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Evaluation of Metabolic and Haematological Impacts of Light-at-Night Exposure on Adult Male Wistar Rats under Sleep Restriction Condition.

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Abstract

Health implications of shift work could not be completely due to exposure to light-at-night (LAN). This study evaluated metabolic and haematological impacts of LAN exposure on adult male Wistar rats under sleep restriction condition. The animals were grouped into control (n=8) and LAN exposed (n=8) groups. The controls were sleep restricted (SR) by gentle handling. In addition to SR, the LAN exposed group were exposed to LAN during the first five hours of scotophase for six weeks. Body weight, fasting blood glucose, lipid profile, full blood counts, $CD4^+$ cells, malondialdehyde, superoxide dismutase and catalase were all assessed using their respective protocols. Statistical Package for Social Sciences (SPSS Version 20) was used to analyze and Mean±SEM was used to analyze and summarize the data. Intergroup differences were investigated using Student's t-test and $p \leq 0.05$ was considered statistically significant. The results have shown that LAN-exposed rats eat less and have gained more body weight than controls. LAN-exposed rats also had higher fasting blood glucose. On the contrary, there is no statistical difference between the two groups for markers of oxidative stress, triglyceride-glucose index, high-density lipoprotein, and atherogenic index of plasma. In conclusion, the present study has shown that LAN exposure could cause metabolic and hematological impairments in sleep-restricted, Wistar rats. Hence, it might predispose exposed subjects to obesity, diabetes mellitus and adverse cardiovascular events.

Keywords: Diabetes mellitus, Light at night, Obesity, Oxidative stress, Systemic inflammation

INTRODUCTION

During the day, light intensity from the sun reaches around 100,000 lux, whereas, during a full moon, with clear nights, the intensity is between 0.1–0.3 lux (Kyba *et al*., 2017; Grubisic *et al*., 2019). This light/dark (L:D) cycle has remained very stable over the course of evolution and humans have adapted their physiology to deal with bright light only during the day as it is the most important cue for their circadian clock synchronization with the external environment (Opperhuizen *et al*., 2017).

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In recent years, our way of life has shifted, away from 12 hours of bright day light and night darkness (12L/12D), towards a society with constant light at all times, thereby polluting our nights with artificial lighting. In addition, due to rapid urbanization, widespread availability of electricity and the advent of energy-efficient lighting with lower operating cost, pollution of our dark nights with this light has become unprecedented with an alarming expectation of duplicity within the next 30 years (Kyba *et al*., 2017).

While the invention of electricity has contributed to our progress, its excessive and inappropriate use has directly and indirectly disrupted our circadian system, affected our health and our natural environment. Although the invention of the electric lighting and light-emitting electronics, dates back to around 140 years, its harmful effects have become apparent only recently (Opperhuizen *et al*., 2017). These effects are evident even at a relatively low level (≤30 lux) illumination, which is typical of a lightened outdoor environment in an urban or peri-urban area (McLay *et al*., 2018).

Several attempts have been made to investigate functional perturbations of exposure to light-at-night (LAN) (Qian *et al*., 2015; Opperhuizen *et al*., 2017; McLay *et al*., 2018; Rumanova *et al*., 2019; Hong *et al*., 2020), however, most of the efforts have been widely centered towards shift work and other non-conventional work schedules (Qian *et al*., 2013; Touitou *et al*., 2017; Fleury *et al*., 2020; Hong *et al*., 2020). While these studies have revealed the implications of exposure to artificial light at night, they lack the strong credibility for extrapolation onto the general populace. Even though shift and night work accounts for 75% of the workforce in industrialized countries (Hong *et al*., 2020), the widespread nature of LAN exposure even in the less developed societies warrants concerted research efforts. As certain behavioral factors, such as sleep and nighttime eating, are peculiar among night-shift workers, and that these behaviors could also cause circadian rhythm disruption and adverse health conditions (Touitou *et al*., 2017), findings from shift work studies could have likely over-expressed the detrimental effects of LAN exposures. Furthermore, although the average duration of LAN exposure in humans is reportedly 5 hours (Dissi *et al*., 2019) and not constant exposure to light (Rumanova *et al*., 2020), most of these studies have chosen to ignore simulating this real-life scenario. Rather, they consistently employed an exposure protocol of 12 hours LAN exposure (Mustonen *et al*., 2002; Dauchy *et al*., 2010; Qian *et al*., 2013; Qian *et al*., 2015; Maroni *et al*., 2018; McLay *et al*., 2018; Rumanova *et al*., 2019; Hong *et al*., 2020), thus subjecting the animals to a constant lighting condition, hence, making human extrapolation highly unreliable. Consequently, this study was designed to capture these peculiarities as well as control other variables with the primary aim of assessing the effect of exposure to light at night on haematological and metabolic parameters of sleep restricted adult male Wistar rats.

