Original Article

The hidden impact: How cigarette smoking and high fat diet alter microscopic structure of kidney

Ulfah Dian Indrayani [1*], Qorry Amanda[1]

ABSTRACT

Background

In low- and middle-income countries, smoking rates remain high while obesity is increasing due to poor diets rich in fat and sugar. Research has already linked smoking and high-fat diets to kidney injury, but we still don't understand the specific mechanisms. Our research aims to explain the relationship between these lifestyle factors and microstructural kidney damage.

Methods

We used 24 male Wistar rats (200-250 grams) and split them into four groups: a control group, a high-fat diet (HFD) group, a cigarette smoke exposure (CSE) group, and a group receiving both treatments. After 28 days, we collected data on several health markers, including blood pressure, urea, and creatinine. We also measured the diameters of the glomerulus and the proximal convoluted tubule (PCT). To do this, we used plethysmography for blood pressure and H&E staining to examine the kidney tissue samples.

Results

The control group had an average weight of 232.2 grams and an SBP of 83.17 mmHg. In the HFD group, we saw a significant increase in both weight (280.5 grams) and SBP (193.2 mmHg) with $p < 0.001$. The rats in the HFD + CSE group reached the highest numbers, averaging 311.5 grams and an SBP of 202.5 mmHg ($p < 0.001$). Urea levels also rose sharply, from 9.46 mg/dl in the control group to 46.34 mg/dl in the combined HFD + CSE group ($p < 0.001$). For the kidney structure, the glomerular diameter increased from 201.46 µm to 315.58 µm, while the PCT lumen diameter shrank from 46.55 µm to only 17.41 µm ($p < 0.001$).

Conclusions

Our findings show that smoking and high-fat diets cause serious damage to kidney health. These results suggest that lifestyle changes are very important to prevent further injury. To protect the kidneys, it is essential for patients to stop smoking and improve their daily diet.

KEYWORDS

High-Fat Diet (HFD); Smoking, Kidney Damage; Oxidative Stress; Renal Function; Glomerular Hypertrophy

INTRODUCTION

Smoking is becoming less common in high-income countries, but the rates are still high or even growing in low- and middle-income nations. Indonesia is a clear example, where more than 60% of men were smokers in 2021. Looking at real-world data, the danger of smoking is very clear in Indonesian patients. A case-control study on people with coronary heart disease in Indonesia found that smoking was the only lifestyle habit that stayed as an independent risk factor after a multivariate analysis. This means that even when other factors are considered, smoking alone causes a massive burden on the heart and other organs in this population. It shows that smoking is not just one of many problems, but a primary cause of systemic health damage for Indonesians. This habit also causes a huge financial loss. In 2012, smoking-related diseases cost $1.85 trillion worldwide, and 40% of that total burden was found in developing countries [1–4]. At the same time, obesity rates in Indonesia have doubled over the last twenty years. Today, about one-third of adults and one in five children are overweight or obese. This change is mostly due to people eating more processed foods that are high in fat and sugar, combined with a more sedentary lifestyle in the cities. [5–7].

Smoking and high-fat diets are well-known risk factors for many different health problems. They are often associated with heart disease

1. Histology Department of Medical Faculty, Universitas Islam Sultan Agung, Semarang, Indonesia

Correspondence

Ulfah Dian Indrayani. Histology Department of Medical Faculty, Universitas. Islam Sultan Agung, Semarang, Indonesia. email: ulfahdian@unissula.ac.id

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and chronic obstructive pulmonary disease (COPD). In addition, these lifestyle factors also lead to other serious conditions like hypertension and atherosclerosis [8,9]. These habits trigger oxidative stress and inflammation, which are the main mechanisms behind kidney damage [9,10](9,10). Smoking is linked to kidney damage even in its early, subclinical stages. We can see this through biomarkers such as KIM-1, NGAL, and NAG. Research also shows that smoking leads to chronic kidney disease (CKD) and other related renal problems. Both active smoking and second-hand smoke exposure correlate with higher urine albumin and serum creatinine levels. These results clearly indicate that kidney function is declining [10]. Research by Milla et al. (2021) suggests that polycyclic aromatic hydrocarbons (PAHs) found in cigarette smoke trigger the production of reactive oxygen species (ROS), which then attack cells across various organ systems through oxidative stress pathways [11]. Even though many previous studies this topic, the exact biological pathways through which smoking damages microanatomy of the kidneys are still not clearly understood.

