2024, Retos, 51, 1194-1209

The Effect of Exercise Intensity on Anthropometric Parameters and Renal Damage in High Fructose-Induced Mice

El efecto de la intensidad del ejercicio sobre los parámetros antropométricos y el daño renal en ratones con alto contenido de fructosa

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Abstract. Excessive fructose intake disrupts carbohydrate and lipid metabolism in the kidney, resulting in kidney injury. Exercise has proven to improve the renal fatty acid metabolism, but the effect of various exercise intensities in preventing renal disorders is still unknown. The purpose of this study is to analyze the effect of various exercise intensities on anthropometric parameters and renal damage in high fructose-induced mice. The subjects were thirty-six male mice (20–30 g), aged 8 weeks were obtained and randomly assigned into 4 groups: HFr-Sed (sedentary), HFr-Ex_1 (low-intensity exercise), HFr-Ex_2 (moderate-intensity exercise), and HFr-Ex_3 (high-intensity exercise). They were fed standard chow and high fructose solution (30%), per-oral, ad libitum for 8 weeks. The exercised groups underwent swimming, with 80% maximum duration/session, 3x/week, for 8 weeks. The result showed that there were significant differences in body weight ($p < 0.001$), body length ($p = 0.001$), Lee index ($p = 0.020$), Body Mass Index (BMI) ($p = 0.004$), and serum creatinine (SCr) level ($p < 0.001$). However, the glomerulosclerosis index and interstitial fibrosis degree were not significantly different in all groups. It can be concluded that various intensities of exercise affect the body composition and SCr level, especially moderate-intensity exercise, but do not impact the improvement of the histological kidney in high fructose-induced mice.

Keyword: Exercise, healthy lifestyle, obesity, renal histology.

Resumen. La ingesta excesiva de fructosa altera el metabolismo de los carbohidratos y lípidos en el riñón, lo que provoca lesión renal. Se ha demostrado que el ejercicio mejora el metabolismo renal de los ácidos grasos, pero aún se desconoce el efecto de diversas intensidades de ejercicio en la prevención de los trastornos renales. El propósito de este estudio es analizar el efecto de varias intensidades de ejercicio sobre los parámetros antropométricos y el daño renal en ratones inducidos con alto contenido de fructosa. Los sujetos fueron treinta y seis ratones macho (20–30 g), de 8 semanas de edad, y se asignaron aleatoriamente en 4 grupos: HFr-Sed (sedentario), HFr-Ex1 (ejercicio de baja intensidad), HFr-Ex2 (ejercicio moderado- ejercicio de alta intensidad) y HFr-Ex3 (ejercicio de alta intensidad). Fueron alimentados con comida estándar y una solución alta en fructosa (30%), por vía oral, ad libitum durante 8 semanas. Los grupos ejercitados se sometieron a natación, con un 80% de duración máxima/sesión, 3 veces por semana, durante 8 semanas. El resultado mostró que hubo diferencias significativas en el peso corporal ($p < 0,001$), longitud corporal ($p = 0,001$), índice de Lee ($p = 0,020$), índice de masa corporal (IMC) ($p = 0,004$) y creatinina sérica (SCr).) nivel ($p < 0,001$). Sin embargo, el índice de glomeruloesclerosis y el grado de fibrosis intersticial no fueron significativamente diferentes en todos los grupos. Se puede concluir que varias intensidades de ejercicio afectan la composición corporal y el nivel de SCr, especialmente la intensidad del ejercicio moderado, pero no tuvieron impacto en la mejora del riñón histológico en ratones con alto contenido de fructosa.

Palabras clave: Ejercicio, estilo de vida saludable, obesidad, histología renal.

Fecha recepción: 27-07-23. Fecha de aceptación: 07-11-23

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Introduction

Fructose is one of carbohydrates that is widely used all over the world, including in Indonesia (Atmarita, 2018; Ebrahimpour-Koujan, 2020). Excessive consumption of fructose may leads to the development of several diseases such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, insulin resistance, and cardiovascular diseases (Khorshidian et al, 2021; Malik & Hu, 2015; Ter Horst & Serlie, 2017). In the world, China is the country with the highest carbohydrate usage (67.0%), followed by South Asia (65.4%) and Africa (63.3%) (Dehghan et al, 2017). Prospective and meta-analytical studies reported that high-carbohydrate diets increased the development of T2DM, stroke, coronary heart disease (CHD), and mortality risk in Asia, Europe, and the US (Seidelmann et al, 2018; Hardy et al, 2020). A cross-sectional study from 13 provinces in Indonesia reported that high carbohydrate intake enhances the risk of overweight or obesity among adults (Aprilia & Widyaningsih, 2019).

