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ABSTRACT:
Obesity, a widespread global health issue affecting both adults and young individuals, has raised concerns due to its strong correlation with chronic kidney disease and end-stage renal disease, significantly contributing to the burden of kidney disorders. Renal lipotoxicity, driven by disrupted lipid metabolism in obesity, results in intracellular lipid accumulation in the kidneys, leading to cellular dysfunction. This study investigated how melatonin affects renal function in Wistar rats with diet-induced obesity. Twenty-four animals were separated into four groups: Control (CTL) group, which received a standard diet and distilled water; Melatonin group (MEL), received melatonin at a dose of 4 mg/kg of body weight; the Obese group (OBS), which was fed a 40% high-fat diet (HFD); and Obese treated with melatonin group (OBS + MEL), which received both the high-fat diet and melatonin daily for 12 weeks. The findings revealed that the high-fat diet led to increased food consumption and body weight, and melatonin supplementation helped mitigate these effects. Notably, there was no significant increase in renal mass. The results also revealed increased fasting insulin, fasting glucose levels and insulin resistance. Total cholesterol and triglyceride concentrations were significantly increased, while HDL was decreased in HFD group. However, melatonin ameliorated the altered lipid profile. Melatonin also attenuated increased MDA and GGT concentrations and restored decreased GSH and NO levels affected by HFD. The present study therefore indicates that melatonin alleviates oxidative stress, inflammation, lipid deposition and renal injury induced by high fat diet, suggesting a potential reno-protective property.

Key words: High fat diet; Kidney; Lipid; Melatonin; Obesity.

INTRODUCTION:

Obesity has emerged as a global epidemic, affecting a staggering number of adults and youth, with projections indicating a significant increase in the coming years. Its association with chronic kidney disease (CKD) and end-stage renal disease (ESRD) has raised concerns, with a substantial portion of kidney disease cases attributed to obesity [1,2]. This escalating obesity-related kidney disease has prompted a closer examination of the interplay between obesity, kidney dysfunction, and the underlying mechanisms driving this correlation. The surge in both obesity and kidney disease from 1980 to 2000 underscores the intricate relationship between the two conditions, as

ESRD incidence nearly quadrupled over a decade later [3]. Although conditions such as diabetes mellitus and hypertension have traditionally been linked to kidney disease, emerging evidence indicates that obesity and its associated metabolic syndrome play a more pivotal role in this epidemic [4]. The influence of obesity extends beyond its coexisting conditions, as epidemiological studies demonstrate its autonomous association with CKD and ESRD [5,6,7].

The mechanisms by which obesity engenders kidney disease remain elusive, but one compelling pathway is the concept of lipotoxicity. As obesity ensues, an imbalance between energy intake and expenditure triggers adipose tissue expansion, which, when limited, leads to ectopic lipid accumulation in organs, culminating in lipotoxicity [8,9]. Dysregulated lipid metabolism in obesity fosters the intracellular buildup of lipids and lipoproteins, inducing cellular dysfunction across tissues, from cardiomyocytes to hepatocytes [10,11,12]. In the kidney, this abnormal lipid metabolism manifests as renal lipotoxicity, characterized by the accumulation of triglycerides and cholesterol in glomerular and tubulointerstitial cells [13]. Excessive lipid accumulation within the renal tissue can precipitate injury to renal tubular cells [14], structural changes in glomeruli and lead to kidney dysfunctions [15,16,17]. Renal lipotoxicity is also significantly linked to the onset of conditions such as excess protein in the urine, inflammation of the glomeruli, and CKD [18].

The kidneys are particularly vulnerable to oxidative stress due to their susceptibility to lipid peroxidation when subjected to a diet rich in fat. Reactive oxygen species (ROS) production leads to the oxidative degradation of biological molecules such as lipids, resulting in the initiation of lipid peroxidation, which results in the production of malondiadehyde (MDA), within renal tissues. This process subsequently disrupts the endogenous antioxidant defense system [19,20]. Additionally, this process sets off a sequence of interconnected reactions within renal tissues that culminate in reno-toxicity [21,22]. The repercussions of renal lipotoxicity are multifaceted, triggering the upregulation of proinflammatory cytokines [23]. Notably, this cascade parallels the association between ectopic lipid deposition and decreased insulin sensitivity, contributing to the development of type 2 diabetes [2]. Furthermore, the kidney, like other affected organs, becomes a target for detrimental lipid accumulation, fostering a deleterious environment.

