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Histomorphometric and Histological Evaluation of Renal Cortex in Response to Sleep Disturbance in Adult Male Rat

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ABSTRACT

Background: *Sleep disturbance affects kidney structure reflected in functional derangement causing renal diseases; this occurs through sympathetic system activation and inflammation. Changes in the renal vascular bed affect the renal corpuscle-related structures such as the glomerular area, and urine space, in addition to the kidney tubular apparatus. Sleep deprivation or sleep interruption differ in their effect on systolic blood pressure causing renal tissue changes that predispose to chronic kidney disease (CKD).* ***Aim of the study:*** *The study aims to evaluate the effect of sleep disturbance on histological changes of renal tissue in control and experiment groups.*

Patients and methods: *An experimental study on a sample of thirty adult male albino Rats, was divided into three groups (10 animals per group). The control group had a normal sleep rhythm which was 12 hours in the dark and 12 hours in light. Group A: at 12 hours light and 12 hours dark with the production of a flashlight at three-time intervals, every 2 hours, during their sleep period, while Group B includes rats that were exposed to a reduction in sleep time by continuous flashlight stimulation for 7 hours per day, during their sleep period. Then, the kidneys were dissected and prepared for histological evaluation and quantification. The experiment lasted for 14 days for all groups, and the study was performed during the period between the 1st of January 2023 to the 1st of August 2023 in the anatomy department in Al- Nahrain Medical College.*

Results: *This study showed the effect of sleep disturbance patterns (sleep reduction, and sleep interruption) by light stimulation in adult male rats on cortical renal tubules and cortical vessels. A prominent dilatation in cortical renal tubules with the presence of cortical hemorrhagic areas and cortical necrosis with inflammatory cell infiltration was seen to be associated with sleep deprivation prominently. Histological changes of renal corpuscular areas, glomerular tuft area, and renal space area showed significant variations in sleep disturbance groups, in a p-value ≤ 0.05.*

Conclusions: *Changes in sleep patterns indicate the importance of sleep in maintaining renal cortical tissue structural integrity by its effect on local hemodynamics of cortical vessels that ultimately affect the structure and area of the renal corpuscles. Sleep deprivation represents a powerful factor for renal cortical changes that lead to corpuscular and tubular damage.*

Keywords: Blood Pressure, Kidney, Light Stimulation, Sleep Disturbance.

Article Information

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INTRUDUCTION

Sleep is the most significant peripheral factor that sustains a circadian rhythm. Sleep issues may have a role in the renal system function and diseases (1). Since the physical function of the kidneys has a diurnal rhythm (2), the volume of the urine excreted, the renal blood flow, and the glomerular filtration rate, some chemical compounds filtration including sodium (3), calcium, potassium, and phosphorus (4), and several other metabolites, are dependent on the circadian pattern of the kidney. The typical circadian rhythm is mainly derived from a self-sufficient mechanism which is named the circadian clock system which is composed of a central part called the circadian clock positioned in the suprachiasmatic nucleus (SCN) in the anterior part of the hypothalamus, and a peripheral clock primarily located in the liver, kidneys, heart, lungs, skeletal muscles, adipose tissue, and other tissues. These components respond to and are derived from upstream signals from the circadian setup in the SCN (5). The central biological clock depends upon the light stimulus which is transformed from optical signals to electrical signals on the retina; these signals are then transmitted to the SCN via the retinal hypothalamic tract and have a role in the regulations of the expression of core clock gene in the brain, as well as having a direct effect on the expression of peripheral genes in various organs. This is all done to regulate the functions of these organs (6). Additionally, the timing mechanism of the central and peripheral nervous system can be disrupted when exposed to light at night, which impairs the transmission of internal rhythm to the external environment, and dysfunctions of normal and ideal 24-hour physiological and behavioral habits of the individuals. Though the direct impact of artificial light at night (ALAN) on the human circadian clock has not been studied directly by human researchers, the data collected from human correlative studies and various data from nocturnal and periodic studies on animals, suggest that the circadian rhythm is disordered, resulting in nocturnal and diurnal similar result found in mammals (7). Sleep disorder could activate the sympathetic nervous system (8), or activate systemic inflammation which leads to damaging glomerular endothelium and proteinuria (9), however, both sympathetic nervous system activation (10) and systemic inflammation (11) lead to the progression of chronic kidney disease. A growing number of studies have demonstrated that sleep disturbance affects the evolution of kidney disease, probably via the increased inflammation and sympathetic activity present at the renal vascular bed, these effects negatively affect the glomerular basement membrane and the tubular kidney apparatus (12,13). The renal corpuscle, is the component of the kidney that is responsible for filtration, is composed of the glomerulus and Bowman's capsule (14). A glomerulus is made by a bunch of capillaries through which blood flows to produce urine filtrate through a blood-urine barrier (15). The kidneys are vital organs that participate in the control of blood pressure, and previous research has demonstrated that the kidneys are involved in the body's periodical adjustment of blood pressure. For example, Bankir et al. (2008) (16) showed that the diurnal pattern of renal excreted sodium is crucial to the nocturnal drop in blood pressure. Studies of adults have proved a link between sleep duration and increased blood pressure (17). Other studies have demonstrated that individuals with short sleep duration have a higher probability of experiencing a decrease in eGFR as demonstrated by research on the connection between short sleep time and the rapid decrease in kidney function (18). The present study aims to evaluate the effect of sleep disturbance on histological changes of renal tissue in control and experiment groups.

