ZINC SUPPLEMENTATION MODERATE BODY WEIGHT GAIN IN NIGHT SHIFT WORK AND INSUFFICIENT SLEEP MODELS OF CHRONIC SLEEP DEPRIVATION

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ABSTRACT

Background: About 20 to 30 percent of employed adults are Sleep deprived in modern societies, either by extending working hours into the night as in Insufficient Sleep (IS) or works all through the night as in Night Shift Work (NSW). On the other hand, the increasing prevalence of overweight and obesity in these modern societies has been described as a global pandemic.

Aim: We therefore set up IS and NSW models of chronic sleep deprivation (SD) to study their effects on body weight and the role of concomitant Zinc supplementation on the SD induced body weight changes.

Methods: Forty adult male Wistar rats equally grouped into five; Control, NSW, NSWZ, IS and ISZ models. Each rat was given either 1 ml of distilled water (Control, NSW and IS models) or 5mg of Zinc sulfates (NSWZ and ISZ models) orally daily for 56 days of the study respectively. The NSW and NSWZ models were subjected to 12 hours of SD (07:00am – 07:00pm) while ISS and ISSZ models subjected to 18 hours of SD (07:00pm – 01:00pm next day) using improvised Modified Multiple Platform Method (MMPM). Bi-weekly body weight changes and serum Corticosterone were evaluated. Differences between models were examined with One-way ANOVA and Bonferonni's post-hoc test. Statistical significance considered at $p< 0.05$.

Results: The NSW model recorded the highest percentage total body weight gain, while IS model recorded the highest serum corticosterone concentration. The SD models, most especially NSW incurred significant weight gain which may result to overweight and obesity, while Zinc supplementations significantly moderate the body weight changes.

Conclusion: The NSW and IS models of chronic SD induced increased body weight gain which was attributed to Hypothalamo-Pituitary-Adrenal axis activation, evidence by increase in serum corticosterone concentration. Concomitant Zinc supplementation significantly moderates chronic SD induced body weight gain.

Keywords: Night Shift Work**;** Insufficient Sleep**;** Sleep Deprivation; Percentage of Body Weight Gain; Corticosterone;

INTRODUCTION

Sleep is a universal dynamic brain process that is associated with important restorative functions for every organ in the body (Liu *et al.,* 2017). For optimal health, the American Academy of Sleep Medicine and the Sleep Research Society have recommended a regular seven or more hours of night sleep for adults aged 18 to 60 years (Watson *et al*., 2015).

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But due to modernization and industrialization in global 24/7 society, about 20 percent of employed adults are sleep deprived, either by extending working hours into the night as in Insufficient Sleep (IS) or works all through the night as in Night Shift Work (NSW) (CDC, 2014; Rodrigues *et al.*, 2015). On the other hand there was increasing rates of overweight and obesity in these industrialized countries which was extrapolated that, by 2030, 38 % of the world's adult population will be overweight and 20 % will be obese (Kelly *et al*., 2008). In the last decade, it was reported that overweight and obesity affects over one-third of the world's population (Ng *et al*., 2014). It was also if the trends continue, We therefore set up NSW and IS models of SD to determine their effects on body weights and determine the role of concomitant Zinc supplementation on the SD induced body weight changes.

MATERIALS AND METHODS

Fifteen plastic cages measuring (55×35×35 cm) with MMPM structure installed in ten of them, digital weighing balance (American weigh triple beam scale, model: TB-2610, with readable load of 610 g and sensitivity of 0.1g), commercially available dispersible Zinc sulphate tablet 20mg (Emzor Pharmaceuticals, Nigeria). The Zinc sulfate was reconstituted in deionized distilled water to form $ZnSO_4$ 5mg/1mL suspension.

Animals

Forty male Wistar rats (aged 10- 12 weeks, weighing 190-210 g) obtained from the animal house of Department of Human Physiology, Bayero University Kano. The rats were housed in plastic cages, with adequate ventilation and natural light/dark cycle maintained, food and water was *ad libitum*. Animal's care was in accordance with the National and International Regulations on Use of Animals for Research and Teaching (2017). Animal Research Committee, Ahmadu Bello University Zaria, granted ethical clearance (ABUCAUC/2020/65).

Animal Grouping

The forty male Wistar rats were randomly divided into five groups of eight animals each.