Numerous organs can be affected by high fructose ingestion, comprising the kidney, liver, skeletal muscles, and pancreas (Zhang et al, 2017). Sustained exposure of excessive fructose might lead to renal injury and subsequent to renal dysfunction in chronic kidney disease (Nakagawa et al, 2020). Kidneys are vulnerable to fructose-induced damage, which promotes ATP depletion, oxidative stress, inflammation and fat accumulation (Nakagawa et al, 2020; Bier et al, 2022). These conditions cause endothelial dysfunction, vascular injury, inflammation, and fibrosis that lead to glomerular hypertension and tubulointerstitial injury (Nakagawa et al, 2020; Nakagawa et al, 2021). Several studies reported that disturbance of fatty acid metabolism in kidney leads to progressive renal impairment (Gai et al, 2019; Jang et al, 2020). Bier et al. (2022) found that high fructose diets affect the kidney through upregulation of fructokinase and fructose transporters, induce triglyceride accumulation, increase the expression

of ChREBP, and other genes involved in carbohydrate and fat metabolism (Bier et al, 2022). Therefore, alternative efforts should be needed to overcome the effects of high fructose consumption on the body, particularly in the kidney.

Exercise provides several health benefits in the prevention and management of noncommunicable diseases, i.e. hypertension, diabetes, dyslipidemia, and also improves obesity and insulin resistance (Luan et al, 2019; Shakil-ur-Rehman et al, 2017; Esmailiyan et al, 2021). The proper dose of exercise should be implemented to reach the optimum result and has an impact on regulating body weight, prevention, and treatment of diseases (Anderson & Durstin, 2019; Jakicic et al, 2019). Exercise that was performed for 10–60 min/day, 5 days/week for 8 weeks, provided protective effects on the early progression of diabetic nephropathy in Zucker diabetic rats by upregulating Nitric Oxide Synthases (NOS) expression, repressing NADPH oxidase activity, and -oxoaldehydes in the kidney (Ito et al, 2015). Another study showed inhibition of glomerulosclerosis and interstitial fibrosis progressions through ameliorating renal collagen turnover and the renin-angiotensin system (RAS) in chronic renal failure rats treated with 12-weeks exercise at 20 m/min, 60 min/day, and 5 days/week (Yamakoshi et al, 2021).

Exercise intensity is essential in preventing the deleterious effects of certain diseases (Bond et al, 2015). Low-intensity exercise improves renal damage and epithelial-mesenchymal transformation in hypertensive rats (Luo et al, 2023). Moderate-intensity exercise plays a role in cardiac function of hypertensive mice by preventing mitochondrial damage (Mi et al, 2019). Besides that, high-intensity exercise failed to ameliorate the hypertensive renal injury (Luo et al, 2023). High-intensity exercise may stimulate nitric oxide production, leading to vascular damage (Zhang & Gao, 2021).

However, comparisons of the effects of various exercise intensities on anthropometric parameters and renal damage in carbohydrate-induced diseases have not been revealed. Based on this issue, this study aims to investigate the effect of low-, moderate-, and high- intensity exercises on anthropometric parameters, SCr levels, and histological changes of the kidney in high fructose-induced mice.

Materials and Methods

Ethical approval

This study has met animal welfare principles by the European Convention for the Protection of Vertebrate Animals. The Health Research Ethics Commission, Faculty of Medicine, Universitas Airlangga has authorized all of the research procedures with the registration number 90/EC/KEPK/FKUA/2022.

Research design

This study was a true experimental study with a randomized posttest only control group design. Thirty-six male mice (*Mus musculus*), weighing 20–30 g, were obtained at 8 weeks of age and maintained on ambient temperature of 26±2°C, humidity of 50-60% under 12:12-h light-dark cycle at the Animal Laboratory of Medical Physiology and Biochemistry Department, Faculty of Medicine, Universitas Airlangga. They were fed standard chow BR1 (PT. Japfa Comfeed, 2013) with 4100 Kcal/kg energy, 21% protein, 3-7% fat, 0.9-1.1% calcium, and 0.6-0.9% phosphor. All animals were exposed by high carbohydrates using 30% fructose solution, per-oral, ad libitum for a period of 8 weeks (Kanuri et al, 2011; Wulansari, 2018). Food and drink were provided daily at 07.00 a.m. with a dose of 20 gram/mice per day, and body weight was measured every 2 weeks (Fauzi et al, 2022). Mice were euthanized 24 hours after the last intervention. The blood and right kidneys were taken for examination of SCr level and histological preparation, respectively.

Protocol of exercise

After a week of acclimatization, mice were randomly divided into 4 groups: HFr-Sed (n=9, high fructose-sedentary group), HFr-Ex_1 (n=9, high fructose-low intensity exercise group), HFr- Ex_2 (n=9, high fructose-moderate intensity exercise group), and HFr-Ex_3 (n=9, high fructose-high intensity exercise group). The exercised groups were adapted to swim for 7 days without load before intervention. The exercise groups underwent swimming for 80% of the maximum duration/session three times a week, at 03.00 pm during 8 weeks (Kim et al, 2013; Nogueira et al, 2017; Pranoto et al, 2020). Differences in intensity between exercise groups using weights placed on the mice's tails. Swimming exercise was carried out with a load of 3% of body weight for low-intensity exercise (Rahayu et al, 2021), 6% of body weight for moderate-intensity exercise (Antoni et al, 2022), and 9% of body weight for high-intensity exercise (Rahayu et al, 2021). The water temperature was maintained between 30-32°C (Evangelista et al, 2003). The maximum durations of low-, moderate-, and high-intensity exercises were 15 minutes, 12.5 minutes, and 10 minutes, respectively.