PATIENTS AND METHODS

An experimental study was performed during the period between the 1st of January 2023 to the 1st of August 2023 and conducted at the Anatomy Department in Al-Nahrain Medical College

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Subjects

A sample of thirty adult male albino rats (Rattus Norvagigus) was selected and maintained at a temperature of 22 ± 2 °C. All animals in this experiment are kept and used according to the National Institute of Health (NIH) guidelines, in the Anatomy Department at Al Nahrain College of Medicine. The rats were divided into three groups of 10 animals per group.

Controls

At normal sleep rhythm which is 12 hours in the dark and 12 hours in light; Group A: at 12 hours in light and 12 hours dark with the production of a flashlight at three-time intervals of every 2 hours, during their sleep period; and Group B: rats were exposed to a reduction in sleep time by continuous flashlight stimulation for 7 hours per day, during their sleep period.

Method

Animals were euthanized in a chloroform closed chamber, and the kidneys were dissected, and fixed by formaldehyde (10%), for paraffin block preparation. Then, a thin series of sections of (5 µm) thickness were cut and placed on a regular glass slide for H&E staining according to (Suvarna et al., 2013) (19), and the slide was examined under a light microscope (LEICA DM750, Germany), for histological evaluation and quantification, the field captured by using Digital Microscope Camera, Image J analysis was done using the software Image J (Java8–based image processing program developed at the National Institutes of Health, USA) for morphometric study and measuring the areas of the renal corpuscle, which are the capsule, glomerulus, and renal space.

STATISTICAL ANALYSIS

An SPSS version 25 was used for statistical analysis by using an unpaired t-test to compare between groups, a significant P value ≤ 0.05 was selected as statistically significant.

RESULTS

The cortex is characterized by the presence of renal corpuscle and convoluted tubules; proximal convoluted tubules (PCT) are lined by simple cuboidal to low columnar epithelium with a characteristic brush border, while the distal convoluted tubule (DCT) is lined with simple cuboidal epithelium with smaller and flattened cells, that lake of brush border.

The renal corpuscle appeared as a rounded structure that is surrounded by Bowman capsules which are lined by simple squamous epithelium with the presence of a tuft of capillaries (glomerulus) in the center, and the glomerulus fills the space of renal corpuscles. Fig. 1 (a & b).

The mean total capsular area measured by image j was 5036.33; the mean glomerular area was 4343.98, and the mean renal space was 692.35. Tab. 1