MATERIALS AND METHOD

Sixteen adult male Wistar rats (8-10 weeks old) were purchased from the laboratory unit of the Department of Human Physiology, Bayero University, Kano, where the research was conducted. The rats were divided into controls (n=8) and LAN exposure group (n=8). The animals were kept in cages under laboratory room temperature of 22^{o}C – 25^{o}C. During a two weeks acclimatization period, the rats were maintained on 12 hours of light and 12 hours of dark condition and were fed only at nights. For the 6 weeks of the intervention period, feeds and tap water were made accessible throughout the dark portion of the day and equally, during the first five hours of photophase (from 6:30 am to 11:30 am), at which time, all the groups were subjected to a gentle handling sleep restriction protocol as detailed previously (Dissi *et al*., 2020a). Group 2 (LAN-exposed) animals were subjected to a 5-hour LAN exposure protocol, during the first five hours of scotophase (lights on at 6:30pm; lights off at 11:30pm), using a light rack system designed to produce ≈750 lux of white light as previously reported

(Dissi *et al*., 2020a). Ethical approval for the study was granted by Ahmadu Bello University, Zaria's animal use and care committee, with approval number ABUCAUC/2020/64.

Body weight and feeds intake determination: fasting body weights of the rats were obtained, on day zero and then subsequently after 2, 3, 4, 5 and 6 weeks respectively into the intervention, using a weighing scale with sensitivity and readable load of 0.1g and 610g, respectively. All the measurements were started at 6:00 pm and finished by 6:30 pm, just before the introduction of feeds to the rats at scotophase, on the respective occasions. Changes in body weight were assessed by subtracting present weight from previous week's body weight (i.e w_6- w_5, w_4-w_3). Assessment of the amount of feed consumed by the rats was as previously reported (Dissi *et al*., 2020b).

Sacrificing of the rats, collection of samples and samples analysis: After the 6 weeks of intervention, the rats were resumed to their previous acclimatization protocol for 23 hours and were anaesthetized with diazepam and ketamine, as a cocktail, in the 24th hour post intervention. Cardiac puncture was employed to obtain blood samples for biochemical analysis. Assessment of fasting blood glucose (FBG) was done using a digital Glucometer and strips (Accu-Check Active® Roche Diagnostics, GMBH 68298; Germany) on days 0, 14 and 56, between 5:30 pm to 6:00 pm accordingly. Assaying for lipid profiles was done as previously reported (Dissi *et al*., 2020b) and from the lipid profile parameters, triglyceride-glucose (TriG) index was computed as Ln [TG(mg/dl) × FPG (mg/dl)/2], Cardiac Risk Ratio (CRR) and Atherogenic Index of Plasma (AIP) were calculated as TC/HDL and log (TG/HDL) respectively while Atherogenic Coefficient (AC) and Castelli's Risk Index-II (CRI-II) were determined as (TC–HDL)/HDL and LDL/HDL respectively (Castelli *et al*., 1983; Ikewuchi *et al*., 2009; Du *et al*., 2014). Lipid peroxidation was estimated calorimetrically by measuring malondialdehyde (MDA) whereas catalase (CAT) activity was measured spectrophotometrically using Abebi's method and superoxide dismutase (SOD) was determined by the method described by Fridovich (Abebi, 1974; Albro *et al*., 1986; Fridovich, 1989; Das *et al*., 1990). Full blood count was done using an Automated Hematology analyzer (Mindray BC-10) while CD 4$^+$ T-cells were estimated by impedance-based flow cytometry using an automated Cyflow counter 1 (Partec, Germany, 2017). Monocyte counts were divided by high density lipoprotein and lymphocytes values to obtain monocyte-high density lipoprotein ratio (MHR) and monocyte to lymphocyte ratio (MLR) respectively, while platelets count was divided by lymphocyte counts to obtain platelets to lymphocytes ratio (PLR).

