Sex-related Changes in Circadian Rhythm of Inflammatory and Oxidative Stress Markers in CKD

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Introduction. Circadian system is deeply involved in renal function. The circadian timing system may be disrupted in chronic kidney disease (CKD) patients. Gender differences in CKD have been reported. This research aimed to investigate the gender differences in the circadian rhythm of inflammatory and oxidant markers of CKD.

Methods. Male, intact female, and ovariectomized (OVX) female rats (twenty-four in each group) were randomly assigned to control and CKD groups. The rats were further divided into day (12:00 p.m.) and night (12:00 a.m.) subgroups. Evaluations of each sample were carried out a day after the last day of adenine administration.

Results. Final results revealed that the circadian rhythm of plasma melatonin , kidney malondialdehyde (MDA), and transforming growth factor- β (TGF-β) levels in CKD group were the same as the control group. Melatonin and total antioxidant capacity (TAC) levels significantly decreased in the CKD group compared with the control group in day and night subgroups, whereas MDA and TGF-β levels increased. Male group in comparison with the intact female group significantly showed less melatonin and TAC but higher MDA and TGF-β levels which could be due to CKD.

Conclusion. Findings of this study represent gender differences in circadian rhythm amplitude of inflammation, melatonin, and oxidative stress in CKD animals, probably in favor of female sex steroids. These findings emphasize on the importance of gender differences in CKD progression; therefore, considerable attention must be paid to gender in the treatment of CKD.

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INTRODUCTION

The circadian system causes daily fluctuation of physiological functions in the body. The central clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, generates physiological rhythms in the peripheral clocks located in each organ.[1,2] Melatonin, a hormone secreted from the pineal gland predominantly at night, plays a significant role in regulating the circadian rhythms in biology.[3] Numerous studies have attempted to explain that a robust circadian rhythm is essential for health and its disruption can accelerate disease progression.[1,4]

The circadian system plays an active role in renal function. The circadian timing system may be disrupted in CKD (chronic kidney disease) patients.[1,2] Most of the circadian clock or clock-regulated genes show rhythmicity in the conditions of the CKD

group the same as the control group. Some of them show phase changes in CKD, and the direction of the phase changes depends on the genes.[5]

Inflammatory and fibrosis (transforming growth factor- β, TGF-β) markers increase in CKD patients throughout the day and night.[5] A variety of studies show that chronic inflammation can affect the SCN and reduce the amplitude of rhythms in clock gene expression[6,7] The study also shows that intrarenal reactive oxygen species (ROS) increase in CKD.[8,9]

It is well known that endogenous melatonin levels decrease according to renal dysfunction.[10,11] Melatonin produces a variety of biological effects, including anti-inflammation, anti-oxidation, anti-adrenergic, and enhancement of nitric oxide.[12] The disruption of melatonin circadian rhythm has been shown in CKD.[13]

Sex differences in CKD patients and CKD experimental models have been reported, with fewer adverse effects in females.[14,15] CKD females have shown a smaller reduction in urine creatinine levels compared to males (71, 81% reduction; respectively).[5] Testosterone, a male sex hormone, has been suggested as a risk factor for the progression of renal disease, while estrogens decrease this progression. However, a low dose of testosterone can protect the renal injury by increasing NO and decreasing inflammation.[16] Anti-inflammatory and antioxidant effects of estrogen and progesterone have been confirmed in the previous studies.[17,18]

Gender differences in the circadian rhythm of inflammatory and oxidant markers in CKD have not yet been studied.[5] We speculate that targeting sex circadian dysfunction in the management of CKD patients could help prohibit disease progression. Chronotherapy, treatment schedule according to circadian cycle for greater efficacy, has been recently considered.[19] Therefore, the circadian rhythm of kidney inflammatory and oxidant factors associated with plasma melatonin levels, and urea and creatinine levels were investigated in adenine-induced CKD male and female rats in this study. Furthermore, ovariectomized (OVX) rats were used for investigating the probable role of female sex steroids.

MATERIALS AND METHODS

Animals and Housing Conditions

The study code was 97000756 based on Kerman university study submitted. Mature male and female Wistar rats (weighing 180 to 220g at the ages between 10 and 14 weeks) were provided from animal center of Kerman University of Medical Sciences for this experiment. All the study procedures and animal care protocols were approved by the Ethics Committee of Kerman University of Medical Sciences (EC: IR.KMU.REC.1399.093). The animals were kept in a conventional animal room at 23 ± 2 °C and 12-hour light per day (light on: 6:00 a.m.; light off: 6:00 p.m.).

Study Groups

Male, intact female, and OVX female rats (twenty-four of each) were randomly assigned to control and CKD groups (n = 12 per group). The rats were further divided into day (12:00 p.m.) and night (12:00 a.m) subgroups. Estrus cycle was synchronized among intact female rats living together to prohibit the interactions of the reproductive cycle phase on experiment results. Anesthesia of rats was performed by ketamine (60 mg/kg) and xylene (10 mg/kg) in the present study. The evaluations of each sample were repeated three times and a day after the last day of CKD induction (12:00 a.m. and 12:00 p.m) (Figure 1). For each animal the weights of kidney and body were obtained and reported as kidney weight to body weight (KW/BW) ratio (mg/g).

Method of Ovariectomy

Ovariectomy was performed bilaterally under anesthesia. Briefly, a ventral midline incision (2 cm) was induced between the umbilicus and vagina to open skin and abdominal muscle. The fallopian tubes were pulled out of the abdominal cavity and were tied by catgut thread below the ovaries and the ovaries were removed. Then the uterine tubes were returned to the abdomen and the muscle and skin were sutured.[20]

Model of CKD Induction

CKD was induced by daily oral gavage 200 mg/kg body weight of adenine dissolved in 1% (w/v) gum acacia solution for ten consecutive days.[21,22] Urea and creatinine of plasma were measured, a day after the last day of CKD induction (12:00 a.m. or 12:00 p.m.), by an Olympus AU640 automatic analyzer to confirm kidney dysfunction.