High-fat diets are also linked to kidney injury and poor renal function, often marked by a rise in proinflammatory cytokines. Research by Yu et al. showed that these diets activate the Wnt/β-Catenin signaling pathway, which leads to renal damage. Furthermore, Prem and Kurian found that high-fat intake makes oxidative stress and mitochondrial dysfunction worse, especially in cases of ischemia-reperfusion injury. However, not all studies agree. For instance, Cheff et al. (2023) reported that a high-fat diet might actually protect the kidneys in specific models, such as hypertensive-diabetic mice [12,13].

So far, we still do not fully understand the exact biological pathways of how smoking and high-fat diets cause microstructural damage to the kidneys. It is important to map out these pathways so we can predict future health risks. This is a critical issue because smoking and poor eating habits are not likely to decrease anytime soon, and we need to be prepared for their long-term impact on patients.

METHODS AND MATERIALS

Experimental animal and groups

Twenty-four healthy male Wistar rats (200-250 g, 8-10 weeks old) were randomly assigned to four groups: (1) Control group was fed a standard diet; (2) High-fat diet (HFD) group was fed a high-fat diet, using 10 g of egg yolk, for 28 days; (3) Cigarette smoke exposure (CSE) group was exposed to cigarette smoke for 30 minutes daily over 28 days; and (4) Combination group (HFD+CSE) was subjected to both the high-fat diet and cigarette smoke exposure. The duration and protocol of the CSE (cigarette smoke exposure) study were conducted in accordance with the OECD Guidelines for the Testing of Chemicals, specifically the 28-day (subacute) inhalation toxicity study. Meanwhile, the high-fat diet using egg yolk followed the study by Budianto, which confirmed that a 28-day high-fat diet induced by duck egg yolk results in increased total cholesterol, low-density lipoprotein, high-density lipoprotein, and atherogenic index in experimental animals. [14,15]

Rats were maintained in a controlled environmental condition, with the temperature kept at 22 ± 3°C and relative humidity at 75 ± 5% to ensure the comfort and health of the animals during the study. These animals were housed on a 12-hour light/dark cycle, mimicking the natural pattern of day and night. The rats were provided ad libitum access to food and water, meaning they could eat and drink at any time as needed. These maintenance conditions were designed to create a stable and optimal environment for the experiment.

All animals in this study were treated in compliance with the latest version of Declaration of Helsinki by World Medical Association. The euthanasia procedure was carried out in accordance with the American Veterinary Medical Association (AVMA) guidelines.

Physiological and Biochemical Assessments

Body weight was monitored weekly using a digital scale to assess the health and general condition of the animals. Each rat was gently restrained, and the weight was recorded to the nearest gram. Systolic blood pressure was measured daily using a tail-cuff plethysmography device after acclimatizing the rats for 3 days prior to the study. Malondialdehyde (MDA) levels was measured at the end of the study from serum samples collected via retro-orbital puncture. Serum urea and creatinine level were assessed at the end of the study using an automated biochemical analyzer.

Histological Analysis

Kidneys were fixed in 10% formalin, embedded in paraffin, sectioned at 5-µm, and stained with hematoxylin-eosin (H&E). Morphometric evaluation, glomerular diameter and proximal convoluted tubule (PCT) lumen diameter, were measured in 10 randomly selected fields per sample using calibrated image analysis software (Image-J).

Statistical analysis

Data were expressed as mean(SD). Differences among groups were analyzed using one-way ANOVA with Tukey's post hoc test in SPSS version [XX]. A p-value < 0.05 was considered statistically significant. Normality was tested using the Shapiro-Wilk test, and variance homogeneity was assessed with Levene's test.

Ethical Clearence

This study was conducted in accordance with the relevant guidelines and regulations for animal research, and all procedures involving animal subjects were approved by the Ethical Review Board of the Faculty of Medicine, Universitas Islam Sultan Agung (approval no. 216/VII/2021).

RESULTS

A total of 24 Wistar rats were successfully followed from the beginning to the end of the study without any dropouts during the experimental period.