Melatonin (MEL), a hormone produced by the pineal gland in response to darkness, is a versatile compound with potent antioxidant properties and various endocrine functions [24]. MEL is particularly abundant in mitochondria, where its well-characterized antioxidant actions prevail [25]. Upon release into the cerebrospinal fluid and bloodstream, MEL becomes widely available throughout the central nervous system (CNS) and peripheral tissues respectively,

holding potential clinical relevance in various diseases [26]. One of MEL's primary roles lies in maintaining proper energy balance by regulating energy flow to and from storage and directly influencing energy expenditure, primarily through the activation of brown adipose tissue. Additionally, MEL promotes the transformation of white adipose tissue into brown, aiding in the regulation of body weight [27]. Furthermore, MEL serves multiple biological functions, including anti-inflammatory and antioxidant effects, suppression of the sympathetic nervous system, and the maintenance of endothelial cell function. It is well-documented that MEL administration lowers blood pressure (BP), and endogenous MEL secretion levels diminish with declining renal function [28, 29, 30]. Moreover, MEL plays a pivotal role in renal physiology and has been associated with the pathophysiology of the kidneys. Some animal models have been utilized in experimental settings to investigate the effects of MEL on renal function and structure [31,32]. Through these models, it was shown that MEL plays a crucial role in preserving renal function and ameliorating renal structure. Despite this wealth of knowledge, the role of MEL in obesity-associated renolipotoxicity remains inadequately understood. Therefore, this current study investigated the influence of MEL on the intricate interplay between obesity, renal lipotoxicity, and kidney dysfunction.

METHODOLOGY:

Experimental Animals and grouping:

All experimental procedures in this study adhered to the guidelines set forth in the National Institutes of Health Guide for the Care and Use of Laboratory Animals [33]. The Institutional Ethical Review Board of Afe Babalola University, Nigeria, granted approval for this study (ABUADERC/10/2020). The ethical considerations of the 3 Rs, namely replacement, reduction, and refinement, were duly considered.

A total of twenty-four male Wistar rats, 170 – 200 grams, were sourced from the animal facility at the College of Health Sciences, Afe Babalola University, Nigeria. These rats were provided unrestricted access to standard rat chow and tap water. Following a 2-week acclimatization period, the rats were randomly divided into four groups, with six rats in each group. The rats were housed in a controlled environment with standard conditions, including a temperature range of 22–26°C, relative humidity between 50–60%, and a 12-hour light/dark cycle.

Treatment:

The study included four groups of animals with different treatments: the control group (CTL) received regular rat chow and distilled water; the melatonin-treated group (MEL) received melatonin at a dose of 4 mg/kg body weight; the obese group (OBS) was given a high-fat diet (HFD) consisting of 40% fat; and the obese group with melatonin treatment (OBS + MEL-

treated) received both the 40% high-fat diet and melatonin at a dose of 4 mg/kg daily.

Melatonin administration for groups 2 and 4 took place between 8:00 and 10:00 am daily. Obesity was induced in groups 3 and 4 by providing them with unrestricted access to the 40% HFD, as previously described [34,35]. This treatment regimen continued for 12 weeks. At the beginning and end of the 12-week period, the animals' initial and final body weights were measured, and the amount of weight gained was calculated. Furthermore, daily food and water consumption were carefully monitored during week 0 (initial) and week 12 (final) by subtracting any remaining food and water after 24 hours from the initial quantities provided to the animals. Changes in food and water consumption were determined by subtracting the initial consumption from the final consumption. All the results were recorded appropriately.

Assay of metabolic parameters:

Fasting blood glucose was determined with a hand-held glucometer (ONETOUCH1-LifeScan, Inc., Milpitas, CA, USA). The insulin concentration in the plasma was determined using Rat ELISA kits obtained from Calbiotech Inc. (El Cajon, USA). This study followed the manufacturer's instructions and used the direct sandwich approach, which involves using two monoclonal antibodies that target different antigenic regions on the insulin molecule. Insulin resistance was determined using the homeostatic model assessment of insulin resistance (HOMA-IR), calculated as fasting glucose (mmol/l) multiplied by fasting insulin (μU/l) divided by 22.5, following the methods described in previous studies [36].

Sample Preparation:

Following 12 weeks of treatment, the animals underwent a 12-hour overnight fast. Subsequently, they were anesthetized via intraperitoneal injection of 50 mg/kg body weight of sodium pentobarbital. Blood was collected through cardiac puncture into heparinized tubes and then centrifuged at room temperature for 5 minutes at 3000 rpm. The plasma was separated and stored frozen until it was required for biochemical assay.

Preparation of kidney tissue homogenates:

Following the kidney's weight measurement, a 100 mg tissue section was meticulously excised and homogenized using a glass homogenizer in a phosphate buffer solution. The homogenate was then subjected to centrifugation at 10,000 rpm for 10 minutes at 4°C.