Control model: No SD + 1ml/animal/day of distilled water

NSW model: 12 hours of SD + 1ml/animal/day of distilled water

NSWZ model: 12 hours of SD + Zinc sulfates 5mg/animal/day (Dissanayake *et al*., 2009)

IS model: 18 hours SD + 1ml/animal/day of distilled water

ISZ model: 18 hours SD + Zinc sulfates 5mg/animal/day (Dissanayake *et al*., 2009)

Experimental Design

The research was a longitudinal interventional study designed to simulate the two most common modes of SD (NSW and IS models) in global 24/7 society. Each rat was given either distilled water (Control, NSW and IS models) or $ZnSO_4$ (NSWZ and ISZ models) by gavage between 07:00 - 08:00am daily for the 56 days of the study. NSW and NSWZ models were subjected to 12hrs SD (07:00am – 07:00pm) and returned to their home cages (07:00pm-07:00am) for 12hrs of sleep/rest window every day. The 12 hours of SD (07:00am – 07:00pm) which is the biological night of the rats, simulates our night shift work. IS and ISZ were subjected to 18 hours SD (07:00pm – 01:00pm next day), which is the whole of the rats biological day time (07:00pm – 07:00am) and first half their biological night time (07:00am – 01:00pm), then returned to their home cages for 6hrs (01:00pm-07:00pm same day) sleep/rest window every day. The IS model simulates those who works throughout the day time and forced themselves to stay awake for the first half of the night, due to their contemporary lifestyle, work-related pressures and the growth of round-the-clock entertainment televisions and Internet services. Food and water was *ad libitum* during the sleep deprivation periods.

Sleep Deprivation Induction

Sleep deprivation was induced using our customized modified multiple platform method (MMPM).

It consist of a plastic tank (55×35×35 cm) containing 10 round platforms (made from metallic pipe with plastic cap welded to iron base) of 7cm height, 5cm diameter, and placed 7cm apart, improvised from Zager *et al.,* (2009) and Choi *et al.*,(2016) descriptions (plate 1). The tank was filled with water to about 1 cm below the platform surface. The rats can move around by leaping from one platform to another. Whenever the rat sleeps, it falls into the water and then wakes up. The water in the tank was changed daily throughout the period of the experiment. The Control rats were placed in similar plastic tank, but filled with saw dust instead of water.

Plate 1: Customized Modified Multiple Platform Methods

Live Body Weights and Percentage Body Weight Changes

Live weights of the rats were measured at week 0, 2, 4, 6 and 8 before sacrifice. Percentage body weight changes were determined by (initial weight minus current weight) / (initial weight) x 100.

Animals Sacrifice and Samples Collection

Each rat was anaesthetized with Diazepam and Ketamine at a dose of 2 and 20 mg/kg body weight. Blood samples were collected through cardiac puncture using 10ml syringe. The collected blood samples transferred into plain bottles, allowed to clot at room temperature, and then centrifuged at 3000rpm for 5 minutes as described by Sadri and Ahmadi (2013). The serum was used for hormonal assays.

Serum Corticosterone Assay

Serum Corticosterone concentration was determined using ELISA kit (Sunlong Biotech Co.,Ltd: tel: 0086-571-56623320: China.) according to manufacturer's instructions.

Data Analysis

The collected data was analyzed using the Statistical Package for Social Sciences (SPSS for Windows, Version 23, SPSS Inc., Chicago, IL, USA). All values are presented as mean ± standard error mean (SEM). One-way ANOVA analysis and Bonferonni's post hoc test were performed to determine the differences among the models. The significance level was set at $p< 0.05$.

RESULTS

Body Weights and Percentage Body Weight Changes

The initial body weights and bi-weekly percentage body weight changes of the different models within the period of the study are shown in Table 1. The mean Initial Body Weights (g) of the animals in all the groups were not significantly different ($F = 0.579$, $p = 0.680$). The ISS model recorded significant ($p\leq0.05$) percentage body weight lost (-0.99±0.67) in week-2 of the study in comparison to both Control (3.62±0.37) and NSW (4.54±1.12) models. Interestingly, at week-4 ISS model recorded significantly the highest percentage body weight gain (6.75±0.74) compared to both Control (1.23±0.32) and NSW (2.29±0.82) models. At week-6, the NSW model recorded significantly higher percentage body weight gain (14.26±1.23), compared to the Control (10.56±0.23) model.

At week-8 the percentage body weight changes among the models does not differ significantly (f = 0.600, p>0.05). However, the total percentage body weight change over the eight week period of the study differ significantly among the models (f = 12.414, p<0.05). The percentage Body Weight Gain (BWG) in NSW (53.57±1.75) model was significantly (p≤0.05) the highest compared to both Controls (44.26±0.50) and ISS (47.19±0.30) models respectively.