Anthropometric measurement

Body weight and length were measured prior to the first and after last intervention using digital harnic HL-3650 heles (Rejeki et al, 2021). The Lee index and body mass index were used to estimate obesity in animals. The Lee index was measured by dividing the cube root of the body weight (g) by the naso-anal length (mm) and multiplying the whole expression by 10 (Bernandis & Patterson, 1968). Obese mice were considered if their weight was > 0.3. The BMI was calculated by dividing the weight (g) by the length (cm^2) (Novelli et al, 2007).

SCr level assessment

SCr levels were measured through 2-3 mL of blood from a cardiac puncture using the Enzyme-Linked Immunosorbent Assay (ELISA) kit (Catalogue Code:

MOFI00744, Mouse Cr (Creatinine) ELISA Kit, Assay Genie., Ireland) with an assay range of 1.25 - 80 nmol/mL and a kit sensitivity of 0.75 nmol/mL.

Histological Analysis

The right kidneys were collected after euthanization. Kidneys were fixed in 10 % neutral buffered formalin for at least 48 h at room temperature. The kidney tissues were embedded in paraffin wax, and longitudinally sectioned at 4 µm using microtome (Layton & Bancroft, 2019). To measure the index of glomerulosclerosis (IGS) and the interstitial fibrosis degree, paraffin-embedded tissues were stained with Periodic Acid-Schiff and Masson's Trichrome staining, respectively. The IGS and the ratio of the relative interstitial volume were estimated by methods previously described (Hu et al, 2020).

Level of glomerulosclerosis were identified by a 0–4 scale from 10 visual fields with 400x magnification as follows: 0 (a normal glomerulus), 1 (loss of 1–25% glomerular capillary area), 2 (loss of 26–50% glomerular capillary area), 3 (loss of 51–75% glomerular capillary area), and 4 (loss of > 75% glomerular capillary area). The IGS was calculated based on the following formulation.

The degree of interstitial fibrosis was calculated by the interstitium of the renal cortex percentages per unit area, except for the blood vessels and glomerulus. The mean values of relative interstitial volume (RIV) were calculated from 10 visual fields with 400x magnification.

The histological preparations were examined and captured using an Olympus CX31 microscope equipped with an Olympus DP 22 color camera and cellSens software. Images from each animal were measured using ImageJ 1.53k and Adobe Photoshop 21.0.0 versions.

Statistical Analysis

Data were presented as mean ± SD and analyzed by SPSS (version 25, IBM). Shapiro-Wilk and Levene's tests were used to test the normality and homogeneity of variance, respectively. Comparisons between groups were performed using the one-way ANOVA test, followed by the least significant difference (LSD) post hoc test or the Kruskal Wallis test followed by Mann-Whitney test, as appropriate. A paired t-test or Wilcoxon Signed Rank test was used to analyze the comparison between two dependent samples. The p-values < 0.05 were considered statistically significant.

Results

The analyses of the exercise effect with different intensities on body weight and length, Lee Index, BMI, serum creatinine, index of glomerulosclerosis, and degree of interstitial fibrosis in high fructose-induced mice are displayed in Table 1 and Figure 1. The comparisons of pre- and post-exercises with different intensities on anthropometric parameters in all groups are presented in Table 2 and Figure 1.

$$\text{IGS} = \frac{(4 \times \text{number of level 4}) + (3 \times \text{number of level 3}) + (2 \times \text{number of level 2}) + (1 \times \text{number of level 1}) \text{ glomeruli}}{\text{Total number of glomeruli}}$$

Table 1.
The effects of swimming exercise with different intensities on anthropometric parameters, creatinine level, and histology of the kidney in high fructose-induced mice.