Body Weight, Systolic Blood Pressure (SBP), Urea , Creatinine Levels and Lipid Profile

Body weight significantly increased in all treatment groups compared to the control group. The control group had an average weight of 232.2 ± 5.12 grams. Rats in the HFD group gained significantly more weight, reaching 280.5 ± 2.35 grams ($p < 0.001$). Similarly, the CSE group exhibited an average weight of 283.2 ± 4.17 grams. The highest weight gain was observed in the HFD + CSE group, with an average of 311.5 ± 3.21 grams ($p < 0.001$), indicating an additive effect of the diet and cigarette smoke exposure on body weight.

The systolic blood pressure (SBP) was significantly lower in the control group compared to all treatment groups ($p < 0.001$). The control group had a mean SBP of 83.17 ± 2.14 mmHg. As illustrated in Figure 1 (Bar Chart), both the HFD and CSE groups exhibited significant increases in SBP to 193.2 ± 2.48 mmHg and 193.2 ± 2.78 mmHg, respectively, with no notable difference between them ($p > 0.05$). The highest SBP was observed in the HFD + CSE group, with an average of 202.5 ± 5.24 mmHg, showing an additive effect of these two factors.

Serum urea and creatinine levels also increased significantly across all treatment groups compared to the control ($p < 0.001$). As seen in Figure 2 (Boxplot), the control group had baseline urea levels of 9.46 ± 0.27 mg/dl. In contrast, urea levels in the HFD and CSE groups rose dramatically, reaching 41.02 ± 1.15 mg/dl and 42.15 ± 0.67 mg/dl, respectively. The HFD + CSE group had the highest urea levels at 46.34 ± 1.15 mg/dl, indicating a more substantial renal burden. Similarly, creatinine levels, represented in Figure 1, increased significantly in all treatment groups. The control group recorded a baseline creatinine of 0.79 ± 0.06 mg/dl. In the HFD group, creatinine levels increased to 3.28 ± 0.03 mg/dl, while the CSE group exhibited levels of 3.25 ± 0.03 mg/dl. The combined HFD + CSE group had the highest creatinine levels at 3.61 ± 0.09 mg/dl ($p < 0.001$), demonstrating a combined adverse effect on kidney function.

Figure 1 highlights the changes in lipid profile across all groups. The control group had an LDL level of 23.65 ± 2.42 mg/dl. In contrast, the HFD and CSE groups showed significant increases in LDL levels to 83.28 ± 1.50 mg/dl and 83.28 ± 1.94 mg/dl, respectively. The HFD + CSE group had the highest LDL level at 90.54 ± 1.60 mg/dl, indicating a cumulative effect of the treatments on lipid accumulation. HDL levels dropped significantly in all treatment groups. The control group had a baseline HDL level of 78 ± 1.86 mg/dl. However, HDL levels decreased to 29.25 ± 1.43 mg/dl in the HFD group, 28.23 ± 1.03 mg/dl in the CSE group, and 24.49 ± 1.22 mg/dl in the HFD + CSE group ($p < 0.001$), indicating reduced protective lipid levels. Triglyceride levels increased significantly in the HFD and CSE groups compared to the control. The control group had a triglyceride level of 78.21 ± 1.93 mg/dl, while the HFD group showed an increase to 143.3 ± 2.66 mg/dl ($p < 0.001$). The CSE group exhibited similar levels at 143.2 ± 2.78 mg/dl, and the HFD + CSE group recorded the highest triglyceride level at 148.2 ± 3.15 mg/dl.

Table 1 Physiological and Biochemical assessment

	Control Mean (SD)	HFD Mean (SD)	CSE Mean (SD)	CSE&HFD Mean (SD)
Body weight (g)	232.2 (5.11)	280.5 (2.34)	283.2 (4.16)	311.5 (3.20)
Systolic blood pressure (mmHg)	83.17 (2.13)	193.2 (2.48)	193.2 (2.78)	202.5 (5.24)
Ureum level (mg/dl)	9.46 (0.26)	41.02 (1.14)	42.15 (0.66)	46.34 (1.14)
Creatinine level (mg/dl)	0.78 (0.05)	3.27 (0.03)	3.25 (0.03)	3.61 (0.08)
LDL (mg/dl)	23.65 (2.41)	83.28 (1.49)	83.28 (1.94)	90.54 (1.60)
HDL (mg/dl)	78.00 (1.85)	29.25 (1.46)	28.23 (1.03)	24.49 (1.21)
Triglyseride (mg/dl)	78.21 (1.93)	143.3 (2.66)	143.2 (2.77)	148.2 (3.15)