Biochemical assays:

Lipid profile:

Concentrations of triglycerides (TG), total cholesterol (TC) and high -density lipoprotein (HDL) were estimated in the kidney tissue homogenates by standardized colorimetric methods using reagents obtained from Fortress Diagnostics Ltd. (Antrim, UK) [37,38].

Oxidative stress markers:

Malondialdehyde (MDA) was determined from the kidney tissue homogenate by standard non-enzymatic spectrophotometric method using assay kits from Randox Laboratory Ltd. (Co. Antrim, UK). Whereas Reduced Glutathione (GSH) was determined using non-enzymatic spectrophotometric method with assay kits obtained from Oxford Biomedical Research Inc. (Oxford, USA). Glutathione was determined by spectrophotometric method based on the oxidation of GSH in the sample by the sulfhydryl reagent 5,50 -dithio-bis (2-nitrobenzoic acid) (DTNB) to form the yellow derivative 50 -thio-2-nitrobenzoic acid (TNB), measured at 412 nm. These assays were carried out as previously described [35,38].

Renal Nitric Oxide (NO), Gamma-glutamyl transferase (GGT), Nitric oxide levels were determined spectrophotometrically by quantifying the stable degradation products, nitrate and nitrite, utilizing kits from Oxford Biomedical Research Inc. in Oxford, UK [35]. This assay kit employs the NADH-dependent enzyme Nitrate reductase to convert nitrate to nitrite before quantifying nitrite with the Griess reagent, ensuring precise measurement of total NO production. Renal GGT was assessed using a conventional enzymatic colorimetric method, and assay kits for this purpose were procured from Fortress Diagnostics Ltd. in Antrim, UK [37].

Plasma Urea and Creatinine concentration:

Plasma urea levels were assessed using a standard spectrophotometric method with kits from Oxford Biomedical Research Inc., Oxford, UK. Plasma creatinine concentrations were measured via a non-enzymatic colorimetric method using assay kits from Randox Laboratory Ltd., Co. Antrim, UK, following the manufacturer's assay protocols [38].

Statistical analysis:

The results were presented as mean values with standard error of the mean (SEM). Statistical group analysis was conducted using GraphPad Prism 9.5.1. One-way ANOVA was employed to compare the variable means among the groups. Subsequently, Bonferroni's test was applied for post hoc analysis. Statistically significant differences were considered when p-values were less than 0.05.

RESULTS:

Effect of melatonin on food and water intake, body weight, and renal mass in high-fat diet-induced obese Wistar rats:

The results showed a significant ($p<0.05$) increase in food consumption in the obese group compared to the control group, which was mitigated with concurrent melatonin treatment. Water intake exhibited no significant variation when compared to the control group. However, body weight significantly ($p<0.05$) increased in the obese group in comparison to the control. Nevertheless, supplementation with melatonin

significantly ($p<0.05$) reduced body weight when compared to the untreated obese group. Furthermore, renal mass remained largely unchanged across all the experimental groups in comparison to the control (Table 1).

Table 1: Effect of Melatonin on Food and Water Intake and Body Weight Gain in High-Fat Diet-Induced Obese Wistar Rats.

GROUPS	CTL	MEL	OBS	OBS+MEL
Food intake (g/day)				
Initial	25.22 ± 0.81	33.15 ± 2.30	30.59 ± 4.24	31.85 ± 2.27
Change	8.01 ± 2.71	5.33 ± 1.79	19.21 ± 3.77*	4.42 ± 0.35#
Water intake (mL/day)				
Initial	32.62 ± 1.47	27.79 ± 3.16	26.63 ± 3.43	35.63 ± 3.43
Change	7.34 ± 2.52	5.44 ± 10.19	6.18 ± 5.44	5.86 ± 3.88
Body weight (g)				
Initial	172.71 ± 6.41	174.93 ± 8.12	171.00 ± 6.65	171.43 ± 5.70
Gain	44.40 ± 6.70	36.67 ± 9.30	75.87 ± 4.72*	26.69 ± 3.62#
Renal mass (g/kg)	6.59 ± 0.40	5.49 ± 0.84	7.42 ± 1.02	7.16 ± 0.82

Data are expressed as mean ± SEM. n=7. Data were analyzed by one-way ANOVA followed by Bonferroni *post hoc test*. (*p<0.05 VS. CTL; #p<0.05 VS. OBS). Control (CTL), Melatonin (MEL), Obesity (OBS).

Effect of melatonin on metabolic indices in high-fat diet induced obese Wistar rats:

There was a significant ($p<0.05$) elevation in fasting insulin levels in obese animals when compared to the control group, although fasting blood glucose remained unaltered. However, the supplementation of melatonin led to a reduction in fasting insulin in the OBS+MEL group in comparison to OBS, which did not receive melatonin supplementation. Exposure to a high-fat diet induced insulin resistance, as indicated by a concurrent increase in HOMA-IR in obese animals in contrast to the control group. Nevertheless, melatonin supplementation resulted in a decrease in HOMA-IR, thereby reducing insulin resistance in the OBS+MEL group in comparison to OBS without melatonin supplementation (Table 2).