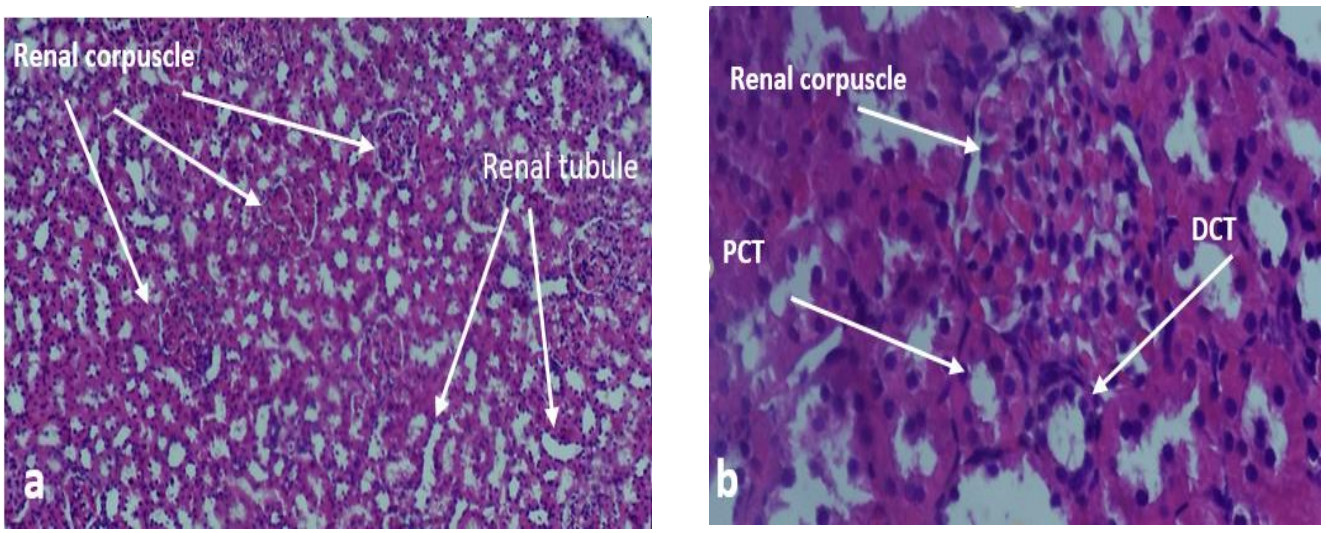


Figure 1: The cross-section in the kidney cortex of the control group shows: a) renal corpuscles and convoluted tubules (10X H&E stain), b) proximal and distal convoluted tubule and renal corpuscle (40x H&E stain).

Table 1: The difference in the capsule, space, and glomerular area between group A and the control group by unpaired t-test.

Parameter	Control group N=35 / Mean±SD	Group A N=35 / Mean±SD	P value*
Capsule	5036.33±916.47	4518.19±1152.52	0.041
Space	692.35±209.22	827.72±435.31	0.104
Glomerulus	4343.98±817.45	3690.48±1007.58	0.004

Significant P-value ≤ 0.05

Vascular structures seen in the cortex are small interlobular arteries that are distributed evenly within the cortex in between the glomeruli, the interlobular arteries give to the afferent arteriole that enters the renal corpuscle and exits as an efferent arteriole.

At the vascular pole, there is a row of closely packed nuclei that densely stained part of the distal convoluted tubule which is considered part of the juxtaglomerular (Jg) apparatus called Macula densa. Fig. 2 (a & b).