Parameter	Mean ± SD					p-value
	All groups (N=36)	HFr-Sed (N=9)	HFr-Ex_1 (N=9)	HFr-Ex_2 (N=9)	HFr-Ex_3 (N=9)	
Body weight pre-exercise (g)	23.56 ± 1.60	24.44 ± 1.81	23.11 ± 1.27	23.56 ± 1.59	23.11 ± 1.54	0.245
Body weight post-exercise (g)	31.44 ± 3.65	34.67 ± 3.71	32.78 ± 1.86	28.56 ± 2.30*†	29.78 ± 3.11*†	**<0.001**
Delta Body Weight (g)	7.89 ± 3.23	10.22 ± 2.28	9.67 ± 2.12	5.00 ± 2.00*†	6.67 ± 3.35*†	**<0.001**
Body length pre-exercise (cm)	8.79 ± 0.43	8.86 ± 0.56	8.90 ± 0.33	8.67 ± 0.37	8.73 ± 0.45	0.651
Body length post-exercise (cm)	9.70 ± 0.48	10.22 ± 0.60	9.38 ± 0.21*	9.57 ± 0.35*†	9.62 ± 0.18*†	**0.001**
Lee Index pre-exercise (g/mm)	0.32 ± 0.02	0.32 ± 0.02	0.32 ± 0.01	0.33 ± 0.02	0.32 ± 0.02	0.612
Lee Index post-exercise (g/mm)	0.32 ± 0.02	0.31 ± 0.02	0.34 ± 0.01*	0.32 ± 0.02†	0.32 ± 0.02†	**0.020**
BMI pre-exercise (g/cm^2)	0.31 ± 0.03	0.32 ± 0.04	0.29 ± 0.02	0.32 ± 0.03	0.30 ± 0.03	0.230
BMI post-exercise (g/cm^2)	0.34 ± 0.04	0.33 ± 0.04	0.37 ± 0.02*	0.31 ± 0.04†	0.32 ± 0.04†	**0.004**
Serum Creatinine (nmol/mL)	36.80 ± 11.52	50.60 ± 8.70	37.54 ± 8.16*	24.93 ± 1.65*†^	34.13 ± 7.37*	**<0.001**
Index of Glomerulosclerosis (IGS)	2.23 ± 0.25	2.10 ± 0.21	2.21 ± 0.26	2.28 ± 0.20	2.33 ± 0.30	0.236
Degree of interstitial fibrosis (%)	0.47 ± 0.85	0.29 ± 0.30	0.71 ± 1.33	0.24 ± 0.22	0.62 ± 1.03	0.743

HFr-Sed, high fructose-sedentary group; HFr-Ex_1, high fructose-low intensity exercise group, HFr- Ex_2, high fructose-moderate intensity exercise group, HFr-Ex_3, high fructose-high intensity exercise group.
(*) significant vs. HFr-Sed group; (†) significant vs. HFr-Ex_1; (^) significant vs. HFr-Ex_3, with one-way ANOVA test or Kruskal Wallis test.

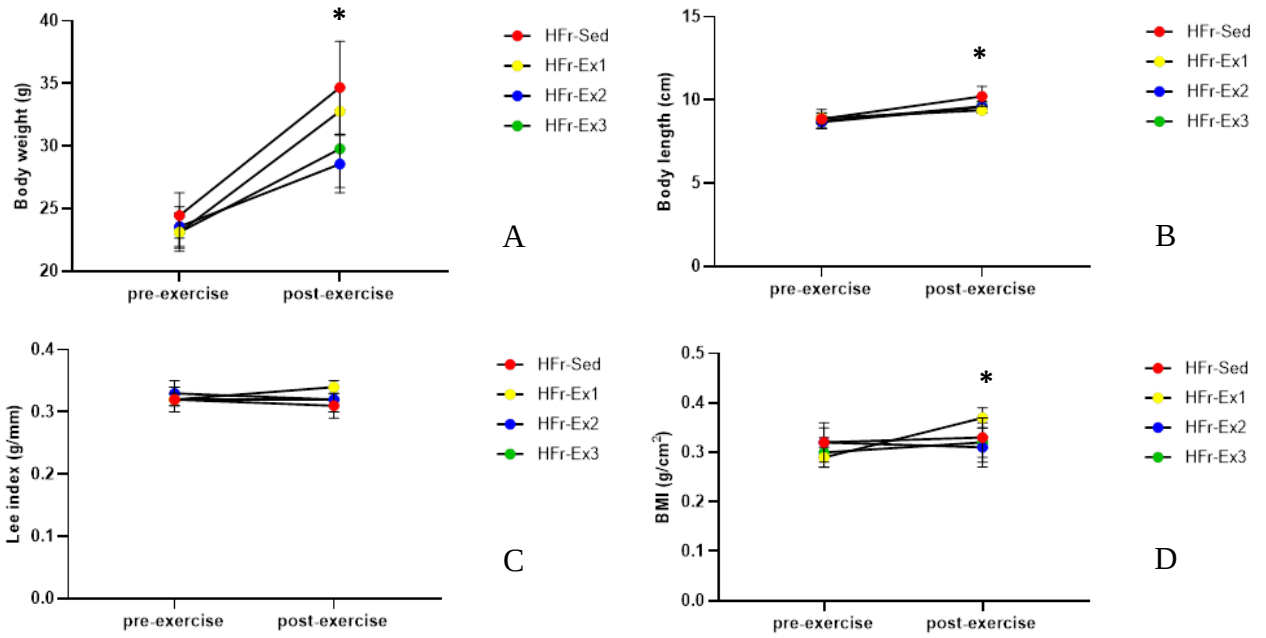


Figure 1. The effect of high fructose and exercise on body weight, body length, Lee Index and BMI. A. Pre-and post-exercise body weight, B. Pre-and post-exercise body length, C. Pre-and post-exercise Lee Index, D. Pre-and post-exercise BMI (*significant vs. pre-exercise).

Table 2.
The analysis of pre- and post-swimming exercise with different intensities on anthropometric parameters in high fructose-induced mice.