Table 2: Effect of melatonin on fasting blood glucose, fasting insulin and HOMA-IR in high-fat diet-induced obese Wistar rats

GROUPS	CTL	MEL	OBS	OBS+MEL
Fasting blood glucose (mmol/L)	4.97 ± 0.21	5.42 ± 0.36	5.08 ± 0.36	5.02 ± 0.30
Fasting insulin (µIU/mL)	1.77 ± 0.03	1.95 ± 0.08	2.98 ± 0.09*	1.82 ± 0.04#
HOMA-IR	0.39 ± 0.02	0.47 ± 0.04	0.67 ± 0.05*	0.40 ± 0.02#

Data are expressed as mean ± S.E.M. n=7. Data were analyzed by one-way ANOVA followed by Bonferroni *post hoc test*. (*p<0.05 VS. CTL; #p<0.05 VS. OBS). Control (CTL), Melatonin (MEL), Obesity (OBS)

Effect of melatonin on lipid profile in the kidney in high-fat diet-induced obese Wistar rats:

A significant ($p<0.05$) rise in the levels of TC and TG was observed in the kidney tissue of the obese group when compared to the control group. Nevertheless, melatonin treatment led to a significant decrease in TC and TG concentrations in the kidney. In addition, a significant drop in HDL levels was noted in the kidney tissue of the obese group in comparison to the control group. Conversely, the kidney tissue of the OBS+MEL group displayed an increase in HDL concentrations (Fig 1).

Effect of melatonin on MDA levels in high-fat diet-induced obese Wistar rats:

A significant increase ($p<0.05$) in kidney tissue MDA levels was evident in the obese group when compared to the control group. Nonetheless, melatonin supplementation led to a significant reduction in MDA concentration in the OBS+MEL group when compared to the untreated obese group (Fig 2).

Effect of melatonin on GSH level in high-fat diet-induced obese Wistar rats:

A significant reduction ($p<0.05$) in kidney tissue GSH levels was observed in the obese group when compared to the control group. Nevertheless, melatonin supplementation resulted in a significant increase in kidney GSH concentration in the OBS+MEL group when compared to the untreated obese group (Fig 3).

Effect of melatonin on Nitric oxide concentration in high-fat diet-induced obese Wistar rats:

A significant reduction ($p<0.05$) in kidney tissue NO levels was observed in the obese group when compared to the control group. Nevertheless, melatonin treatment led to a significant increase in kidney Nitric oxide concentration in the OBS+MEL group when compared to the untreated obese group (Fig 4).

Effect of melatonin on gamma-glutamyl transferase concentration [GGT] in HFD-induced obese rats:

A significant increase ($p<0.05$) in the level of GGT in kidney tissue was observed in the obese group compared to the control group. On the other hand, treatment with melatonin resulted in a significant decrease in GGT levels in obese animals (Fig 5).

Effect of melatonin on urea and creatinine concentrations in high-fat diet-induced obese Wistar rats:

No significant changes ($p<0.05$) in plasma urea and creatinine levels in the OBS group when compared to the control group, as well as in the OBS+MEL group when compared to the OBS group (Fig 6).