Plasma and Kidney Tissue Collection

The blood sample was taken from the anesthetized

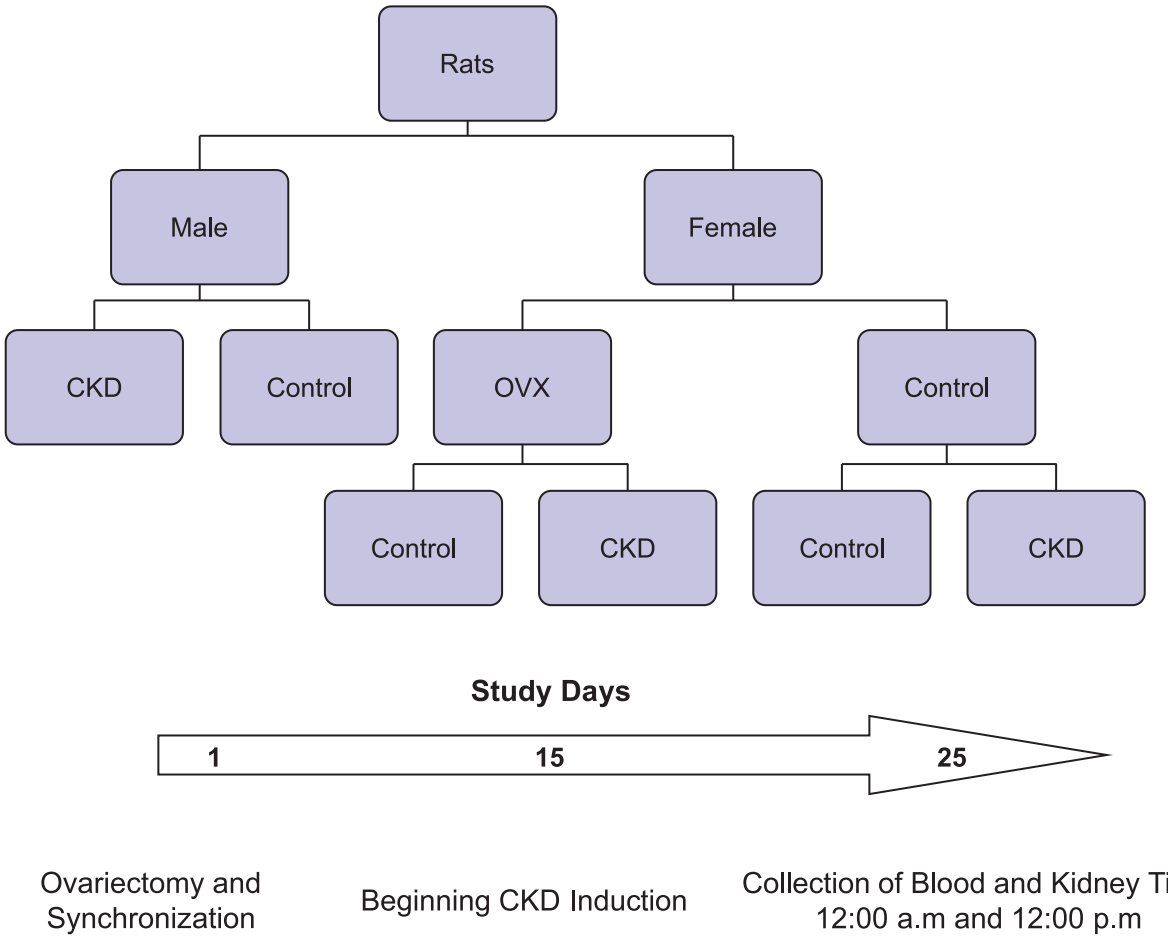

Figure 1. Study groups and protocol (OVX: ovariecetomized)

animals. Plasma was provided to determine blood urea, creatinine, and melatonin levels. The left kidney of the anesthetized animals was removed, weighed, and homogenized by T-PERTM tissue protein extraction reagent (500 mg tissue per 2 mL of the reagent).[23] The supernatant was obtained to determine the total antioxidant capacity (TAC), TGF-β, and malondialdehyde (MDA) content in the kidney.

Measurement of Plasma Melatonin Levels

ELISA kit for melatonin (sensitivity range: 40 to 1280 ng/L) was provided (Cat. No: ZB-10601S-R9648, Gmbh Zellbio, Germany), and the manufacturer's protocols were executed. The concentration of melatonin was expressed as nanograms (ng) of antigen per liter (L) of the plasma.

Measurement of Kidney TGF-β Levels

ELISA kit for TGF-β (sensitivity range: 75 to 2400 pg/L) was provided (Cat. No: ZB-10779S-R9648, Zellbio Gmbh, Germany), and the manufacturer's protocols were executed. The concentration of TGF-β was expressed as ng per milligrams tissue.

Determination of Total Antioxidant Capacity in the Kidney

Total antioxidant capacity (*TAC*) of kidney was determined by measuring FRAP as the ability to withstand the oxidative effects of reactive species generated according to Benzie and Strain method.[24] This method measures the levels of reducing a ferric–tripyridyltriazine (Fe III-TPTZ) complex to the ferrous (Fe II)-TPTZ form by the colorimetric method.

Determination of Lipid Peroxidation Levels in the Kidney

MDA is an indicator of lipid peroxidation. Thiobarbituric acid reactive substance (TBARS)

assay was used to determine MDA levels in the kidney.[25] Results were reported after reading the reaction color of the mixture at 532 nm as nmol per mg tissue.

Statistical Analysis

Data were expressed as mean ± SEM. The normality of data was investigated using the Shapiro-Wilk test. Data with normal distribution were analyzed using three-way repeated measures ANOVA (group × sex × time) followed by Post hoc analysis of Bonferroni's correction. Statistical significance was considered when *P* value was less than .05. Data analysis was done using the SPSS software package version 20.

RESULTS

Amplitude of Circadian Rhythm for Plasma Urea and Creatinine Levels Increased by CKD and the Amount of the Increase Was Sex-dependent

The levels of urea at the day were more than its level at the night, in the intact female and OVX-CKD groups ($P < .001$) (Figure 2A). However, levels of creatinine at the day were more than the levels at the night, in the male, intact female, and OVX-CKD groups ($P < .05$, $P < .001$, and $P < .001$; respectively) (Figure 2C). Plasma urea and creatinine increased after CKD induction compared to the control groups, at both times ($P < .001$) (Figure 2A, and 2C; respectively). This increase in the intact female group was less than the male and OVX groups, both 12:00 a.m. and 12:00 p.m. ($P < .001$) (Figure 2B, and 2D; respectively). However, the increase of both urea and creatinine in the OVX rats was less than the male rats, both 12:00 a.m. ($P < .001$, $P < .001$; respectively) and 12:00 p.m. ($P < .001$, $P < .01$; respectively) (Figure 2B, and Figure 2D; respectively).