Parameters	p-value	Effect Size (95% CI)
Body weight (g)	<0.001*	2.80 (2.15 - 3.45)
HFr-Sed (N=9)	<0.001*	3.51 (2.03 - 4.98)
HFr-Ex$_1$ (N=9)	<0.001*	6.07 (3.88 - 8.26)
HFr-Ex$_2$= (N=9)	<0.001*	2.53 (1.29 - 3.77)
HFr-Ex$_3$= (N=9)	<0.001*	2.72 (1.44 - 4.00)
Body length (cm)	<0.001*	2.00 (1.43 - 2.56)
HFr-Sed (N=9)	0.007*	2.34 (1.14 - 3.54)
HFr-Ex$_1$ (N=9)	0.012*	1.74 (0.65 - 2.82)
HFr-Ex$_2$= (N=9)	0.007*	2.50 (1.27 - 3.73)
HFr-Ex$_3$= (N=9)	0.007*	2.60 (1.34 - 3.85)
Lee Index (g/mm)	0.574	-
HFr-Sed (N=9)	0.167	-
HFr-Ex$_1$ (N=9)	0.011*	2.00 (0.87 - 3.13)
HFr-Ex2= (N=9)	0.014*	-0.50 (-1.44 - 0.44)
HFr-Ex$_3$= (N=9)	0.248	-
BMI (g/cm2)	0.001*	0.85 (0.37 - 1.33)
HFr-Sed (N=9)	0.280	-
HFr-Ex$_1$ (N=9)	0.007*	4.00 (2.40 - 5.60)
HFr-Ex$_2$= (N=9)	0.750	-
HFr-Ex$_3$= (N=9)	0.086	-

HFr-Sed, high fructose-sedentary group; HFr-Ex$_1$, high fructose-low intensity exercise group, HFr- Ex$_2$, high fructose-moderate intensity exercise group, HFr-Ex$_3$, high fructose-high intensity exercise group.
(*) significant vs. pre-exercise with Paired t-test or Wilcoxon Signed Rank test.

The analysis indicated that the body weight and length, Lee Index, and BMI among groups were not significantly different during the early study (p>0.05) (Table 1). This implies that the conditions of all mice in the initial study had similar starting points, therefore the experimental bias can be avoided in this study.

Based on Table 1, high fructose intake affects body weight and length. The post-exercise body weights of the HFr-Ex$_2$ (ES= -1.98, 95% CI: -3.11 to -0.85, p<0.001) and HFr-Ex$_3$ (ES = -1.43, 95% CI: -2.46 to -0.39, p=0.001) groups were significantly lower than the HFr-Sed group. Both of those groups were also markedly lower than the HFr-Ex$_1$ group (HFr-Ex$_2$ ES = -2.02, 95% CI: -3.15 to - 0.88, p=0.003; and HFr-Ex$_3$ ES = -1.17, 95% CI: -2.17 to -0.17; p=0.032), where the HFr-Ex$_2$ group had the lowest body weight among groups. The post-exercise body length of all exercised groups significantly lower compared to HFr-Sed group (HFr-Ex$_1$ ES= -1.87, 95% CI: -2.98 to -0.76, P=0.004; HFr-Ex$_2$ ES= -1.32, 95% CI: -2.34 to -0.30, p=0.004; HFr-Ex$_3$ ES= -1.36, 95% CI: -2.38 to -0.33, p=0.005) with the lowest body length was found in HFr-Ex$_1$ group. The groups of HFr-Ex$_2$ (ES= 0.66, 95% CI: -0.29 to 1.61, p= 0.032) and HFr-Ex$_3$ (ES= 1.23, 95% CI: 0.22 to 2.23, p=0.020) had significantly higher body lengths than the HFr-Ex$_1$ group.

In comparison between the pre- and post-exercise body weight and length, there were significant differences in all groups (Table 2). All body weights and lengths were markedly increased at the end of the study (p< 0.001 in each group for body weight, and p=0.007 in HFr-Sed; p=0.012 in HFr-Ex$_1$; p=0.007 in HFr-Ex$_2$; p=0.007 in HFr-Ex$_3$ for body length) with the HFr-Sed group showed the greatest increase in both parameters (10.22 $\pm$ 2.28 g and 1.37 $\pm$ 0.54 cm). Whereas the lowest increase of body weight and length were found in the HFr-Ex$_2$ (5.00 $\pm$ 2.00 g) and HFr-Ex$_1$ groups (0.48 $\pm$ 0.25 cm), respectively. The changes of body weight showed significant differences in HFr-Ex$_2$ (ES= -2.43, 95% CI: -3.65 to -1.22, p< 0.001) and HFr-Ex$_3$ (ES= -1.24, 95% CI:-2.25 to -0.23, p= 0.005) groups compared to HFr-Sed as well as HFr-Ex$_2$ (ES= -2.27, 95% CI: -3.45 to -1.08, p< 0.001) and HFr-Ex$_3$ (ES= -1.07, 95% CI= -2.06 to -0.08, p= 0.016) groups compared to HFr-Ex$_1$ (Table 1).

At the end of study, the highest and lowest Lee Index were found in HFr-Ex$_1$ and HFr-Sed groups, respectively.