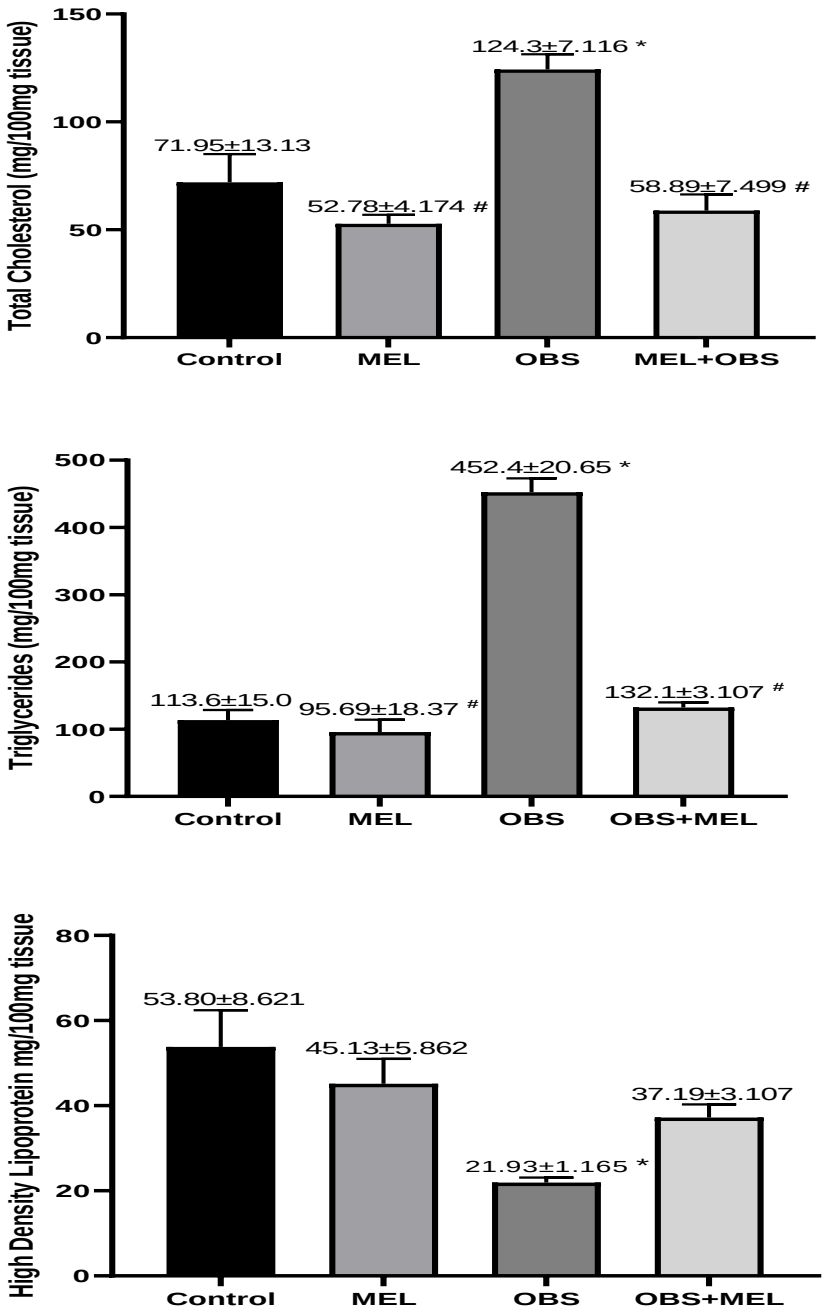

Figure 1: Effect of melatonin on total cholesterol, triglyceride and high density lipoprotein (HDL) levels in the kidney in high-fat diet-induced obese Wistar rat. Data are expressed as mean ± S.E.M. n=7. Data were analyzed by one-way ANOVA followed by Bonferroni post hoc test. (*p<0.05 VS. CTL; #p<0.05 VS. OBS). Control (CTL), Melatonin (MEL), Obesity (OBS).

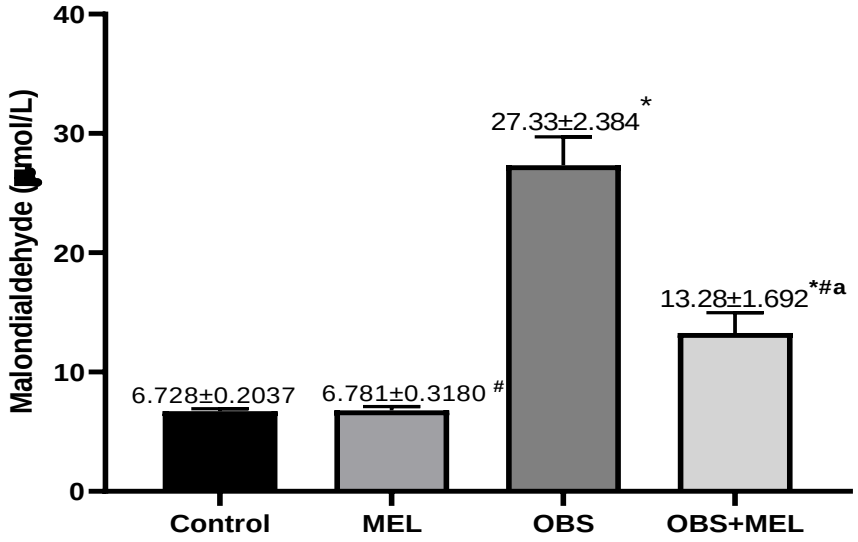

Figure 2: Effect of melatonin on malondialdehyde (MDA) in high-fat diet-induced obese Wistar rats.

Data are expressed as mean ± S.E.M. n=7. Data were analyzed by one-way ANOVA followed by Bonferroni *post hoc test*. (**p*<0.05 VS. CTL; #*p*<0.05 VS. OBS, ap<0.05 VS. MEL). Control (CTL), Melatonin (MEL), Obesity (OBS).