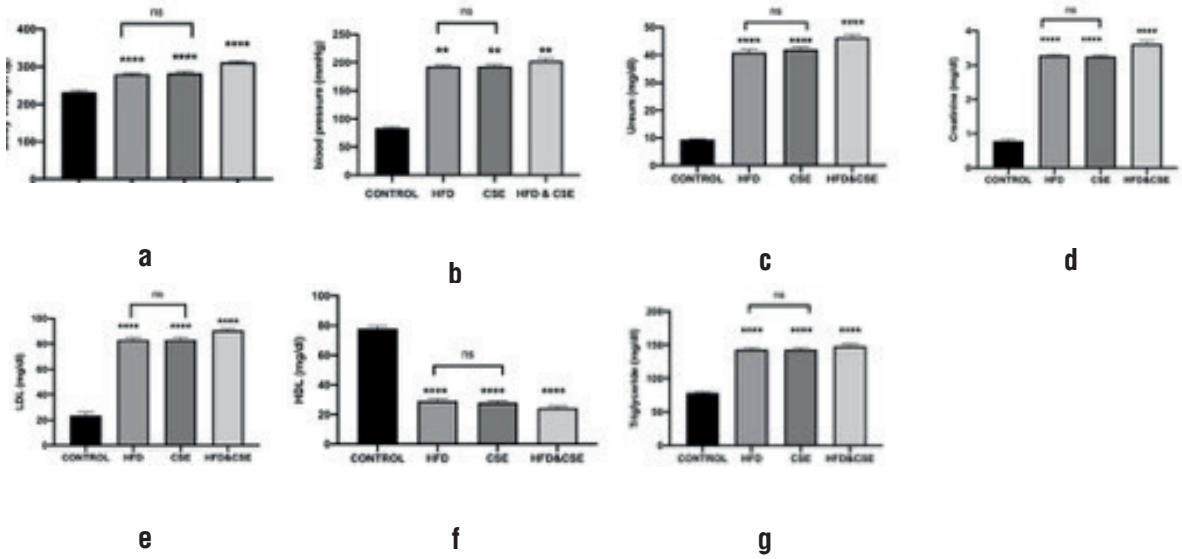

Figure 1 Differences among groups were analyzed using one-way ANOVA with Tukey's post hoc test in SPSS version [XX]. a. Body weight ; b. Systolic blood pressure; c. Serum ureum level; d. Serum creatinine; e. LDL level; f. HDL level; g. Triglyceride level. **** p-value < 0.05 was considered statistically significant. ns not significant.

Glomerular and Proximal Convoluted Tubule (PCT) Diameter

The data (Figure 2) reveal significant glomerular enlargement in response to HFD and CSE exposure. The control group (K0) had a mean glomerular diameter of 201.46 (15.10) µm, while rats in the HFD group (K1) showed an increase to 261.42 (9.54) µm, reflecting metabolic stress. The effect was even more pronounced in the CSE group (K2), with a mean diameter of 303.52 (12.58) µm, suggesting that oxidative stress from cigarette smoke significantly impacts kidney morphology. The largest increase was observed in the HFD + CSE group (K3) at 315.58 (10.46) µm, indicating a synergistic effect of these combined risk factors on glomerular hypertrophy.

