(1-2): 47-54.

[58] S. Iversen, L. Iversen, C.B. Saper, The autonomic nervous system and the hypothalamus. In *Principles of neural science*, 4th ed.; Iversen, S.,Iversen, L.,Saper, C. B., Eds. New York: McGraw-Hill Education, 2000; Vol. 4, pp 960-981.

[59] C.B. Saper, T.E. Scammell, J. Lu. (2005). Hypothalamic regulation of sleep and circadian rhythms. Nature. 437(7063): 1257-63.

[60] F. Kreier, Y.S. Kap, T.C. Mettenleiter, C. van Heijningen, J. van der Vliet, A. Kalsbeek, H.P. Sauerwein, E. Fliers, J.A. Romijn, R.M. Buijs. (2006). Tracing from fat tissue, liver, and pancreas: a neuroanatomical framework for the role of the brain in type 2 diabetes. Endocrinology. 147(3): 1140-7.

[61] M. van den Top, M.F. Nolan, K. Lee, P.J. Richardson, R.M. Buijs, C.H. Davies, D. Spanswick. (2003). Orexins induce increased excitability and synchronisation of rat sympathetic preganglionic neurones. J Physiol. 549(Pt 3): 809-21.

[62] T. Shiuchi, M.S. Haque, S. Okamoto, T. Inoue, H. Kageyama, S. Lee, C. Toda, A. Suzuki, E.S. Bachman, Y.B. Kim, T. Sakurai, M. Yanagisawa, S. Shioda, K. Imoto, Y. Minokoshi. (2009). Hypothalamic orexin stimulates feeding-associated glucose utilization in skeletal muscle via sympathetic nervous system. Cell Metab. 10(6): 466-80.

[63] C.X. Yi, M.J. Serlie, M.T. Ackermans, E. Foppen, R.M. Buijs, H.P. Sauerwein, E. Fliers, A. Kalsbeek. (2009). A major role for perifornical orexin neurons in the control of glucose metabolism in rats. Diabetes. 58(9): 1998-2005.

[64] T. Deboer, S. Overeem, N.A. Visser, H. Duindam, M. Frölich, G.J. Lammers, J.H. Meijer. (2004). Convergence of circadian and sleep regulatory mechanisms on hypocretin-1. Neuroscience. 129(3): 727-32.

[65] J.M. Zeitzer, C.L. Buckmaster, D.M. Lyons, E. Mignot. (2007). Increasing length of wakefulness and modulation of hypocretin-1 in the wake-consolidated squirrel monkey. Am J Physiol Regul Integr Comp Physiol. 293(4): R1736-42.

[66] Y. Serin, N. Acar Tek. (2019). Effect of Circadian Rhythm on Metabolic Processes and the Regulation of Energy Balance. Ann Nutr Metab. 74(4): 322-330.

[67] M.R. Nazem, E. Bastanhagh, A. Emami, M. Hedayati, S. Samimi, M. Karami. (2021). The

relationship between thyroid function tests and sleep quality: cross-sectional study. Sleep Sci. 14(3): 196-200.

[68] D.P. Carvalho, C. Dupuy. (2017). Thyroid hormone biosynthesis and release. Mol Cell Endocrinol. 458: 6-15.

[69] J. Zhang, R. Han, L. Shen, J. Xie, Y. Xiao, L. Jiang, W. Zhou, H. Li, Z. Liu, Y. Zhou, S. Wang, L. Ye, W. Wang. (2020). Mild TPO deficiency characterized by progressive goiter and normal serum TSH level. Endocrine. 68(3): 599-606.

[70] Y. Li, W. Zhang, M. Liu, Q. Zhang, Z. Lin, M. Jia, D. Liu, L. Lin. (2021). Imbalance of Autophagy and Apoptosis Induced by Oxidative Stress May Be Involved in Thyroid Damage Caused by Sleep Deprivation in Rats. Oxid Med Cell Longev. 2021: 5645090.

[71] N.C. Rodrigues, N.S. da Cruz, C. de Paula Nascimento, R.R. da Conceição, A.C. da Silva, E.L. Olivares, M.P. Marassi. (2015). Sleep deprivation alters thyroid hormone economy in rats. Exp Physiol. 100(2): 193-202.

[72] F. Atrooz, S. Salim. (2020). Sleep deprivation, oxidative stress and inflammation. Adv Protein Chem Struct Biol. 119: 309-336.