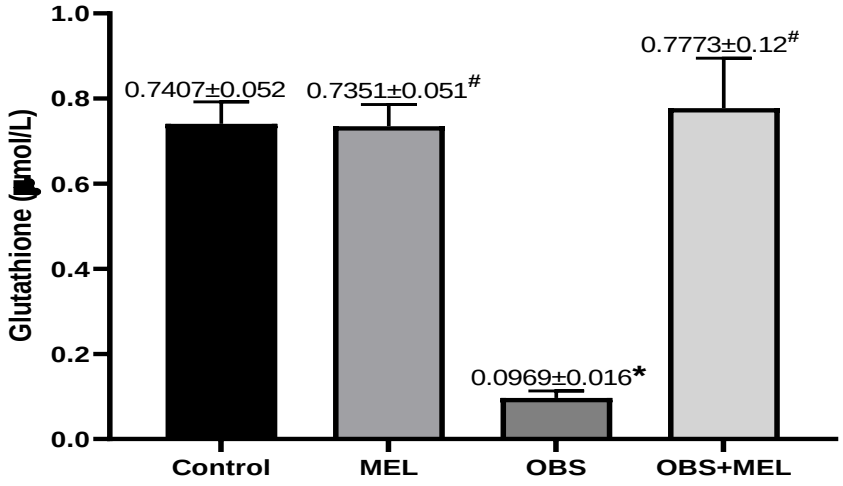

Figure 3: Effect of melatonin on glutathione (GSH) levels in high-fat diet-induced obese Wistar rats.

Data are expressed as mean ± S.E.M. n=7. Data were analyzed by one-way ANOVA followed by Bonferroni post hoc test. (*p<0.05 VS. CTL; #p<0.05 VS. OBS). Control (CTL), Melatonin (MEL), Obesity (OBS).

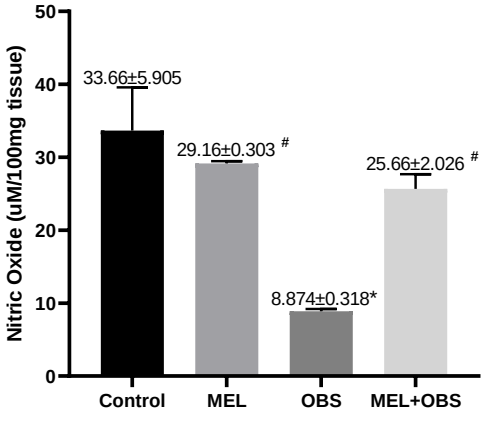

Figure 4: Effect of melatonin on nitric oxide concentration [NO] in high-fat diet-induced obese Wistar rats.
Data are expressed as mean ± S.E.M. n=7. Data were analyzed by one-way ANOVA followed by Bonferroni post hoc test. (*p<0.05 VS. CTL; #p<0.05 VS. OBS). Control (CTL), Melatonin (MEL), Obesity (OBS).

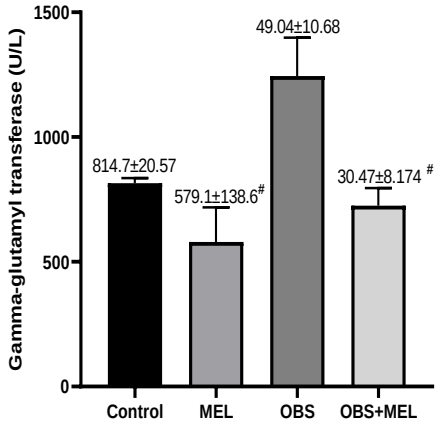

Figure 5: Effect of melatonin on gamma-glutamyl transferase concentration [GGT] in HFD-induced obese rats.
Data are expressed as mean ± S.E.M. n=7. Data were analyzed by one-way ANOVA followed by Bonferroni post hoc test. (#p<0.05 VS. OBS). Control (CTL), Melatonin (MEL), Obesity (OBS).