Amplitude of Circadian Rhythm for Kidney Weight / Body Weight Ratio Increased by CKD and the Amount of the Increase Was Sex-dependent

The KW/BW ratio is an accepted index for kidney hypertrophy. The ratio in the CKD groups at the day was more than it at the night ($P < .001$) (Figure 3A). A significant increase in KW/BW ratio was observed in the CKD groups compared to the control groups, both 12:00 a.m. and 12:00 p.m. ($P < .001$) (Figure 3A). The increase in the OVX and male groups were higher than the intact female group, both 12:00 a.m. and 12:00 p.m. ($P < .001$) (Figure 3B).

Amplitude of Circadian Rhythm for Plasma Levels of Melatonin Decreased Due to CKD, the Amount of Decrease Was Sex-dependent

In both control and CKD animals (Figure 4A) the levels of melatonin were high at 12:00 a.m. compared to its level at 12:000 p.m. ($P < .001$). The levels decreased in the CKD groups compared to the control groups, at day and night periods ($P < .001$) (Figure 4A). The decrease of this parameter in the male and OVX groups was more than it in the intact female group, in the day and night cycle ($P < .001$, $P < .05$; respectively). Meanwhile, the reduction in the OVX rats was less than the male rats ($P < .05$) (Figure 4B).

Amplitude of Circadian Rhythm for Kidney Lipid Peroxidation Increased Due to CKD and the Amount of Increase Was Sex-dependent

The levels of lipid peroxidation were determined by MDA measuring. There was a significant increase in MDA levels at 12:00 p.m. in comparison to 12:00 a.m., in both CKD and control groups ($P < .001$). The variable increased due to CKD as compared to the control groups ($P < .001$), both at 12:00 a.m. and at 12:00 p.m. (Figure 5A). In the control rats, the levels in the male and OVX female groups were higher than the intact female group, both at 12:00 a.m. and at 12:00 p.m. ($P < .001$). However, in the CKD rats, the variable increased in the male and OVX female groups in comparison to the intact female group, both at 12:00 a.m. and 12:00 p.m. ($P < .001$). Meanwhile, the increase in the OVX groups was less than the male groups, at both 12:00 a.m. and 12:00 p.m. ($P < .001$) (Figure 5B).

Amplitude of Circadian Rhythm for Kidney Antioxidant Capacity Decreased by CKD and This Decrease Was Sex-dependent

The TAC index was used to determine the antioxidant activity. The levels were different between day and night in control animals ($P < .001$), lower levels were observed at 12:00 p.m. kidney TAC levels decreased after CKD induction in comparison to the control groups in the day and night cycle ($P < .001$) (Figure 6A). This reduction in intact female rats was lower than male ($P < .05$)