The total percentage BWG in NSWZ (47.42±0.26) model of was significantly (p≤0.05) lower compared to that of NSW model (53.57±1.75).

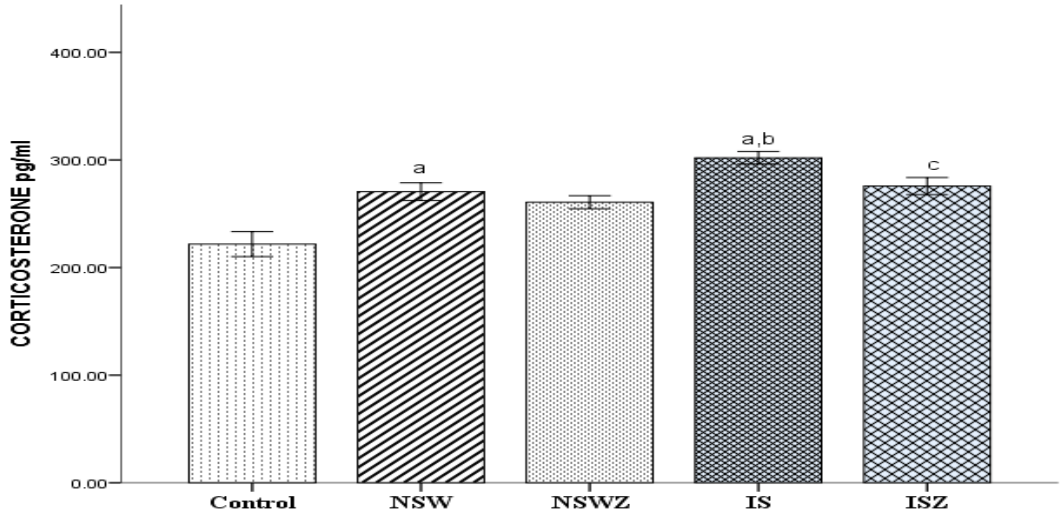
Serum Corticosterone

The serum Corticosterone of ISS (302.04±2.93) and NSW (270.49±4.13) models were significantly higher than that of control model (221.80±5.80) Figure 1. The increase in serum corticosterone was significantly (p<0.05) higher in ISS model compared to NSW model. However, the serum corticosterone in ISSZ model (275.79±3.96) decreases significantly (p<0.05) compared to that of ISS model (302.04±2.93). (F = 50.406, p<0.05).

Table 1: Comparison of Initial Body Weight (IBW), Biweekly Percentage Body Weight changes and Total percentage Body Weight Gain (TBWG) among the Sleep Deprivation models.

Body Weights	Control	NSW	NSWZ	ISS	ISSZ
IBW(g)	205.25±3.16	199.25±4.45	200.38±4.00	203.25±3.14	198.63±3.54
Week-2	3.62±0.37	4.54±1.12	2.12±0.12	-0.99±0.67[a,b]	-2.76±0.76
Week-4	1.23±0.32	2.29±0.82	3.31±0.15	6.75±0.74[a,b]	7.55±0.77
Week-6	10.56±0.23	14.26±1.23[a]	12.22±0.55	12.25±0.55	12.11±0.50
Week-8	24.41±0.39	25.82±1.64	24.54±0.60	24.11±0.43	24.99±0.54
TBWG	44.26±0.50	53.57±1.75[a]	47.42±0.26[b]	47.19±0.30[b]	46.46±0.27

Legend: Mean ±S.E.M, n=8, p < 0.05, a = significant compared to control, b = significant compared to NSW c = significant compared to ISS model, NSW=Night Shift Work, NSWZ= NSW with Zinc Supplementation, IS= Insufficient Sleep, ISZ= IS with Zinc Supplementation



Mean±S.E.M, n=8, p>0.05, a = significant compared to control, b = significant compared to NSW c = significant compared to ISS Group (F = 50.406, p<0.05) NSW=Night Shift Work, NSWZ= NSW with Zinc Supplementation, IS= Insufficient Sleep, ISZ= IS with Zinc Supplementation

Figure 1: Comparison of Serum Corticosterone concentration among SD models.