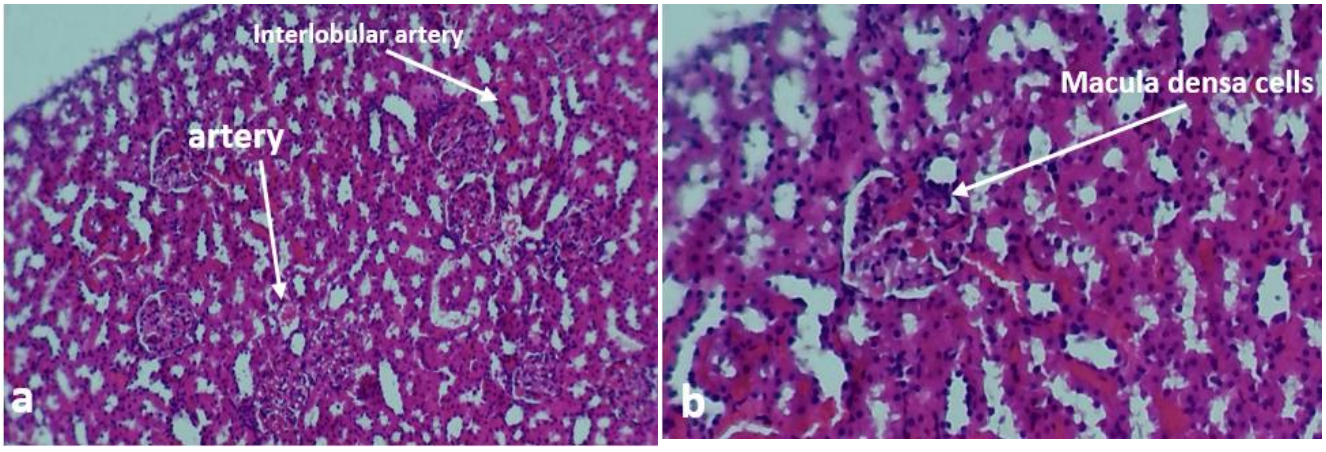


Figure 2: The cross-section in the renal cortex of the control group: a) demonstrates the distribution of cortical vasculature. / b) Macula densa at the vascular pole of the renal corpuscle (40x) H&E stain.

Renal cortex in sleep-interrupted group (A):

This group showed specific variations including widening of the renal tubules at the outer cortex and dilatation of cortical vessels with the presence of small hemorrhagic areas Fig. 3 (a & b).

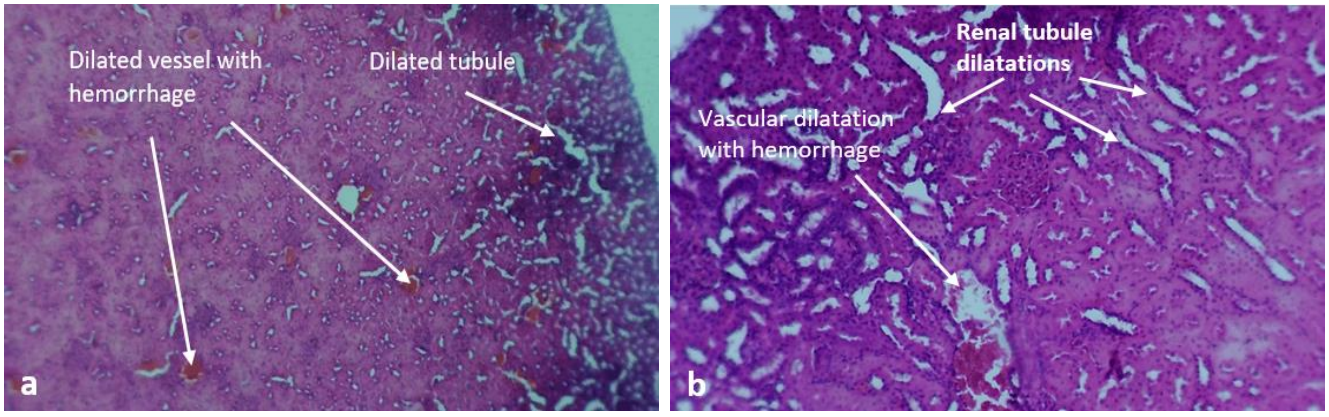


Figure 3: Cross-section in the kidney of group A: shows the dilatations of the renal tubules and vascular dilatation with hemorrhage. a: (4x), b: (10x) H&E stain.

The renal corpuscle seems to be irregular in shape and showed a significant reduction in both the capsular area and glomerular area with P-values 0.041 and 0.004 respectively, with non-significant enlargement in capsular space (Tab 1) Fig. 4