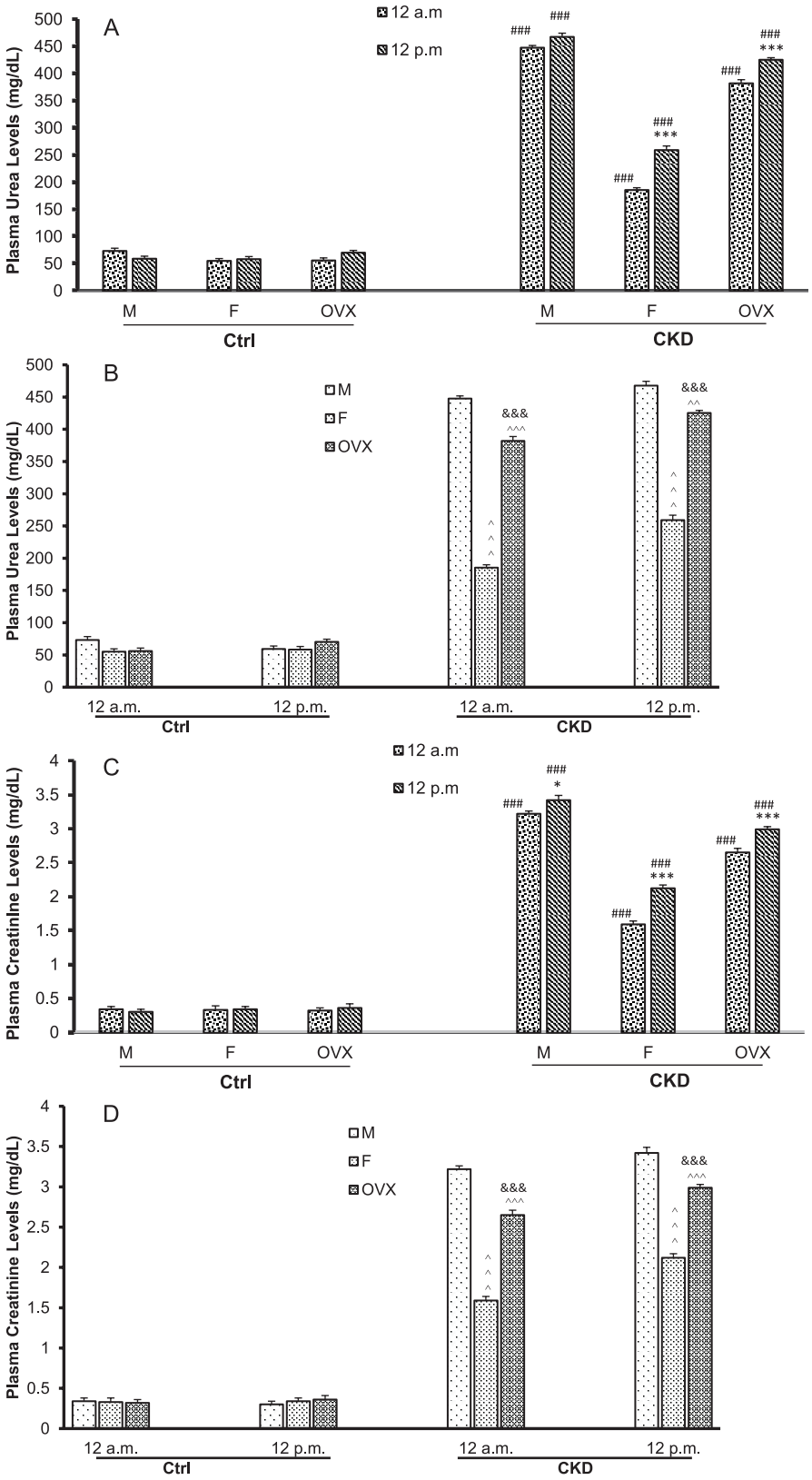

Figure 2. The levels of plasma urea and creatinine (mg/dL) in the day of evaluation according to time, group (A, C; respectively) and sex (B, D; respectively) analysis in rats (n = 6 for each). The data are presented as mean ± SEM ($^{***}P < .001$ vs. 12:00 a.m.; $^{*}P < .05$ vs. 12:00 a.m.; $^{\#\#\#}P < .001$ vs. Ctrl group; $^{\wedge\wedge\wedge}P < .001$ vs. male group; $^{\wedge\wedge}P < .01$ vs. male group; $^{\&\&\&}P < .001$ vs. female group).
Abbreviations: Ctrl, control; M, male; F, Female; OVX, ovariecetomized.

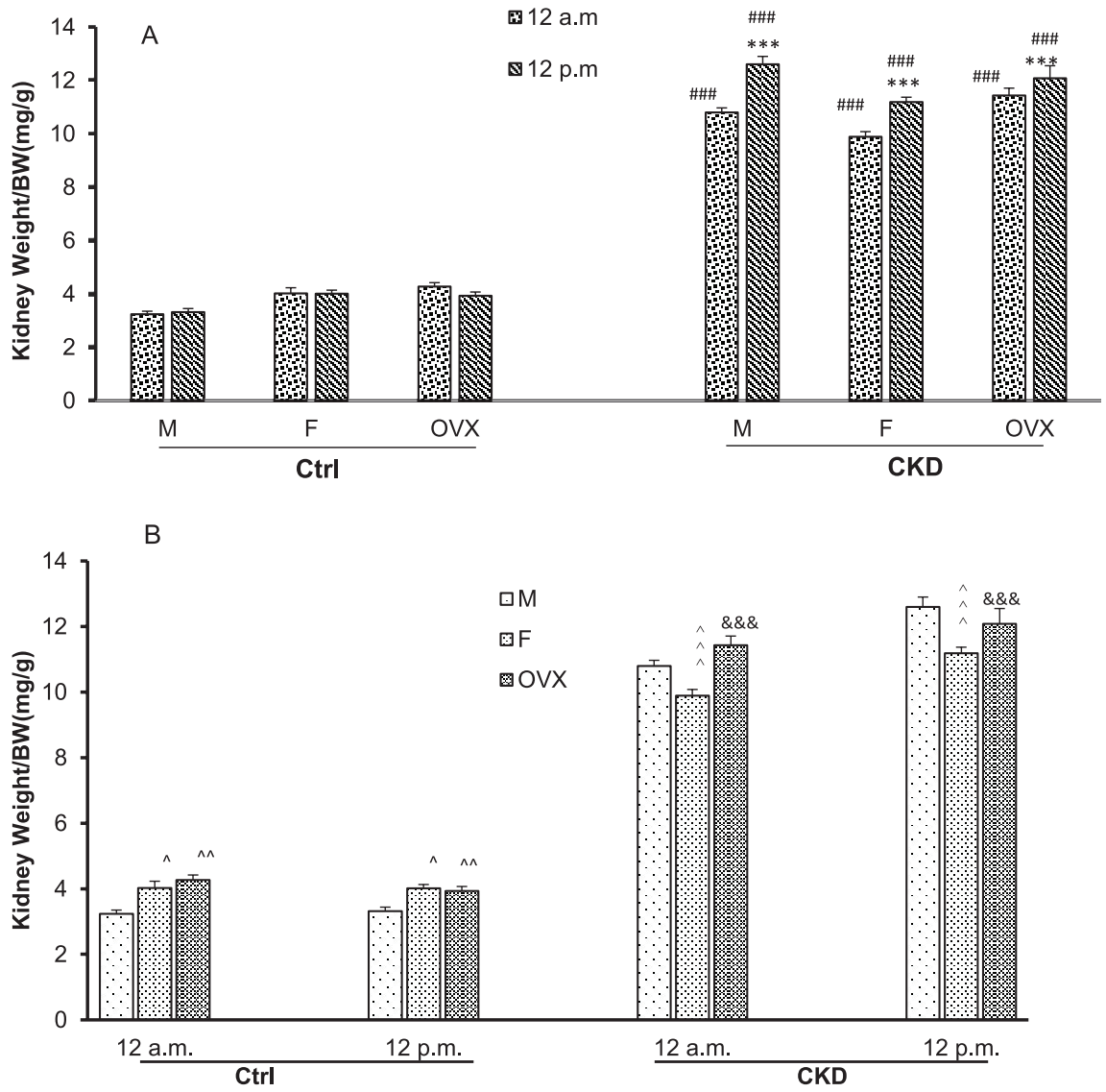

Figure 3. The kidney weight/body weight (KW/BW; mg/g) ratio in the day of evaluation according to time, group (A) and sex (B) analysis in rats (n = 6 for each). The data are presented as mean ± SEM ($^{***}P < .001$ vs. 12:00 a.m.; $^{\#\#\#}P < .001$ vs. Ctrl group; $^{\wedge\wedge\wedge}P < .001$ vs. male group; $^{\wedge\wedge}P < .01$ vs. male group; $^{\wedge}P < .05$ vs. male group; $^{\&\&\&}P < .001$ vs. female group).
Abbreviations: Ctrl, control; M, male; F, Female; OVX, ovariectomized.

and OVX female ($P < .001$) rats (Figure 6B).

Amplitude of Circadian Rhythm for Kidney TGF-β Increased by CKD and This Increase Was Sex-dependent

The levels of kidney inflammation and injury were determined by measuring *TGF-β*. The levels of TGF-β were different between day and night in both CKD and control groups, in the day it was higher than the night ($P < .001$). Kidney TGF-β levels increased after CKD induction in comparison to the control groups in both times ($P < .001$) (Figure 7A). The increase in the intact female group was lower than the male and OVX groups, both at 12:00 a.m. and at 12:00 p.m. ($P < .001$). However, the levels in the OVX-CKD group were different from the male CKD group both at 12:00 a.m. and 12:00 p.m. ($P < .001$) (Figure 7B).