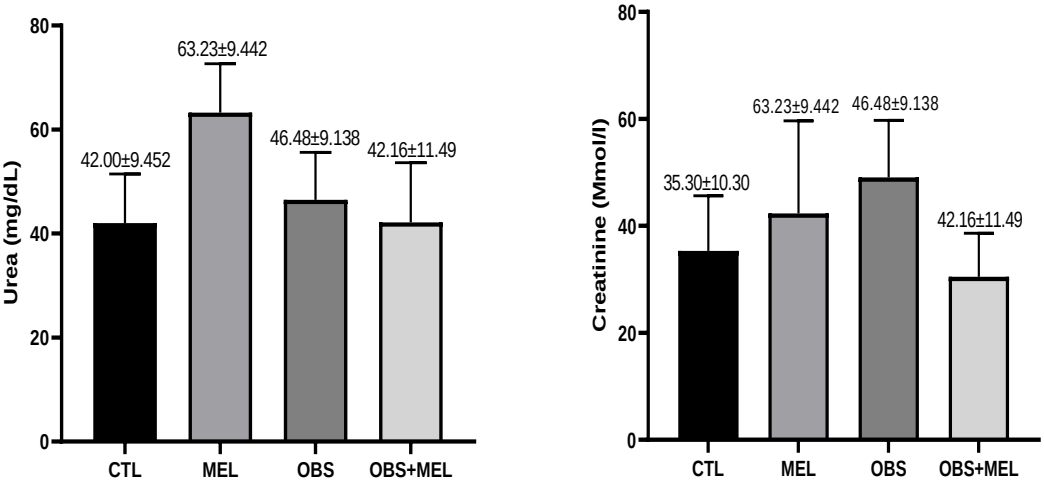

Figure 6: Effect of melatonin on plasma urea and plasma creatinine in high-fat diet-induced obese Wistar rats.
Data are expressed as mean ± S.E.M. n=7. Data were analyzed by one-way ANOVA followed by Bonferroni post hoc test. Control (CTL), Melatonin (MEL), Obesity (OBS).

DISCUSSION:

A high-fat diet (HFD) characterizes a significant risk factor for the onset of metabolic disorders, including hyperlipidemia, hypertension, diabetes mellitus, obesity, insulin dysfunction, and oxidative stress [39]. Among vital organs, the

kidneys are particularly susceptible to functional alterations induced by the influence of a high-fat diet [40]. This dietary pattern disrupts the delicate balance of energy metabolism, leading to the accumulation of lipids in unconventional anatomical locations and intracellular compartments [41]. The ectopic deposition of lipids within the renal tissue, in association with insulin resistance, has been linked to a gradual deterioration in renal function, [42, 43]. This harmful impact exerted by lipids on cells and tissues is referred to as lipotoxicity [2,44]. The present findings seek to assess the effect of melatonin on high-fat diet-induced obesity on kidney parameters in male Wistar rats. The results provide evidence that high-fat diet leads to decreased insulin sensitivity, disturbances in lipid profiles, increased body weight, oxidative stress, elevated concentrations of nitric oxide (NO) and gamma-glutamyl transferase (GGT) which were ameliorated upon melatonin treatment.

In a study reported by Charradi et al., HFD led to evident obesity, characterized by notable increases in body weight, abdominal fat accumulation, and elevated cholesterol, triglyceride, and phospholipid levels [45]. Notably, animals subjected to this HFD regimen did not exhibit a rise in fasting blood glucose levels. However, their area under the curve (AUC) increased, and their Kitt decreased, signifying glucose dysregulation and impaired insulin sensitivity [45].

These findings align with those reported by Higa et al. who observed a similar response in mice subjected to a cafeteria diet [46]. Furthermore, in a separate HFD investigation documented by Charradi et al., kidney mass remained unaffected, but there was a notable deposition of triglycerides without concurrent changes in cholesterol or phospholipid levels [47].

These outcomes parallel this current study, with increasing food consumption, body weight, fasting blood insulin levels, and insulin resistance, without a corresponding alteration in fasting blood glucose levels or renal mass. However, when melatonin was administered, the HFD group exhibited reduced food intake, body weight, insulin levels, and improved insulin sensitivity. The findings are consistent with a study of high-fat-fed mice treated with melatonin, which shows that there was an improvement in glucose tolerance and insulin sensitivity [48]. Furthermore, another investigation revealed that daily administration of melatonin led to a 54% reduction in body weight in high-fat-fed rats [49]. These reports indicated that melatonin mitigates the metabolic consequences of diet-induced obesity.

It has been reported that melatonin receptor 1 (MT1) signaling may regulate several protective metabolic responses, thus presenting the possibility that melatonin through MT1 may counter the metabolic effects of diet-induced obesity [50].

Numerous mice studies have provided evidence linking disrupted lipid metabolism to the onset of

kidney damage to high-fat diets [43,51,52]. Another animal model study depicting metabolic syndrome reported elevated leptin, triglyceride, reduced adiponectin levels and normal concentration of insulin [53]. Furthermore, these observations are in accordance with epidemiological studies that establish a direct relationship between elevated triglyceride levels and the predisposition to CKD [54], as well as the impact of altered lipid profile on the advancement of CKD [55].

In the HFD group in the current study, there was a significant increase in TC and TG levels, while the level of HDL was notably decreased. However, melatonin administration mitigated the alterations in lipid profiles induced by the HFD, restoring kidney lipid metabolism.