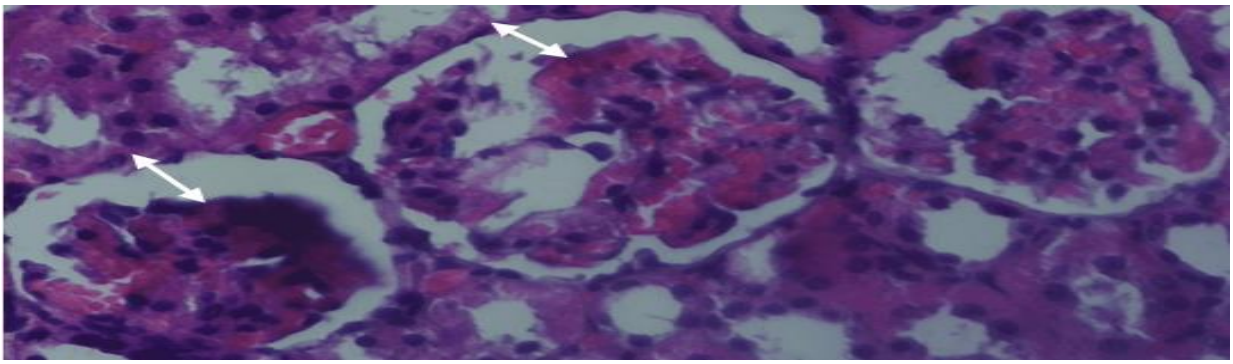


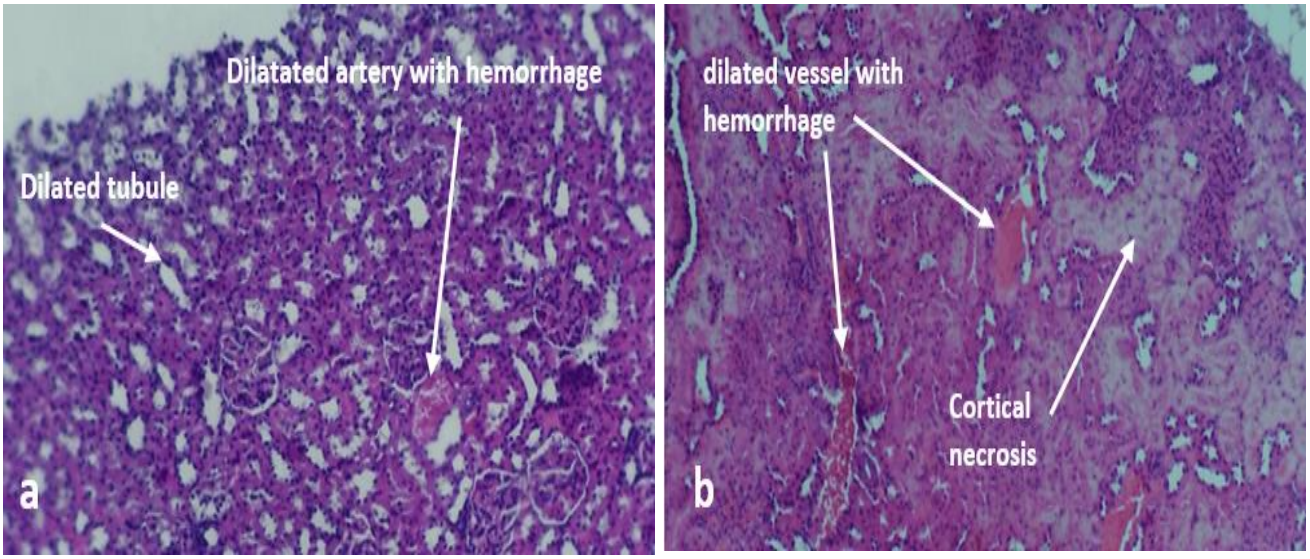
Figure 4: Cross-section in the renal cortex of group A: shows the enlargement of renal space(H&E,40x).

The comparison between the sleep-interrupted group and the control group shows significant changes in the renal capsule and glomerulus at $p \leq 0.05$, but in renal space, there is no significance difference between group A and the control group. Tab 1.

Renal cortex in sleep deprived group (B).

Changes in this group showed multiple variations including marked dilatation of renal tubules of the cortex and blood vessels and the presence of large areas of hemorrhage distributed among renal corpuscles. There is also a cortical necrosis (coagulative necrosis) with inflammatory cell infiltration in which the cell's outline and structure are somewhat preserved but the cells are in fact dead without any visibly stained nuclei and appear more acidophilic than the surrounding tissue.

There is a significant increase in the capsular area of group B compared to the control with a P-value of 0.034 and a highly significant increase in the capsular space with a P-value >0.001 and a non-significant change in the glomerular area. Fig. 5 (a, b, c, d) Tab 2.