DISCUSSION

In this study, the gender difference in circadian rhythm of inflammatory and oxidant factors in CKD was studied for the first time. The findings of this study suggest that: 1) there was circadian rhythm for KW/BW ratio, plasma urea, creatinine and melatonin levels, kidney TGF-β and MDA levels

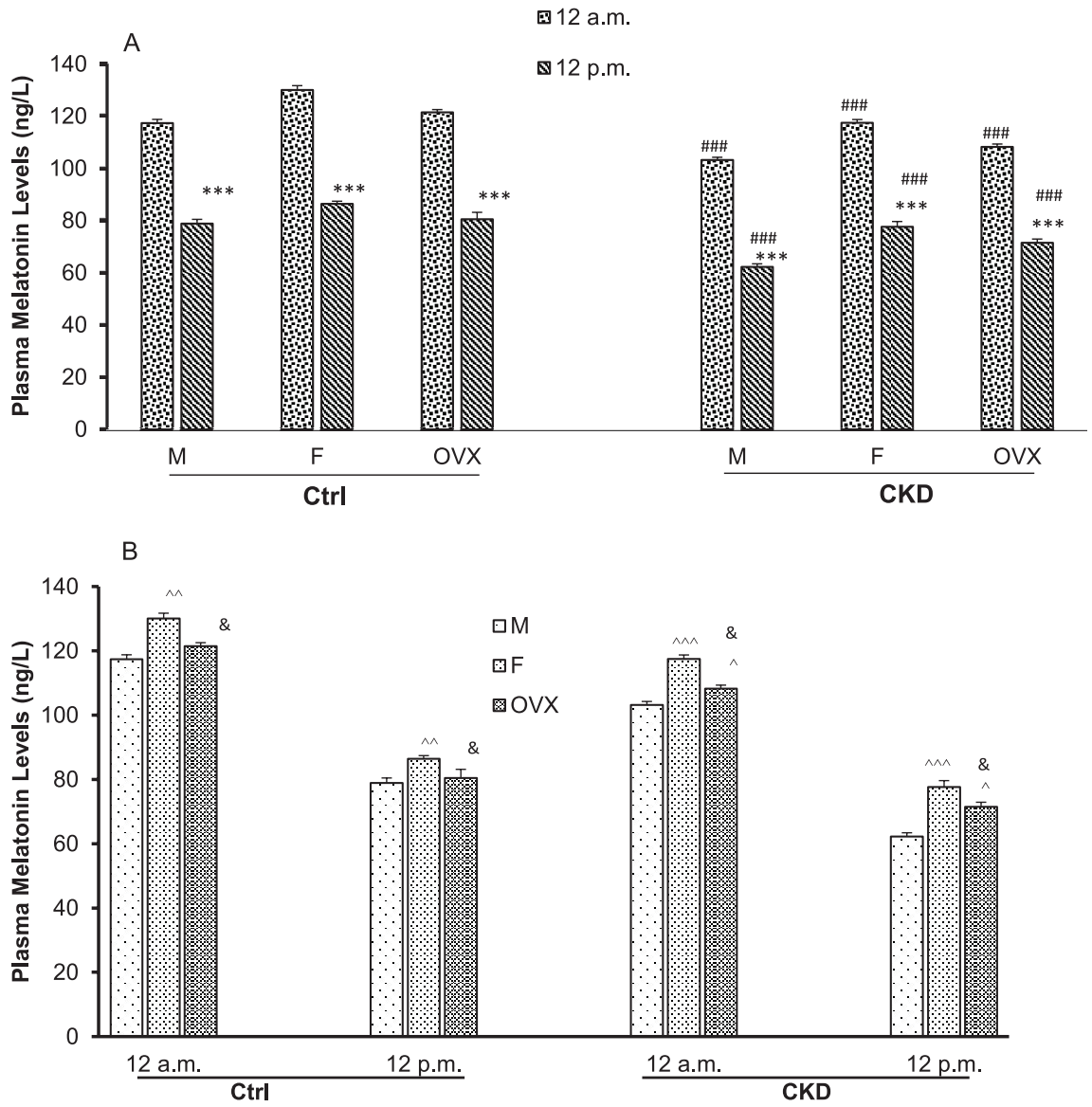

Figure 4. The levels of plasma melatonin (ng/L) in the day of evaluation according to time, group (A) and sex (B) analysis in rats (n = 6 for each). The data are presented as mean ± SEM ($^{***}P < .001$ vs. 12:00 a.m.; $^{\#\#\#}P < .001$ vs. Ctrl group; $^{\wedge\wedge\wedge}P < .001$ vs. male group; $^{\wedge\wedge}P < .01$ vs. male group; $^{\wedge}P < .05$ vs. male group; $^{\&}P < .05$ vs. female group).
Abbreviations: Ctrl, control; M, male; F, Female; OVX, ovariectomized.

in CKD condition; 2) CKD caused an increase in plasma urea and creatinine levels, KW/BW ratio, kidney TGF-β, and MDA levels, whereas there was a decrease in plasma melatonin and kidney TAC levels in the day/night cycle; 3) the changes in circadian rhythm amplitude of urea, creatinine, MDA, TAC, TGF-β and melatonin levels were found to be sex-dependent and there were less detrimental changes in intact female rats.