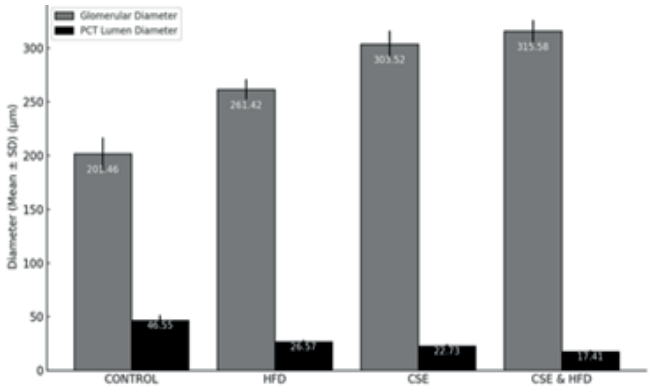

Figure 2 Bar graphs comparing the diameter of glomerulus and PCT Lumen

The PCT lumen diameters showed an opposite trend. The control group had a mean lumen diameter of 46.55 (4.84) µm, while the HFD group saw a sharp reduction to 26.57 (1.91) µm, possibly due to tubular damage from lipid accumulation. This decrease was further exacerbated in the CSE group, with a mean diameter of 22.73 (1.95) µm, and most significantly in the HFD + CSE group, which had a mean lumen diameter of just 17.41 (1.29) µm. This indicates profound tubular atrophy and impaired renal function when exposed to both dietary and environmental stressors. The findings suggest a dual mode of injury: glomerular hypertrophy in response to increased filtration demands, and PCT lumen narrowing indicating functional decline. The combination of HFD and CSE accelerates renal damage more than either factor alone, offering novel insights into how lifestyle risks can synergistically drive kidney disease progression.

DISCUSSION

Our results show that combining a high-fat diet (HFD) with cigarette smoke causes serious damage to the microscopic structure of the kidneys. The glomerular hypertrophy and tubular atrophy we found in our study match previous findings that show how chronic HFD and nicotine speed up kidney injury. This happens because of oxidative stress and inflammation. When fats build up and smoking causes oxidative damage, the renal tissues experience mesangial expansion and fibrosis. These changes eventually make the progression of kidney disease get worse much faster. [12,16].

Impact of Smoking and High-Fat Diet on Systolic Blood Pressure

One major result of our study is how smoking and an HFD work together to increase systolic blood pressure. These two factors cause molecular disruptions that damage kidney function. Specifically, smoking increases homocysteine (HCY) levels, which then triggers oxidative stress in the glomerular endothelial cells. This stress activates NF-κB, a transcription factor that raises the production of pro-inflammatory cytokines. This process leads to mesangial cell proliferation and glomerulosclerosis. As a result, the glomerular filtration rate (eGFR) decreases, sodium excretion is reduced, and blood pressure goes up. [17,18]

A diet high in saturated fats triggers the renin-angiotensin-aldosterone system (RAAS), which raises angiotensin II levels. This angiotensin II binds to AT1 receptors in the kidney cells and activates the MAPK/ERK pathway. As a result, the body reabsorbs more sodium through the Na+/K+-ATPase pump. This process increases blood volume and causes hypertension. There is also a physical side to this problem. When fat builds up around the kidneys (perirenal fat), it physically squeezes the organ. This mechanical pressure interferes with natriuresis and lowers nitric oxide (NO) production, leading to vasoconstriction and even higher blood pressure. [18,19] Therefore, smoking and high-fat diets drive up blood pressure by interfering with molecular pathways. These changes lead to kidney dysfunction, inflammation, and increased sodium retention. This shows why public health strategies must focus on both dietary habits and quitting smoking to effectively reduce heart-related risks.

Elevation of Urea and Creatinine as Indicators of Kidney Damage

High urea and creatinine levels found in this stude are closely linked to smoking and high-fat diets (HFD). These markers are important because they show that kidney filtration is impaired, which often signals the start of chronic kidney disease (CKD). The main cause is the oxidative stress and inflammation triggered by smoking. Specifically, nicotine and other toxins increase the production of reactive oxygen species (ROS), leading to direct damage in kidney cells. As this damage progresses, urea and creatinine levels continue to rise. Interestingly, we can detect early injury in smokers through biomarkers like NAG, NGAL, and