Data analysis: analysis of the obtained data was done using Statistical Package for Social Sciences ($SPSS_V$ 20). To investigate the differences between the groups, student t-test was employed with p-value of ≤ 0.05 considered to be of statistical significance. Mean±SEM was used to summarize the results.

RESULTS

Feeds Consumption and Body Weight Changes

The results indicated that even though the total feeds consumed by the LAN-exposed rats was not significantly higher, their overall weight gain was statistically higher than that of the controls (Figure 1). Importantly, LAN-exposed rats were noted to begin gaining significant weight only after the fifth week and appears sustained, whereas the amount of feeds consumed by the LAN-exposed rats became significantly lower than that of the controls only at the third intervention week (Figure 2).

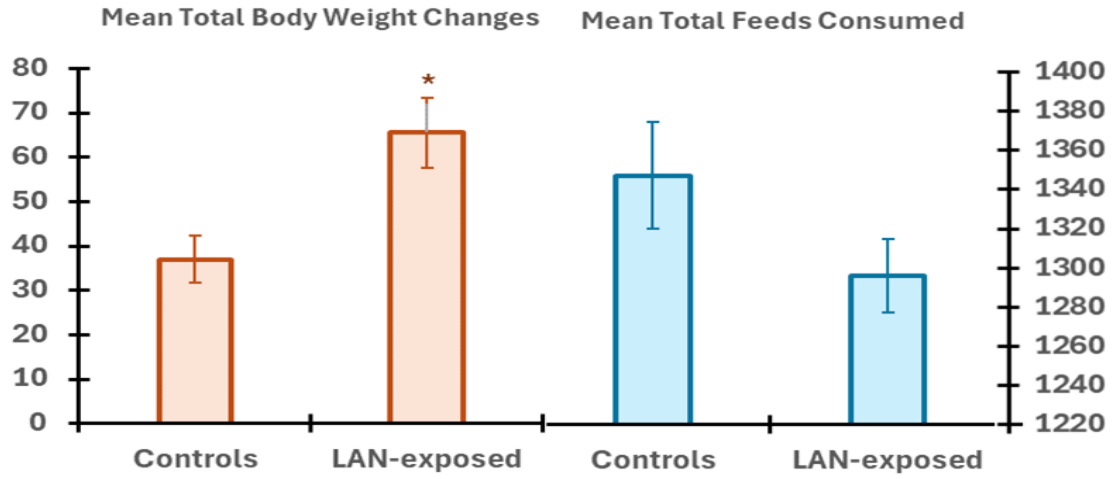

Figure 1: Total amount of feeds consumed and total body weight gained by the research animals