The SCN, the master pacemaker of circadian rhythmicity, receives light intrinsically from photosensitive retinal ganglion cells, accordingly it coordinates the peripheral and central clocks via neuronal, hormonal, and metabolic signaling pathways.[26,27] The physiology of circadian rhythms is complex and understanding the mechanisms in chronobiology is still in progress.[28] Kidneys have molecular circadian clock, and genes responsible for renal function are expressed in a circadian manner.[29,30] It is also suggested that uremic toxins affect SCN.[31] Inflammation and oxidative stress play pivotal roles in the development of CKD complications including cardiovascular dysfunctions and infections.[32] CKD patients suffer

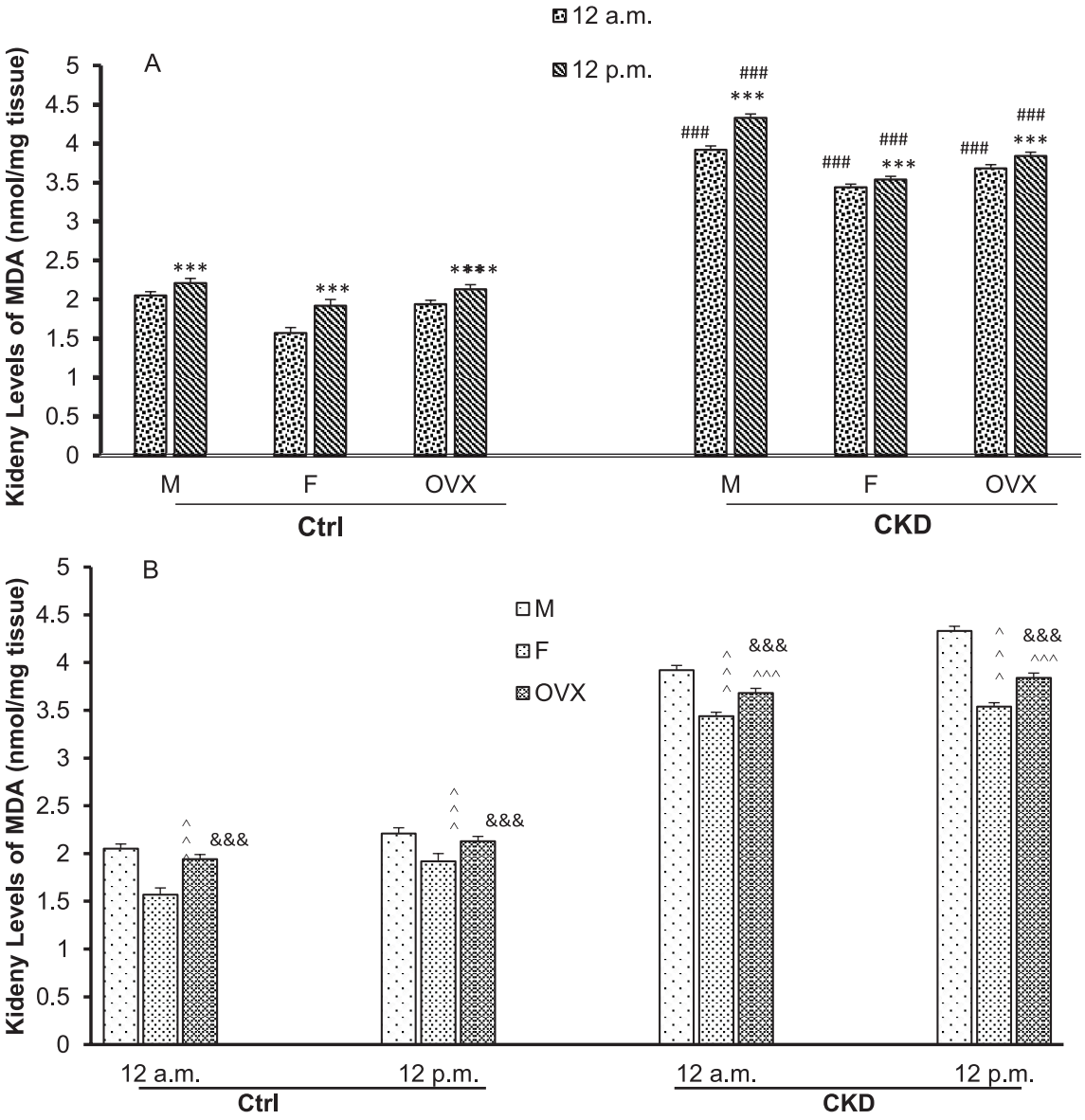

Figure 5. The levels of kidney malondialdehyde (MDA) (nmol/mg tissue) in the day of evaluation according to time, group (A) and sex (B) analysis in rats (n = 6 for each). The data are presented as mean ± SEM ($^{***}P < .001$ vs. 12:00 a.m.; $^{\#\#\#}P < .001$ vs. Ctrl group; $^{\wedge\wedge\wedge}P < .05$ vs. male group; $^{\&\&\&}P < .001$ vs. female group).
Abbreviations: Ctrl, control; M, male; F, Female; OVX, ovariectomized.

from chronic inflammation[33] and antioxidant systems impairment.[34]

In the current study, the circadian rhythm of evaluated variables including KW/BW ratio, plasma, urea, creatinine and melatonin levels, kidney TGF-β and MAD levels due to CKD was observed. The above finding is consistent with the study by Motohashi *et al.*'s (2020) that showed the CKD effect on the amplitude but not the period or phase of the central circadian clock.[5] In another study, a complete phase shift of the circadian rhythm in the CKD rats was not shown,[35] probably because of partial disruption of circadian rhythm in the hypothalamus by uremic toxins. Like the current study, an interesting finding of the research was the appearance of circadian rhythm for plasma creatinine and urea levels following CKD, but the disruption of TAC circadian rhythm, sex-independent.

In this research, there was an increase in circadian rhythm amplitude of urea, creatinine, KW/BW ratio, MDA, and TGF-β after CKD, however, there was a