Previously, a study revealed that melatonin reduced body weight and low-density-lipoprotein (LDL) cholesterol in young Zucker diabetic fatty rats [56]. Additionally, another report conducted by Chen et al. demonstrated that melatonin enhances accumulation and metabolism of lipid in the liver [57]. It has also been observed that melatonin alleviates impaired insulin sensitivity, inflammation, and liver steatosis in HFD induced obese mice [58]. Clinical studies have also corroborated the positive impact of melatonin on lipid metabolism [59,60,61].

Lipotoxicity-induced oxidative stress has been associated with the development of various renal disorders [18,62]. Extended consumption of HFD leads to an overproduction of reactive oxygen species (ROS) within the kidneys, compounding the risk of renal injury due to ROS-induced oxidative stress [63]. Hyperlipidemia can result in the suppression of tissue and cellular antioxidant capacity, resulting in elevated levels of free radicals, along with decreased activities of antioxidant enzymes in both tissues and plasma [64,65]. Moreover, a study reported elevation in renal lipoperoxidation and carbonylation and as well as reduced levels of sulfhydryl radicals and the antioxidant enzymes functions after the administration of HFD confirming the induction of oxidative stress [48]. Similarly, other HFD studies also observed significantly elevated oxidative stress marker and decreased concentration of antioxidant markers [19, 66,67]. The present study, however, demonstrates that melatonin treatment effectively lowers MDA levels and elevates GSH levels, both of which were disrupted by the HFD. These findings support the scavenging role of melatonin as it serves as a protective agent against oxidative stress, safeguarding cells from its detrimental effects. Furthermore, additional studies reinforce this inquiry, indicating that melatonin has the potential to mitigate kidney injury by reducing free radicals, oxidative stress, and enhancing the activity of antioxidant enzymes in renal tissues [68,69,70].

Recent research has illuminated the role of dyslipidemia, a critical element within the multi-hit mechanism, in causing harm to healthy kidneys through lipotoxicity, oxidative stress, and inflammation [71]. This suggests that

disorders stemming from lipid accumulation may trigger oxidative stress or inflammation, both of which are essential factors in lipid-induced kidney damage. Oxidative stress and inflammation share a close relationship, jointly contributing to renal dysfunctions [72]. Hyperlipidemia can greatly increase ROS production in monocytes, acting as ROS activators in the kidneys. These activators stimulate macrophages to produce excessive oxygen radicals, potentially causing tissue dysfunction. Inflammation is a key player in most CKDs, with inflammatory factors being pivotal contributors to this stress. Inflammatory stress fosters kidney lipid accumulation, resulting in glomerular lesions, and kidney injury is positively linked to elevated serum proinflammatory cytokine levels [67,73,74]. Previous research has highlighted that dyslipidemia, systemic oxidative stress, and inflammation are resultant effects of prolonged exposure to HFD and ultimately contributes to CKD [75, 76]. A previous study has linked chronic renal diseases to reduced levels of Nitric oxide (NO) [77]. Another study indicated that HFD provokes renal injury, evidenced by increased plasma urea and uric acid levels, alterations in creatinine clearance, and the presence of protein in urine [47]. Consumption of a high-fat diet led to significant alterations in renal function, demonstrated by a reduction in glomerular filtration rate (GFR) and an increase in serum creatinine levels [78,79].

In the present study, HFD significantly reduced NO levels and increased gamma-glutamyl transferase (GGT) concentrations, which were restored upon melatonin treatment. However, there were no significant alterations in urea and creatinine levels. Melatonin is known for its potent anti-inflammatory properties, demonstrating remarkable efficacy in ameliorating a range of conditions associated with oxidative stress and inflammation in animal experiments [80,81].

The administration of melatonin has shown promise in mitigating oxidative stress, inflammation, and hypertension, while also slowing the deterioration of kidney function and structure in rats with renal ablation [82]. Melatonin exerts a direct scavenging effect against oxidative stress, leading to reduced levels of plasma nitric oxide, lipid peroxidation, and renal MDA and enhances glutathione level [83,84]. Moreover, melatonin has been reported to ameliorate oxidative stress in obesity and diabetes [85,86]. Given that obesity and diabetes often induce oxidative stress, which can detrimentally affect kidney function, melatonin's antioxidative effects hold the potential to mitigate oxidative stress-induced kidney disorders in individuals with metabolic disorders [87].

CONCLUSION:

These current findings suggest that high-fat diet leads to kidney lipotoxicity, characterized by oxidative stress, inflammation, altered lipid

profile, and metabolic disruptions that contribute to kidney damage. Furthermore, these results indicate that melatonin supplementation mitigates renal dysfunctions associated with obesity by reducing oxidative stress and inflammation while improving metabolic parameters.

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