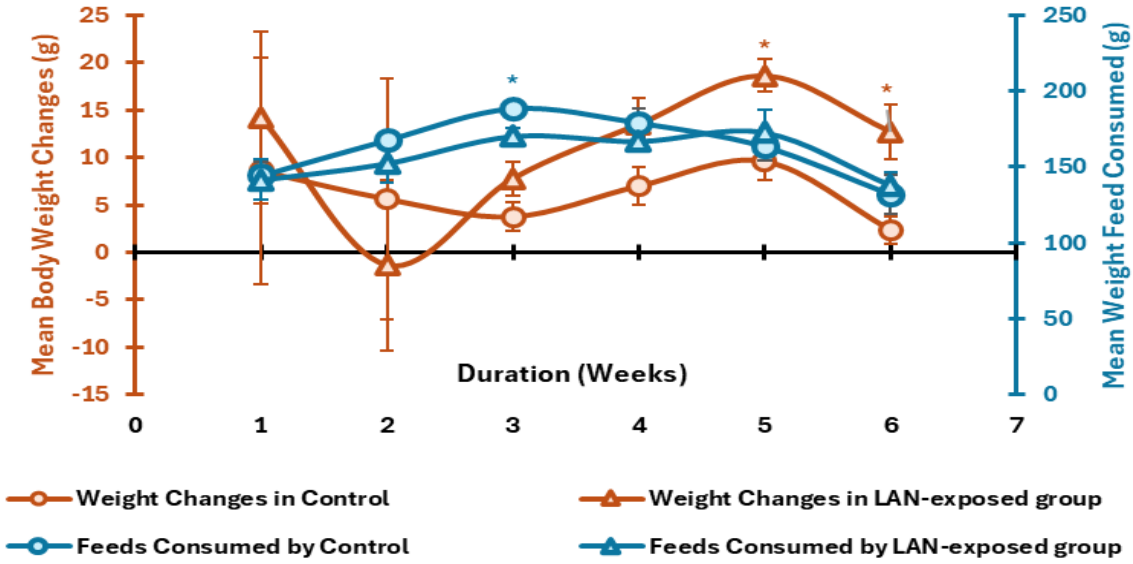

Figure 2: Feeds consumed and body weight gained by the groups over the intervention period

Fasting Blood Glucose and Lipid Profiles

The result showed that rats exposed to LAN exhibited higher final levels of fasting blood glucose as well as blood glucose changes (Table 1). In contrast, there is no statistical difference between the groups with respect to TriG index (Table 1), HDL and AIP (Table 2). On the other hand, LDL, total cholesterol and other lipid ratios, although not statistically significant, but appears higher among the group exposed to LAN (Table 2), implying that LAN-exposed rats are at increased risk of developing hyperglycaemia and cardiovascular morbidities.

Table 1: Fasting blood glucose and triglyceride-glucose index based on groups

Variables	Control	LAN-exposed group	p-value
Initial FBG	100.8±3.6	96.5±2.5	0.355
Final FBG	111.0±3.6	122.1±2.1	0.019
FBG Changes	10.2±2.2	25.6±3.3	0.011
TriG index	6.15±0.13	6.17±0.08	0.894

Values of FBG are expressed in mg/dl (Mean±SEM); FBG=fasting blood glucose; TriG index=triglyceride-glucose index

Table 2: Differences in Lipid profile and indices between LAN-exposed group and controls

Variables	Control	LAN exposed group	p-value
Trigs (mg/dl)	8.66±1.10	7.96±0.64	0.593
VLDL Chol. (mg/dl)	1.73±0.22	1.59±0.13	0.593
LDL Chol. (mg/dl)	16.94±1.99	20.13±2.21	0.301
HDL Chol. (mg/dl)	2.17±0.15	2.25±0.31	0.821
Total Chol. (mg/dl)	20.84±2.10	23.97±2.32	0.334
Total Lipids (mg/dl)	50.34±4.34	55.91±5.13	0.421
Cardiac risk ratio	9.57±0.69	15.75±5.95	0.320
Castelli risk index	7.75±0.69	13.65±5.51	0.306
Atherogenic coefficient	8.57±0.69	14.75±5.95	0.320
Atherogenic index of plasma	0.58±0.07	0.60±0.11	0.893

Values are presented as mean±SEM; VLDL=very low density lipoproteins; LDL=low density lipoproteins; HDL=high density lipoproteins; Chol.=cholesterol

Biomarkers of Oxidative Stress, Systemic Inflammation and haematological parameters

When markers of oxidative stress were compared no statistical difference was noted between LAN exposed group and controls (Table 3). On another hand, markers of systemic inflammation; MLR, PLR and MHR, were slightly higher among the LAN-exposed group (Table 3), even though, immuno-inflammatory cell counts remained statistically similar across the groups (Table 4). Noticeably, erythrocytic and thrombocytic cell counts are insignificantly higher among LAN-exposed rats than in controls (Table 5).

Table 3: Oxidative stress biomarkers and parameters of systemic inflammation

Variables	Controls	LAN-exposed group	p-value
Malondialdehyde (µmol/L)	5.47±0.60	4.71±1.59	0.665
Catalase (U/L)	0.042±0.008	0.028±0.003	0.144
Superoxide dismutase (%)	98.05±0.25	95.82±1.56	0.180
Monocyte: HDL ratio	0.455±0.077	0.804±0.339	0.333
Monocyte: Lymphocytes ratio	0.113±0.014	0.142±0.010	0.107
Platelet: Lymphocyte ratio	57.81±7.34	66.37±7.89	0.441