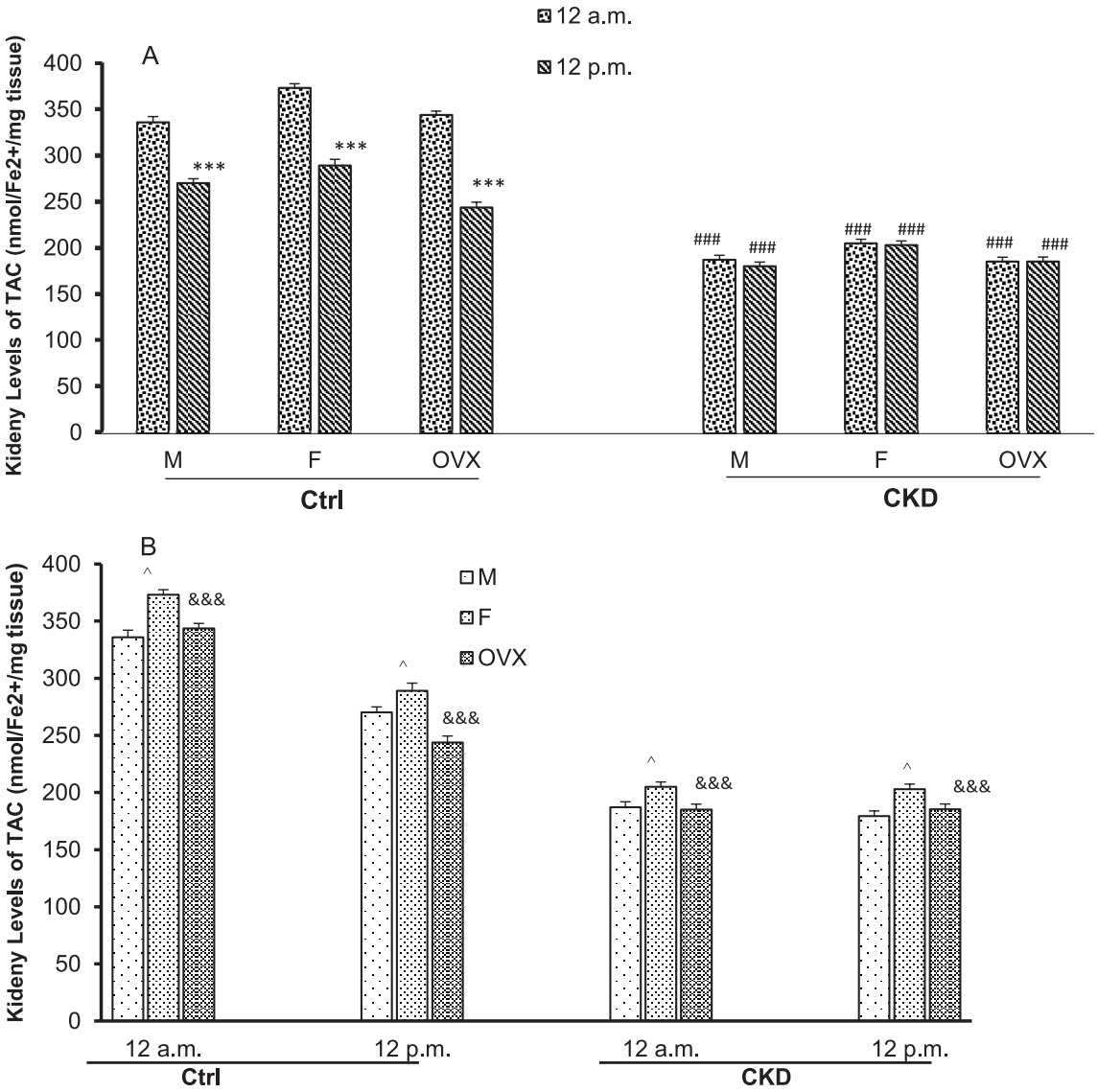

Figure 6. The levels of kidney total antioxidant capacity (TAC) (nmol/Fe^{2+}/mg tissue) in the day of evaluation according to time, group (A) and sex (B) analysis in rats (n = 6 for each). The data are presented as mean ± SEM ($^{***}P < .001$ vs. 12:00 a.m.; $^{\#\#\#}P < .001$ vs. Ctrl group; $^{\wedge}P < .05$ vs. male group; $^{\&\&\&}P < .001$ vs. female group).
Abbreviations: Ctrl, control; M, male; F, Female; OVX, ovariecetomized.

decrease in TAC and melatonin levels. In the study of Motohashi *et al.*, two-week use of adenine in mice reduced body and kidney weights.[5] Therefore, the increase in KW/BW ratio of this research may be due to the decrease in both body and kidney weights. TGF-β1 is a pro-fibrotic potent cytokine that is also implicated in fibrosis and hypertrophy.[36] Oxidative stress plays a significant role in different renal pathologies.[37] Targeting TGF-β1 directly through antibody application reduces the progression of CKD.[38] Many factors contribute to the chronic inflammatory state in CKD, including the increased production of proinflammatory cytokines and oxidative stress.[39] Elevated levels of oxidative stress have been observed in CKD patients, due to the defect in their physiological defense mechanisms.[40] Moreover, inflammation contributes to the progression of CKD, oxidative stress, and CKD complications.[41] Therefore, due to damage to the kidney function in CKD, an increase in intrarenal TGF-β and the imbalance of oxidant and antioxidant factors probably participated in the induction of renal hypertrophy in this study since KW/BW ratio increased.

Melatonin administration in 5/6 nephrectomy (Nx) rats decreased MDA levels in plasma