DISCUSSION

Sleep is very important for most of the biological processes in the body, so invariably, sleep deprivation (SD) can adversely affects health (Medic *et al.,* 2017). The body weights of the rats were statistically the same at the beginning of the experiment. This shows that the rats were well controlled for body weight before the experiment. Subsequently, significant body weight loss was recorded in IS model compared to the Control at the end of the first two weeks of the study. This initial body weight loss recorded is in keeping with the findings of some previous SD studies of acute nature (Vishwanath *et al.*, 2020; Rizk *et al.*, 2020). The first two weeks period was perhaps too short and too stressful for the animals to adjust and adapt to the stress of SD, thus resulted in weight loss. However, at week-4 and week-6 of our study, the SD models significantly incurred more body weight gain compared to both the control and the zinc supplemented SD models. NSW model recorded significantly the highest percentage total body weight gain, at week-8 of our study. Our finding is in keeping some previous chronic SD studies (Spaeth *et al.,* 2015; Medic *et al.,* 2017). From our findings and in comparison to previous studies, it can be deduced that acute SD induce weight loss while, chronic SD induce weight gain. Chronic SD is believed to induced body weight gain due to its influence on two important hormones, leptin and ghrelin, that regulate metabolism and energy expenditure (Spaeth *et al.,* 2015). Leptin is a key adipokine released from adipose tissue and acts on receptors in the hypothalamus of the brain, where it inhibits appetite and promotes satiety thus limiting food intake (Pigeyre, *et al.,* 2016). Ghrelin on the other hand, is released from the stomach and pancreas, and stimulates appetite (Spiegel *et al,,* 2004). Chronic SD has been associated with increase level of ghrelin and decrease level of leptin, which lead to increased appetite and urge to fat dense foods and carbohydrate resulting in increase body weight gain (Cooper *et al.,* 2018). In addition, behavioral mechanisms also have role to play, such as reduced physical activity secondary to increased fatigue, irregular and increased feeding due to more time spent awake, were possible links between chronic SD and increase body weight gain. These behavioral mechanisms were well reported in both rodents and humans. (Hart *et al.,* 2013; Spaeth *et al.,* 2015; Ho *et al.,* 2017).

Surprisingly, considering the duration of SD in ISS model compared NSW model, the body weight gain incurred in ISS model was significantly lower than that of NSW model. This finding does not follow the popular trend in literature that SD duration is directly proportional to weight gain (Tahere *et al.,* 2004; Patel *et al.,* 2008). Our finding may be explained by the facts that, although the NSW model have 12 hours window during their biological day time (the night time) for sleep and rest, but they hardly sleep enough to compensate for the sleep lost. Hence, the wakefulness becomes further extended into their biological night, with resultant increase in extra irregular feedings and subsequent weight gain. Patel *et al*., (2008) and Beccuti and Pannain, (2011) pointed a positive relationship between SD and obesity primarily in young adult and middle-aged population.

Interestingly, Zinc supplementation in SD models resulted in significant reduction in percentage total body weight gain. Our finding is in agreement with Payahoo *et al.,* (2013) and Khorsandi *et al.,* (2019). The protection against body weight gain with Zinc supplementation may be due to its appetite and eating behaviour modulatory role reported by Su and Birmingham, (2002). It was also reported that Zinc decrease food intake, by increasing leptin synthesis and sensitivity (Huang, *et al.,* 2004; Song, *et al.,* 2009).

Sleep deprivation is a known physiological stressor that results in an increase in plasma glucocorticoids (mainly corticosterone in rodents) (Machado *et al.,* 2010; Herman, 2016). In our study, both NSW and ISS models recorded significantly higher serum Corticosterone level compared to that of the control model.

This is suggestive of induction of stress response as a possible mechanism through which SD affects body weight. Our finding parallels previous studies that reported increase in Cortisol, Corticosterone or both in sleep deprived subjects (Olayaki *et al.*, 2015; Choi *et al.*, 2016; Rizk *et al.*, 2020). Contrary to our findings, other studies reported no difference in either serum corticosterone or serum cortisol following periods of sleep deprivation/restriction (Zager *et al.*, 2007; Nedeltcheva *et al.*, 2009). Glucocorticoids exert a wide range of effects on metabolism, which are primarily catabolic in an effort to utilize every available energy resources against the challenge enforced by stressors. Chronic stress prolongs this adaptive shift of metabolism towards a generalized catabolic state and, thus, sustained HPA hyperactivity progressively lead to decreased lean body (muscle and bone) mass, increased visceral adiposity and insulin resistance (Kyrou *et al.*, 2006) resulting in weight gain.

Our study also revealed that Zinc supplementation significantly conserved the serum corticosterone against increase induced by SD. This finding showed the anti-stress effect of Zinc supplementation at tolerable dose of 5mg/animal/day.

Conclusion; The NSW and IS models of chronic SD induced increased body weight gain which was attributed to Hypothalamo-Pituitary-Adrenal axis activation, evidence by increase in serum corticosterone concentration. Concomitant Zinc supplementation significantly moderates chronic SD induced body weight gain.

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