All values are summarized as Mean±SEM; HDL=high density lipoproteins

Table 4: Leucocytic parameters of the LAN-exposed and control rats

Variables	Controls	LAN-exposed group	p-value
White blood cells (x10^3/µL)	10.60±1.47	10.39±0.68	0.898
Lymphocytes (x10^3/µL)	8.31±1.24	8.29±0.60	0.986
Lymphocytes (%)	78.84±2.47	79.61±0.67	0.766
Monocytes (x10^3/µL)	0.94±0.13	1.15±0.07	0.181
Monocytes (%)	8.71±0.59	11.31±0.73	0.015
Granulocytes (x10^3/µL)	1.35±0.22	0.95±0.07	0.107
Granulocytes (%)	12.45±1.99	9.08±0.41	0.118
$CD4^+$ T-cells (cells/µL)	14.5±4.7	11.4±4.4	0.632

All values are summarized as Mean±SEM

Table 5: Red blood cells and platelets parameters of the LAN-exposed rats and controls

Variables	Controls	LAN-exposed group	p-value
Red blood cells (x10^6/µL)	6.06±0.76	7.16±0.16	0.178
Haemoglobin ((g/dL)	11.98±1.50	14.25±0.15	0.154
Haematocrit (%)	30.84±3.74	36.66±0.55	0.146
Mean corpuscular volume (µm^3)	51.26±0.86	51.26±0.71	1.000
Mean corpuscular haemoglobin (pg)	19.60±0.32	19.93±0.29	0.463
MCHC (g/dL)	38.30±0.70	38.89±0.29	0.450
RDWC (%)	17.00±0.27	17.46±0.14	0.147
RDWS (µm^3)	30.11±0.59	30.38±0.75	0.787
Platelets (x10^3/µL)	464.3±63.1	519±27.3	0.437
Mean platelet volume (µm^3)	7.40±0.11	7.60±0.16	0.317
Plateletcrit (%)	34.70±4.79	39.24±2.30	0.407
Platelet distribution width (%)	16.86±1.16	17.33±0.82	0.749
Platelet large cell ratio (%)	9.76±0.67	12.11±1.47	0.168

All values are summarized as Mean±SEM: MCHC= mean corpuscular hemoglobin concentration; RDWS= red cell distribution width standard deviation; RDWC= red cell distribution width coefficient of variation

DISCUSSION

The present study had demonstrated a sustained weekly increase in body weight gain among the LAN-exposed models, even though statistical significance was noted to appear only in the fifth week of the study. The study also showed the overall body weight increase being significantly higher among LAN-exposed rats, demonstrating the effect of LAN exposure on body weight to likely be, time-dependent. This assumption is reinforced by that of Cho *et al*. (2015), who highlighted that health risks associated with light at night exposure are not necessarily limited to its brightness but also its duration of exposure (Cho *et al*., 2015). The findings of significantly higher body weight gain among the LAN-exposed rats in the present study goes in line with the observations that exposure to LAN profoundly disrupts molecular circadian rhythms (Fonken *et al*., 2013; Qian *et al*., 2015) such that plasma melatonin level attenuates throughout the 24-h period and is restored to nocturnal levels upon melatonin administration (Dauchy *et al*., 2010; Hong *et al*., 2020). This change in pineal melatonin levels, induced by LAN, is said to affect metabolic rate and decrease nocturnal as well as total energy expenditure (Coomans *et al*., 2013; McFadden *et al*., 2014). In addition, LAN exposure has been associated with a loss of daily variability in animal feeding activities (Rumanova *et al*., 2020) such that energy intake during the light phase is higher than in the dark phase (Fonken *et al*., 2010; Coomans *et al*., 2013; Hong *et al*., 2020). Similarly, as melatonin increases the release of acetylcholine from the nucleus accumbens with a consequent increase in locomotor activity (Paredes *et al*., 1999), its consistent suppression by LAN could decrease locomotor activity (Mustonen *et al*., 2002; Dauchy *et al*., 2010; Xu *et al*., 2017; Hong *et al*., 2020; Rumanova *et al*., 2020), and hence decrease in activity-related energy expenditure.