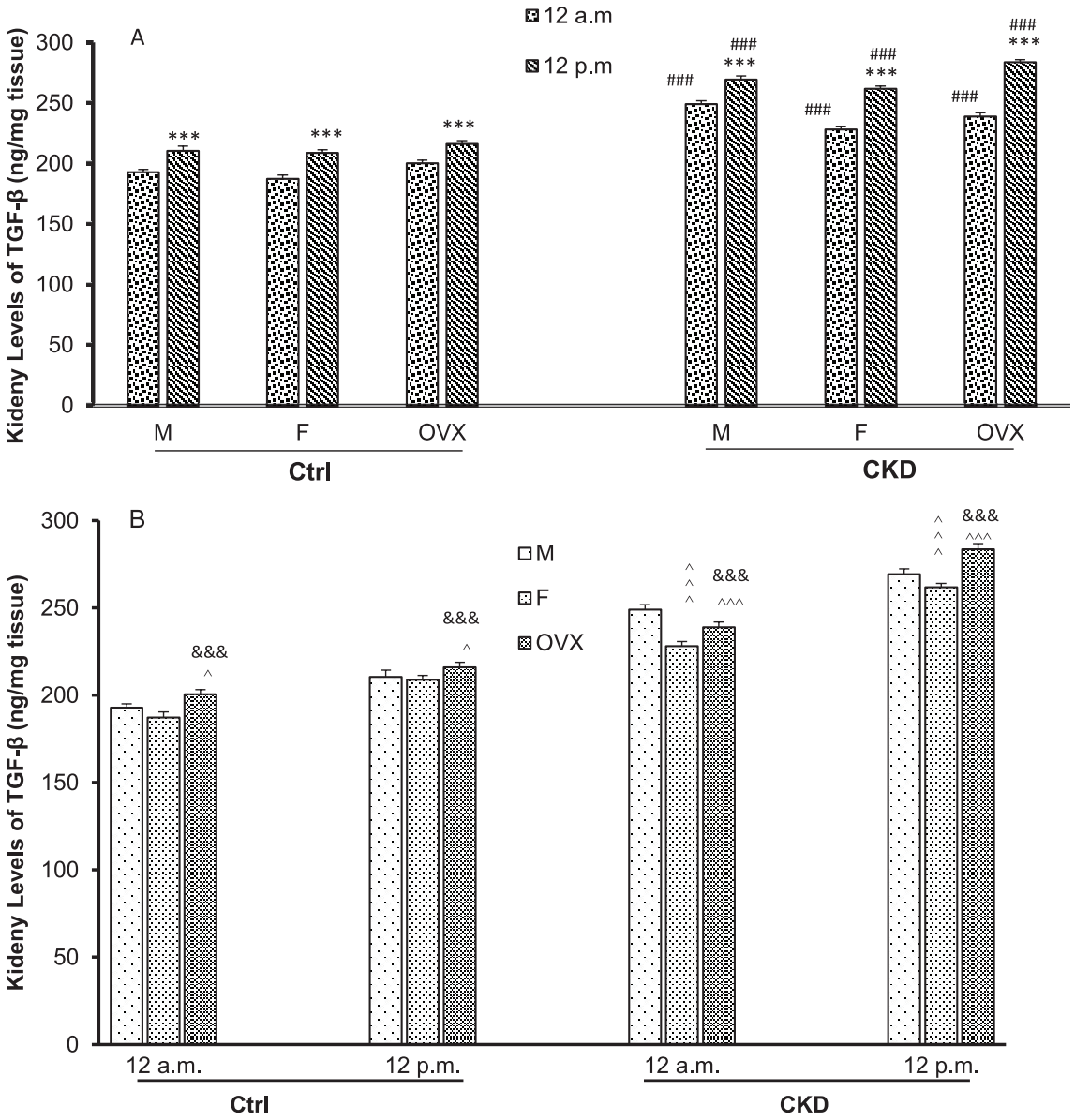

Figure 7. The levels of kidney TGF-β (ng/mg tissue) in the day of evaluation according to time, group (A) and sex (B) analysis in rats (n = 6 for each). The data are presented as mean ± SEM ($^{***}P < .001$ vs. 12:00 a.m.; $^{\#\#\#}P < .001$ vs. Ctrl group; $^{\wedge\wedge\wedge}P < .05$ vs. male group; $^{\wedge}P < .05$ vs. male group; $^{\&\&\&}P < .001$ vs. female group).
Abbreviations: Ctrl, control; M, male; F, Female; OVX, ovariectomized.

and the remnant kidney, renal inflammation, damage, and dysfunction.[42] Melatonin not only neutralizes reactive nitrogen species (RNS) and reactive oxygen species (ROS) but also stimulates antioxidant enzymatic systems.[43,44] It is known that the nocturnal endogenous melatonin rhythm decreases with advanced CKD.[45] Thus, a decrease in plasma melatonin levels due to CKD probably resulted in inflammation and oxidative stress. Uremic toxins and other factors associated with impaired renal function may affect the circadian rhythm in CKD patients.[46] These findings suggest that the changes in circadian rhythm amplitude of inflammation (change in TGF-β levels) and oxidative stress (changes in MDA and TAC levels) markers following CKD may be partly due to the changes in melatonin. The changes in melatonin could be the result of the effect of uremic factors on SCN.

After CKD induction, an increase in lipid peroxidation and circadian rhythm amplitude of urea, creatinine, and TGF-β levels was observed, more in male and OVX rats than intact female rats.

Also, a decrease in circadian rhythm amplitude of plasma melatonin levels and antioxidant activity in CKD animals was observed to be more in male and OVX rats than intact female rats. Hypertensive renal disease has been shown to be more common in men compared to women. However, the incidence of kidney disease in females increases after menopause, suggesting that the loss of sex hormones causes the development of renal diseases. The results recommend the protective role of ovarian hormones on renal disease, and estrogen or progesterone replacement therapy may improve kidney function.[47] In renal ischemia/reperfusion, female rats showed significantly better results in both treated and untreated groups compared to male rats. Inflammation, oxidative stress, and antioxidative markers confirmed the histological results [48]. In the current study, it was observed less detrimental alterations in OVX groups compared to males. However, it should consider surgery for ovariectomy induced inflammation in this study. It seems female sex is less susceptible to injury; however, more information on this matter would help to establish a greater degree of accuracy.

Gender difference of present research suggests two hypotheses: 1) female sex steroids may prevent the promotion of kidney damage by direct renoprotective effect through the reduction of kidney oxidative stress and inflammation development,[49] and by the indirect renoprotective effect, it may be mediated by inducing melatonin effect.[50] More research is needed to examine the theories. 2) Male sex hormone may induce detrimental effects.[51] Further investigation and experimentation into this hypothesis is also recommended.

CONCLUSION

Considering the study findings, there was circadian rhythm of plasma urea, creatinine and melatonin levels, kidney weight, lipid peroxidation, and TGF-β in CKD condition. The amplitude of rhythm for all variables of research had detrimental changes following the CKD. The changes were more frequently observed in male than intact female rats and even it was more than OVX rats for some markers. Our data, along with the established literature, suggest that the changes in circadian rhythm induced by CKD may further exacerbate the progression of the disease. Chronotherapy according to sex might be beneficial for CKD patients and could be considered.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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AUTHORS' CONTRIBUTIONS

Shahrzad Sadat Eftekhar Vaghefi: Collection of data

Zahra Soltani: Design of study, Data analysis and interpretation, Manuscript writing

Mohammad Khaksari and Fatemeh Moosavi: Design of the study

Gholamreza Asadikaram: Collection of data

Abbreviations

BP, blood pressure; CKD, chronic kidney disease; FRAP, ferric-reducing ability power; Fe III-TPTZ, ferric–tripyridyltriazine; KW/BW, kidney weight / body weight; MDA, malondialdehyde; NO, nitric oxide; Nx, nephrectomy; OVX, ovariectomized; RAS, renin angiotensin system; ROS, reactive oxygen species; SCN, suprachiasmatic nucleus; TGF-β, transforming growth factor- β; TBARS, thiobarbituric acid reactive substance; TAC, total antioxidant capacity.

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