There were significant differences of Lee Index between HFr-Sed vs. HFr-Ex_1 (ES= 1.90, 95% CI: 0.79 to 3.01, p= 0.007), HFr-Ex_1 vs. HFr-Ex_2 (ES= -1.27, 95% CI: -2.28 to -0.25, p= 0.012), and HFr-Ex_3 (ES= -1.27, 95% CI: -2.28 to -0.25, p= 0.013) (Table 1). The analysis of the pre- and post-exercise Lee Index exhibited significantly increased in the HFr-Ex_1 group (P= 0.011) and markedly decreased in the HFr-Ex_2 group (P=0.014) (Table 2).

Table 1 indicates that the highest and the lowest post-exercise BMI were found in HFr-Ex_1 and HFr-Ex_2 groups, respectively. There were significant differences of post-exercise BMI between HFr-Sed vs. HFr-Ex_1 (ES= 1.27, 95% CI: 0.25 to 2.28, p= 0.009), HFr-Ex_1 vs. HFr-Ex_2 (ES= -1.90, 95% CI= -3.01 to -0.79, p= 0.003), and HFr-Ex_3 (ES= -1.58, 95% CI: -2.64 to -0.52, p=0.005) groups. All body mass indexes seem to be increased by the end of the study with the exception of the HFr-Ex_2 group which slightly decreased and only the BMI of HFr-Ex_1 group was found increased significantly (p= 0.007) (Table 2).

The post-exercise SCr levels had significant differences among groups. SCr levels were lower in all exercise groups than control group where the HFr-Ex_2 has the lowest SCr level (Table 1 and Fig. 2). The post hoc test results showed that there were significant differences in SCr levels between HFr-Sed vs. HFr-Ex_1 (ES= -1.55, 95% CI: -2.60 to -0.50, p=0.007), vs. HFr-Ex_2 (ES= -4.1, 95% CI: -5.73 to -2.47, p<0.001) and vs. HFr-Ex_3 (ES= -2.04, 95% CI:-3.18 to -0.90, p=0.002); HFr-Ex_1 vs. HFr-Ex_2 (ES= -2.14, 95% CI: -3.30 to -0.98, p<0.001); and HFr-Ex_2 vs. HFr-Ex_3 (ES= 1.72, 95% CI: 0.64 - 2.81, p<0.001).

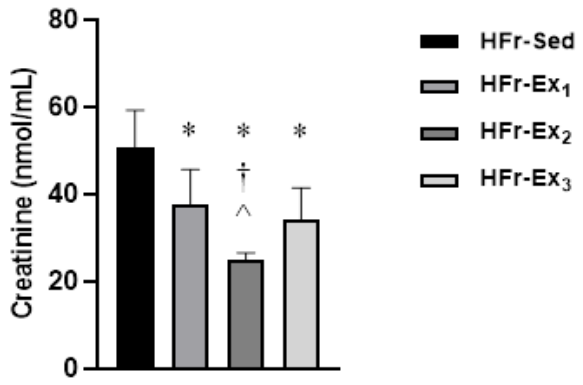


Figure 2. The effect of high fructose and exercise on SCr level. (*) Significant vs. HFr-Sed group; (†) significant vs. HFr-Ex_1; (^) significant vs. HFr-Ex_3.

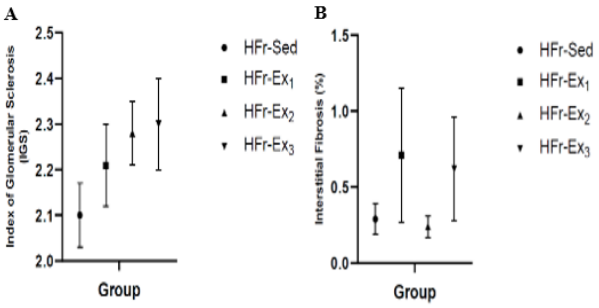
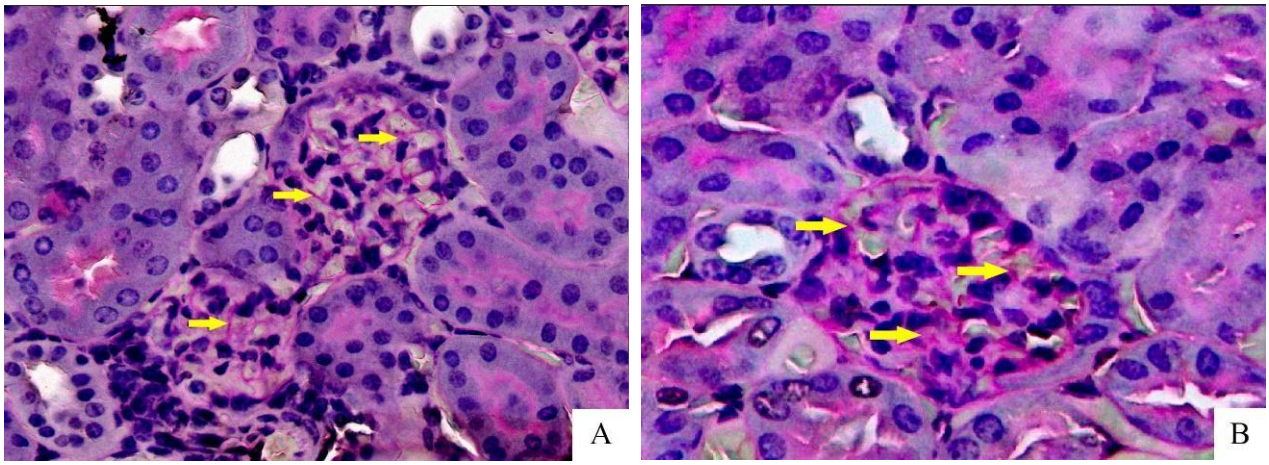