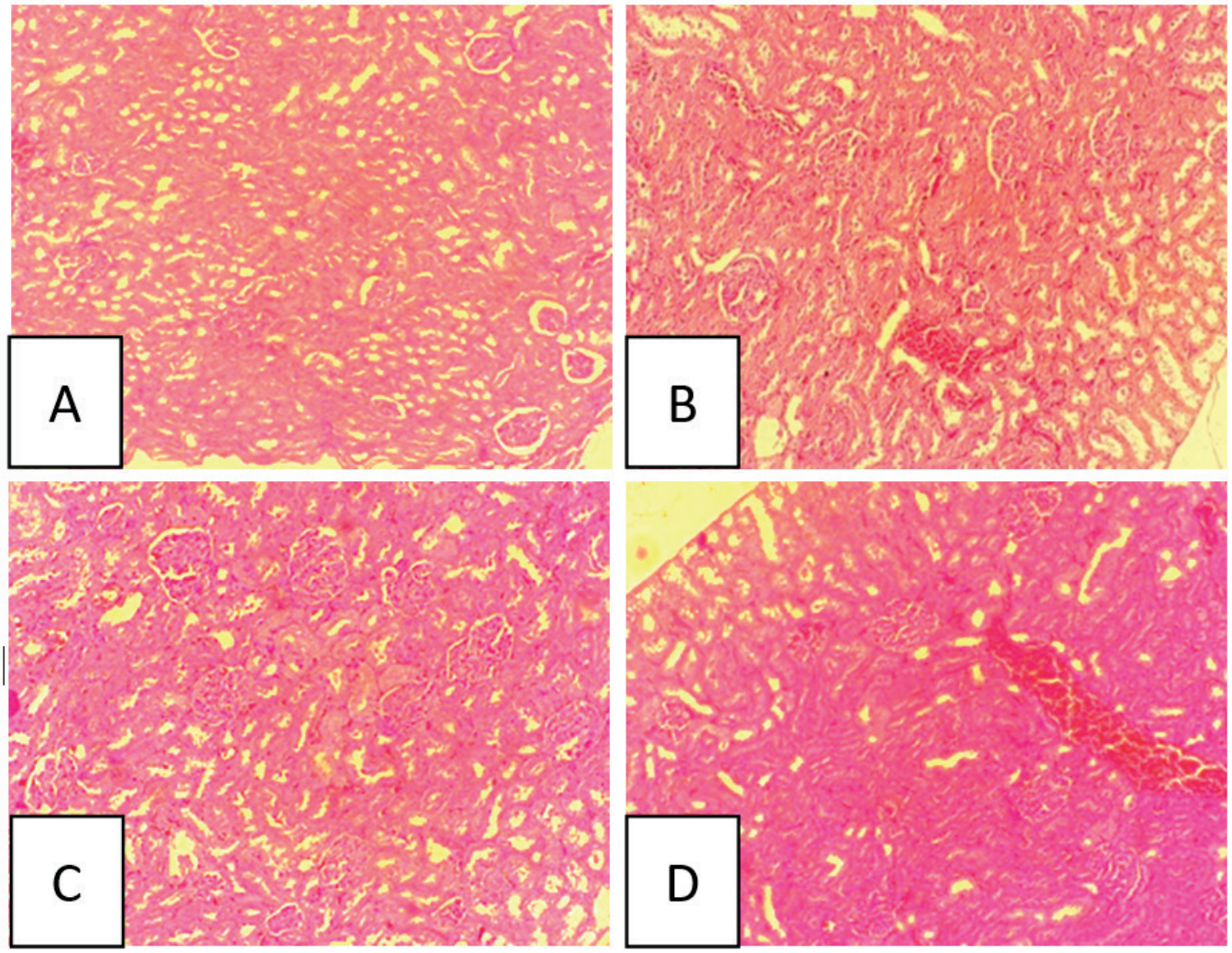

Figure 3 Histological Comparison of Renal Tissues Across Experimental Groups. A shows the kidney in the control group, characterized by uniformly sized glomeruli and predominantly open lumens of the proximal convoluted tubules (PCTs). B depicts the kidney from the high-fat diet (HFD) group, showing initial renal stress, with slight narrowing of the PCT lumens and larger glomeruli, indicating compensatory hypertrophy. C illustrates the kidney from the cigarette smoke exposure (CSE) group, with more pronounced glomerular enlargement and further narrowing of PCT lumens compared to Figures A and B. D represents the kidney from the combined HFD and CSE group, demonstrating significant glomerular hypertrophy and severely narrowed PCT lumens, reflecting the compounded effects of dual stressors.