The combined effects of reduced metabolic rate and locomotor activity as well as eating during the resting phase induced by LAN (Fonken *et al*., 2010; Coomans *et al*., 2013; Hong *et al*., 2020; Rumanova *et al*., 2020), may provide a conducive platform for weight gain over some time. This may, perhaps, be the reason for the present study's observed body weight increase becoming statistically significant only after the firth week of exposure to LAN. Although after the end of the intervention, LAN-exposed rats were found to be significantly heavier than controls, overall feed consumption was observed to be lower in the LAN-exposed rats ($p>0.05$). Interestingly, the observed pattern of weekly lower feed consumption in the LAN-exposed group was reversed at weeks 5 and 6. Even though all the changes were not statistically significant, it is, however, a pointer toward the tendency of LAN exposure to increase energy intake, over time, which will maximize the metabolic impacts of the reduced metabolic rate and locomotor activity reported following LAN exposure. While this study restricted LAN exposure to 6 weeks, a ~~much~~ longer (10 weeks) LAN exposure protocol by Hong and colleagues (2020) revealed a gut microbiota dysbiosis, increased digestion and absorption of lipids in the intestine as well as increased total feed intake (Hong *et al*., 2020). This observation further strengthens this study's proposal that LAN exposure could increase body weight and feed consumption in a duration-dependent manner.

The utility of TriG index as a marker for insulin resistance has gained wide popularity due to its putative nature of discriminating insulin resistance even among normoglycemic subjects (Du *et al*., 2014). Although exposure to LAN has been found to impair glucose tolerance and insulin sensitivity (Mustonen *et al*., 2002; Coomans *et al*., 2013; Rumanova *et al*., 2019; Hong *et al*., 2020), the present study findings of similar TriG index among the groups is indicative that the impairment is unlikely to be insulin-sensitivity mediated. However, it is pertinent to note

that LAN-exposure-related impairment in glucose tolerance has been ameliorated by concomitant melatonin supplementation (Xu *et al*., 2017; Hong *et al*., 2020), thus reiterating the mechanistic relationship between melatonin disruptive tendencies of LAN and glucose metabolism. The demonstration in the present study of LAN-exposed rats having significantly higher fasting blood glucose than controls, therefore, agrees with this notion. Light-at-night exposure has been reported to decrease serum insulin concentration via impaired pancreatic β-cell function and accelerated apoptosis (Qian *et al*., 2013; Qian *et al*., 2015; Rumanova *et al*., 2019; Hong *et al*., 2020). In addition, LAN-exposed animals are noted to take much of their daily energy intake in the light phase (Fonken *et al*., 2010; Coomans *et al*., 2013; Hong *et al*., 2020) during which insulin sensitivity and glucose tolerance are lower (Rumanova *et al*., 2020). Consequently, these alterations may advance the development of a hyperglycaemic state among the LAN-exposed rats.

Disrupted lipids and lipid indices have long been well-associated with adverse metabolic and cardiovascular events (Castelli *et al*., 1983). In addition, dyslipidaemia, subclinical atherosclerosis and central obesity have been linked to LAN exposure (Fleury *et al*., 2020) suggesting that LAN might be a risk factor for cardiometabolic disorders. This is likely due to the ability of LAN to induce increased expression of fatty acid synthesis gene, lipogenesis and fatty acid transport proteins production in the liver, increased digestion and absorption of lipids in the intestine as well as a decrease in fecal cholesterol excretion (Hong *et al*., 2020). Similarly, its ability to reduce β3-adrenergic intracellular signaling in brown adipose tissue may pave the way for a mediatory role in the development of adverse adiposity indices and dyslipidaemia (Kooijman *et al*., 2015). The present study findings of increased LDL, total cholesterol, total lipids and all the lipid ratios, although mild, are corroborative of these hypotheses and imply that LAN exposure can be an important risk factor for adverse cardiovascular events. Recent studies have observed LAN exposure to induce a hyperthyroid-related state (Maroni *et al*., 2018; Kupprat *et al*., 2021) which may affect lipid metabolism thereby masking the dyslipidaemic effects of LAN exposure. In addition, animals that are exclusively fed in the dark have been found to exhibit increased nocturnal activity (De Goede *et al*., 2018), significantly higher nocturnal and total daily core body temperature (Dissi *et al*., 2020a) as well as lower cholesterol, HDL, triglyceride and other unhealthy lipids (Sherman *et al*., 2012). Therefore, the possibility that controlling feeding time in this study could have attenuated dyslipidemia in the LAN-exposed rats could not be excluded, hence, the plausibility of a causal relationship between LAN exposure and dyslipidemia should not be discarded.