Figure 3. Represents The Index of Glomerulosclerosis (A), and The Ratio of Relative Interstitial Volume (B) of each group. HFr-Sed (sedentary), HFr- Ex_1 (low-intensity exercise), HFr- Ex_2 (moderate-intensity exercise), HFr- Ex_3 (high-intensity exercise) groups.



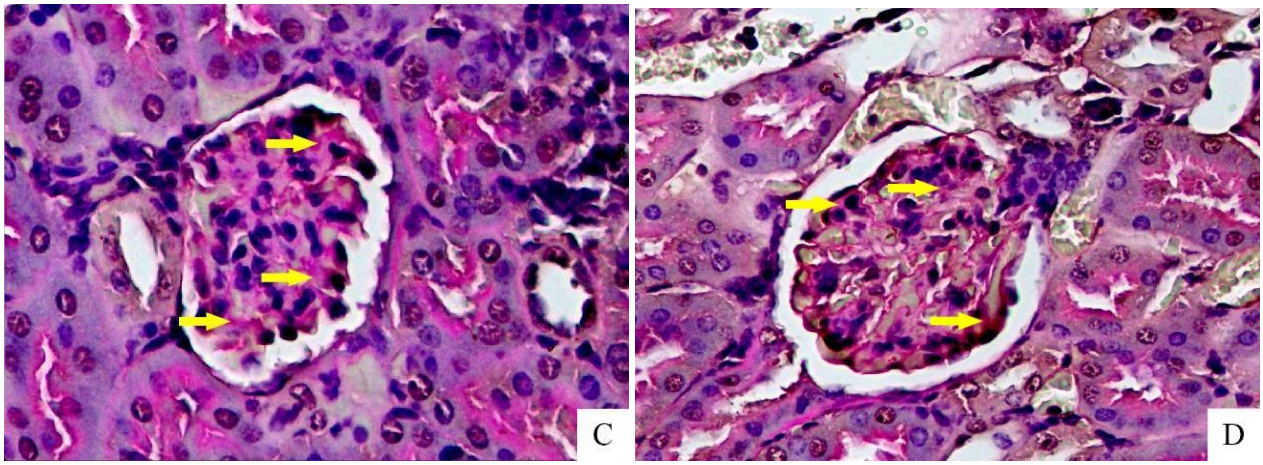


Figure 4. Representative photomicrograph of the effect of high fructose and exercise on renal histology stained with Periodic Acid-Schiff (PAS), scale bar 20µm, and magnification 400X. Glomerulosclerosis was stained purple-magenta (yellow arrow). A. HFr-Sed group (sedentary), B. HFr- Ex_1 group (low-intensity exercise), C. HFr- Ex_2 group (moderate-intensity exercise), D. HFr- Ex_3 group (high-intensity exercise).

Table 1 and Fig. 3 show that exercise did not stimulate histological changes in high fructose-induced mice, either from IGS or relative interstitial volume (RIV) ratio. The IGS did not significantly differ among groups (p= 0.236), with the slightly increased according to exercise intensity. The HFr-Sed group had the lowest IGS score, while the HFr-Ex_3 group had the highest IGS score. The ratio of RIV did not significantly differ among groups (p=0.743), with the lowest and highest percentages were found in the HFr-Ex_2 and HFr-Ex_1 groups, respectively.

Figures 4 and 5 represent photomicrographs of renal histology stained with PAS and Masson's trichrome, respectively. Glomerulosclerosis and interstitial fibrosis were indicated by yellow arrow.