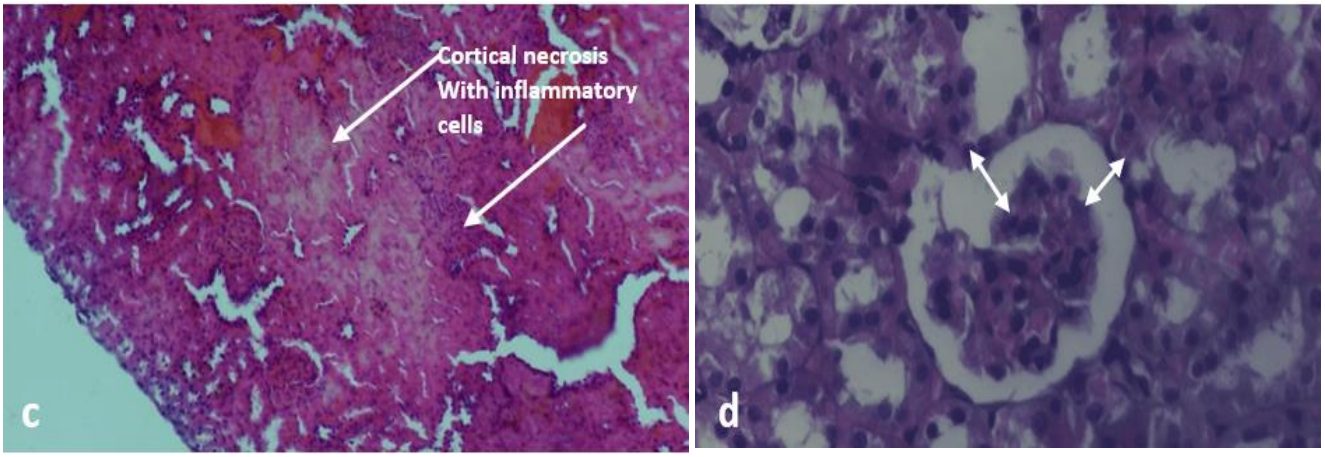


Figure 5: A cross-section of the renal cortex of group B shows: - a) dilated tubules and dilated vessels with hemorrhage. b) dilated vessel with hemorrhage and cortical necrosis (H&E stain,10x). c) ghostly appearance of renal tissue or cortical necrosis. d) enlargement of renal space (H&E,40x).

Table 2: Comparison of capsule, space, and glomerular area between group B and control group by unpaired t-test.

Parameter	Control group N=35 Mean±SD	Group B N=35 Mean±SD	P value*
Capsule	5036.33±916.47	5565.43±1121.77	0.034
Space	692.35±209.22	1081.13±409.84	<0.001
Glomerulus	4343.98±817.45	4484.3±999.82	0.523

Significant P-value ≤ 0.05

Table 3: Comparison of capsule, space, and the glomerular area between group A and group B by unpaired t-test

Parameter	Group A N=35; Mean±SD	Group B N=35; Mean±SD	P value
Capsule	4518.19±1152.52	5565.43±1121.77	<0.001
Space	827.72±435.31	1081.13±409.84	0.015
Glomerulus	3690.48±1007.58	4484.3±999.82	0.002

Significant P-value ≤ 0.05

DISCUSSION

Sleep disturbance has a pronounced effect on body health and life quality. There is a documented relationship between sleep disturbances and kidney diseases but limited knowledge of sleep disturbance and its effect on normal kidneys.

Light changes shift the endogenous oscillator in the suprachiasmatic nucleus (SCN), by the environmental day-night cycle. The setting of circadian rhythms originates in the eye and through an axonal pathway of retinal ganglion cells to the SCN (20). Animal data suggested circadian rhythm changes may induce kidney damage; however, human research on the link of sleep factors with incident kidney disease

needed to be evaluated. In animals, hereditary factors of circadian rhythms change lead to renal impairment such as an increase in serum creatinine, and fibrotic cortical changes with glomerular and tubular damage; these are preventable by strict adjustments of light-dark periodicity to maintain normal circadian rhythms (21).

The current results showed renal tubule dilatation which may be due to tubular injury mentioned previously, which Wang et al., (2011) (22) also mentioned in their study and they considered tubular dilatation, vascular changes, leukocyte infiltration, and edematous capillaries as a specific feature of renal tubular injury. Further, Jones et al., (2008) (23) showed that any elevation in serum creatinine level means a glomerular filtration rate was reduced. Sleep deprivations result in the disruption of circadian rhythm and the local circadian clock in peripheral organs such as the kidney (21).

Results of the present study in the sleep fragmentation group showed vascular dilatation in the renal cortex and discrete cortical hemorrhage while in the sleep reduction group, wider areas of vascular dilatation and hemorrhage were encountered in the cortical area. This may be related to the sleep disturbance effect on cortical blood flow which was explained by Spiegel et al., (2004)(24) who mentioned that sleep disorders and fragmentation lead to an increase in hypoxemia and sympathetic nervous system stimulation and decreased parasympathetic activity which results in a reduced fall in nocturnal blood pressure.