The connection between exposure to LAN, circadian rhythm disruption, metabolic disorders and oxidative stress are overlapping and the molecular mechanisms linking them are complex and still being investigated. Interestingly, circadian rhythm disruption has been noted to decrease the expression of nuclear factor erythroid-2-related factor-2 (Nrf2) ultimately resulting in increased reactive oxygen species accumulation (Lee *et al*., 2013) and oxidative stress. However, the present study findings of significant weight gain, hyperglycaemia and low-grade systemic inflammation among the LAN-exposed rats are not corroborated with a significant difference in oxidative stress biomarkers, as would be expected. This may perhaps be due to the ability of LAN to lower energy expenditure via reduced metabolic rate and locomotor activities thus resulting in reduced production of oxidants (Coomans *et al*., 2013; Raap *et al*., 2016; Rumanova *et al*., 2020) as can be observed from the relatively lower MDA levels among this study's LAN exposed rats. In addition, since the present study's experimental animals are young (10 weeks old), were exposed to LAN for only six hours, and because LAN exposure induces oxidative stress in a tissue, age, duration and intensity-specific manner (Cho *et al*., 2015; McLay *et al*., 2018; Verma *et al*., 2020), the LAN exposure protocol

used in this study could have caused significant oxidative stress if it were assessed in another tissue other than blood or if the animals were exposed to a constant light protocol or were older; since duration, timing and intensity of LAN exposure can determine its health effects (Cho *et al*., 2015) and because aged rats are more susceptible to LAN induced redox imbalance (Verma *et al*., 2020).

Melatonin is reported to have immune-modulatory and anti-inflammatory potentials (Xu *et al*., 2017; Hajam and Rai, 2020), therefore, its suppression by LAN could induce systemic inflammation via increased body temperature, excessive reaction of inflammatory cells and increased expression of pro-inflammatory cytokines (Fonken *et al*., 2013; Kang *et al*., 2016; Yang *et al*., 2020). Although the raised levels of systemic inflammatory markers (MLR, PLR, MHR and PLCR) observed among this study's LAN-exposed rats were not statistically significant, the percentage of monocytes was significantly higher, signifying a raised inflammatory status. On another hand, total white blood cells, $CD4^+$ T-lymphocytes, absolute and percentage granulocytes appeared mildly reduced among the LAN-exposed rats indicating a trend towards impaired immunity. It was noted that LAN-exposed rats exhibit a significant increase in nocturnal and total 24-hour body temperature (Fonken *et al*., 2013; Kang *et al*., 2016; Dissi *et al*., 2020a). Since LAN-induced body temperature increment is said to be via immuno-modulation and pro-inflammatory processes (Fonken *et al*., 2013; Kang *et al*., 2016), the present finding of reduced immunological cells and raised inflammatory markers could be viewed in that regard.

While it was expected that LAN exposure would adversely impair thrombopoiesis and erythropoiesis, paradoxically, increased erythrocytes and thrombocytes were noted among the LAN-exposed rats. This could be a response to the increased inflammatory state observed among the LAN-exposed rats of this study. By stimulating erythrocytes and thrombocyte formation, inflammation could counter the adverse hematopoietic effects of LAN exposure anticipated. In addition, and worthy of notice, the mechanism through which light at night exposure distorts physiology is complex and with the field of chronophysiology still evolving, extensive research is still required to understand how LAN exposure may affect the hematopoietic system.

CONCLUSION

Overall, the present study findings have demonstrated the obesogenic, diabetic and adverse cardiovascular potentials of LAN exposure, perhaps, via reduced metabolic rate and systemic inflammation. This conclusion will prompt a fear, that, increasing trends of cardiometabolic disorders will mirror an increasing trend of pervasive global illumination, and hence could be a potential risk factor for obesity and its related morbidities in humans.

Therefore, practically speaking, combating these deleterious effects of LAN exposure can be near impossible. However, much can be achieved through behavioral changes, including; avoidance of sleeping with lights on, limiting the use of blue light to the day, use of blue-to-violet light filters and generally, minimizing exposure to light late into the night.

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