KIM-1, which show that kidney damage often starts at a subclinical level. Such early changes are not just temporary; they often represent the beginning of a long-term decline. A longitudinal study by Tascón et al. showed that these biomarkers stayed high over a two-year period. This suggests that the kidney damage caused by smoking is stable and can eventually lead to permanent kidney failure if the patient is not treated. Smoking also activates the renin-angiotensin system (RAS), which increases levels of angiotensin II. This hormone causes the blood vessels to narrow and raises the blood pressure inside the glomerulus. It also triggers transforming growth factor-beta (TGF-β), a process that leads to fibrosis and makes the urea and creatinine levels even higher. Furthermore, angiotensin II makes the glomerular walls more permeable, causing protein to leak into the urine. This proteinuria damages the filtration units further and leads to glomerulosclerosis.

As these issues progress, the kidney's ability to filter waste continues to drop, making the overall impact on renal health much worse. [20,21]

Glomerular Hypertrophy and Impaired Kidney Filtration

Our study shows kidney damage is closely tied to molecular changes caused by high-fat diets (HFD) and smoking. HFD and nicotine both activate the Wnt/β-catenin signaling pathway in the kidney tissues. This increases the levels of Wnt ligands, such as Wnt1 and Wnt3a, and β-catenin, which causes cells to multiply too quickly and leads to glomerular hypertrophy. Nicotine makes this effect even stronger in the mesangial cells. Since these cells are vital for the glomerulus, their overgrowth eventually leads to scarring, or glomerulosclerosis. Furthermore, the combination of lipid buildup and nicotine creates oxidative stress and reactive oxygen species (ROS). These ROS trigger the release of inflammatory cytokines like IL-6 and TNF-α, which then damage the podocytes and tubules. These processes work together to drive the kidneys toward fibrosis and chronic disease.[11,21–23]

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Fibrosis and apoptosis also play a major part in damaging the tubules by causing extracellular matrix proteins to build up. These changes are driven by growth factors like EGFR and PDGFR-β. These signals cause the tissue to remodel and scar, which eventually leads to the narrowing of the PCT lumen and reduces the kidney's ability to filter blood. Furthermore, Angiotensin II can activate EGFR, which speeds up cell growth and makes the fibrosis even worse. This combination of oxidative stress, hormones, and scarring shows how lifestyle habits can damage the kidneys. In our study, the narrowing of the PCT lumen serves as a primary marker for this progressive disease [25].

Synergistic Effects of Smoking and HFD on Kidney and Cardiovascular Health

They share molecular pathways that increase oxidative stress and inflammation. For example, both factors activate the Wnt/β-catenin signaling pathway, causing glomerular hypertrophy and kidney dysfunction. We also see higher angiotensin II levels from HFD and smoking, which makes the kidneys reabsorb more sodium and raises blood pressure. This speeds up the progression of chronic kidney disease (CKD) [26]. Additionally, the narrowing of the PCT lumen shows that there is significant tubular damage. This damage disrupts how the kidneys reabsorb nutrients and starts more oxidative stress and fibrosis. These results prove that public health interventions must target both diet and smoking to prevent hypertension and kidney disease [27]. This idea is supported by Wardani et al. (2023), who found that combining different lifestyle changes clearly improved blood flow markers, such as the ankle brachial index, in Indonesian diabetic patients. Their research suggests that focusing on multiple lifestyle habits is a practical and effective way to help high-risk groups in this country. By addressing both smoking and poor diet together, we can better prevent the progression of chronic kidney disease and other cardiovascular problems [28].

Strength and Limitation

This study is important because it addresses a major public health issue in countries like Indonesia, where smoking and high-fat diets are very common. By using a controlled setup with male Wistar rats, we were able to create a clear framework to compare the histopathological effects of these two factors. Measuring body weight, blood pressure, and kidney biomarkers together helped us see the direct link between lifestyle and renal injury. However, there are

limitations. Since we used Wistar rats, the results may not apply perfectly to humans. Also, the 28-day period was relatively short, so future studies should look at the effects over a longer time. Researching molecular pathways, genetics, and physical activity would also give us a better understanding of kidney damage.

CONCLUSION

In summary, our study confirms that combining a high-fat diet with smoking speeds up kidney damage. This happens through increased oxidative stress, inflammation, and direct injury to the cells. These findings support the idea that changing lifestyle habits, such as quitting smoking and improving the diet, is essential to prevent chronic kidney disease and heart problems.

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