In this study, vascular changes in the experimental groups may related to the incident light on the retina that is connected to the SCN which leads to the activation of the sympathetic nervous system and changes in cortical vascular resistance. This was mentioned by Pepin et al . (2014)(25) who explained that the sleep disturbances were related to activations of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, as well as chronic inflammation, which may promote a non-dipping pattern, hypertension and subsequently alter renal function.

The present results showed significant histopathological changes in the capsular area, glomerular area, and renal space between experimental and control groups. This could be due to the effect of light stimulations on sympathetic activation which in turn affects cortical hemodynamics leading to changes in the histopathological parameter. This was explained by Qiu et al. (2019)(26) that hypertension alters peripheral resistance and blood flow pulsation leading to glomerular microvascular damage and alteration in glomerular filtration rate (27). Cottone et al., (2009) (28) linked changes in blood pressure during night shift work to endothelial dysfunction and symptoms of renal damage, specifically a decrease in GFR.

Blood pressure is closely linked to generalized endothelial dysfunction and subclinical atherosclerosis which may also be another pathophysiological mechanism of blood pressure-related early symptoms of renal damage (28). Therefore, blood pressure may be on the causal pathway between night shift work and decreased eGFR. Oberleithner., (2005) and Ishigaki et al., (2016) (29,30) mentioned that stress factors lead to sympathetic activation and a decrease in renal plasma flow and GFR, which affect renal function and activation of the renin-angiotensin-aldosterone system (RAAS) that lead to an increase in intraglomerular pressure and vascular endothelial cell damage.

The current results showed dilatations in cortical renal tubules specifically in the outer cortex of sleep disturbance groups and specifically in sleep reduction patterns. This may be due to changes in hemodynamics concerning circadian changes that affect GFR; this was mentioned by Martino et al. (2008) (21) as circadian disruption affects the proliferation of renal tubular epithelium and cell apoptosis. In addition, Kannan et al., (2014) and Sata et al., (2018) (31,32) mentioned that sympathetic activation leads to an increase in renin secretion and renal tubular sodium reabsorption and a decrease in renal blood flow.

The present results showed a prominent large area of cortical necrosis in the sleep reduction group (group B) which is related to sympathetic stimulation and parasympathetic suppression due to sleep reduction. This is supported by Emans et al. (2017) (33) as the oxygen content is more vulnerable to changes during the night, also Rabelink et al., (2007) (34) mentioned hypoxia induces endothelial dysfunction, leukocyte infiltrations and blocked blood flow leading to tissue loss of nephron. On

the other hand, McGettrick and O'Neill, (2020) (35) reported ischemia/hypoxia is one of the commonest causes of inflammation and inflammatory cell infiltration.
Moreover, (Sradnick et al., 2016) (36) reported selective epithelial injury in the tubular epithelial cells concerning a reduction in regional renal oxygen supply leading to inflammation, ischemia, necrosis, and reflecting the imbalance between arterial pressure and vascular resistance.
Furthermore, melatonin supplementation showed a beneficial effect in reducing blood pressure, inflammation, apoptosis, and promoting angiogenic properties, this was confirmed by (Nava et al., 2003) (37) as melatonin treatment reduces blood pressure, renal tissue inflammation, and oxidative stress.
Research has shown that melatonin regulates the biological circadian clock, and acts as an antioxidant, inhibiting sympathetic activity, and preservation of endothelial function (38-40). Its effects on the kidney have been proven by experimental data. Animal studies have demonstrated that melatonin treatment improves hypertension, and the mechanism of effect is associated with decreased renal inflammation resulting, in turn, from a reduction in local oxidative stress (37).

CONCLUSIONS

Sleep disturbance provides a stressful activation on the hypothalamic-pituitary axis, leading to local changes in peripheral organs including the kidneys mainly through an increase in blood pressure specifically by sympathetic over-activation. Kidney structural changes in response to changes in cortical hemodynamics including vasodilatation and hemorrhage were more prominent in the sleep reduction group. Glomerular structure change, including changes in capsular, glomerular, and renal space areas in response to sleep disturbance, is more pronounced in the sleep reduction group. High blood pressure due to sympathetic over activation can lead to damage of small blood vessels in the kidney over time and narrowing or blockage of these vessels can reduce blood flow to the renal cortex, leading to ischemia and then to necrosis of the affected region.

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