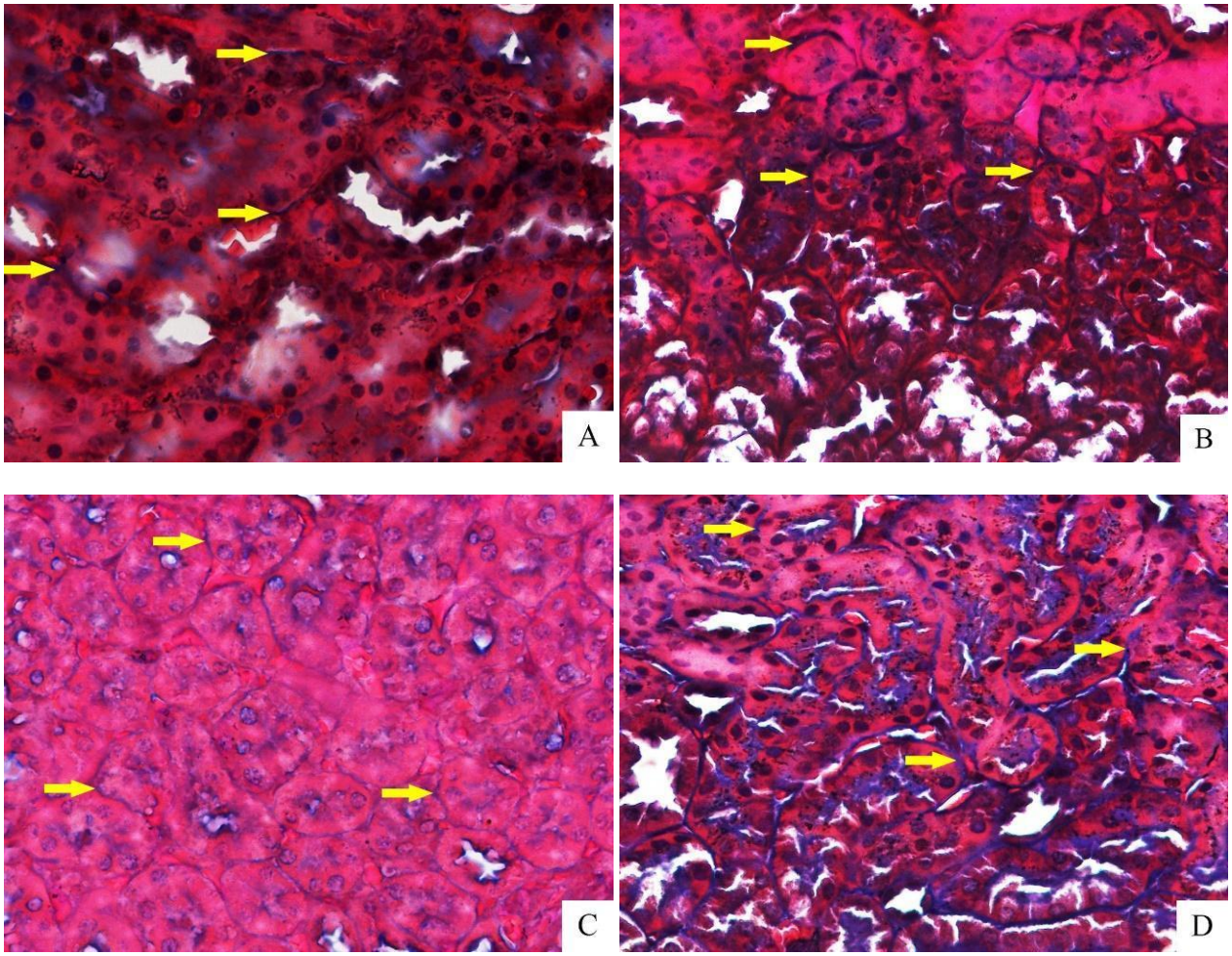


Figure 5. Representative photomicrograph of the effect of high fructose and exercise on renal histology stained with Masson's trichrome (MT), scale bar 20µm, and magnification 400X. Interstitial fibrosis was stained blue (yellow arrow). A. HFr-Sed group (sedentary), B. HFr- Ex_1 group (low-intensity exercise), C. HFr- Ex_2 group (moderate-intensity exercise), D. HFr- Ex_3 group (high-intensity exercise).

Discussion

Several studies have reported the positive impact of exercise on obesity and regulation of carbohydrates and lipids, but the effects on renal protection in mice with high fructose-induced conditions remain unclear. This research investigates the effects of low-, moderate-, and high-intensity exercises on kidney parameters and histological changes in mice with high fructose-induced conditions.

Our study found that high fructose intake in mice increased body weight and length, indicating chronic fructose consumption contributes to weight gain. Fructose promotes visceral fat accumulation, inflammation, and insulin resistance. Prolonged fructose intake induces fructolysis, gluconeogenesis, and lipogenesis in the liver (Ter Horst & Serlie, 2017). Fructose is metabolized by fructokinase into fructose-1-phosphate, broken down by aldolase B into glyceraldehyde and dihydroxyacetone-phosphate, then glyceraldehyde-3-phosphate, pyruvate, acetyl-CoA, and fatty acids, forming triglycerides and primarily accumulating as fat (Chan et al, 2021). Prolonged fructose consumption is a significant factor in the build-up of white adipose tissue (Hernández-Díazcouder et al, 2019). Excessive adiposity and lipogenesis contribute to the heightened production of adipocytokines, including leptin (Rizkalla, 2010). Excessive leptin production leads to leptin resistance, characterized by diminished satiety, increased appetite, and overall weight gain. Consequently, this condition contributes to obesity (Rizkalla, 2010; Obradovic et al, 2021).

Our findings are similar to previous study that reported body weight and length were significantly increased in Sprague-Dawley rats treated with a high fructose solution (20–40%) for 6 weeks compared with the early period of study (Mustafa & Hasan, 2019). Conversely, Ferreira-Santos, et al (2020) found that there were no significant changes of Wistar rats body weight after drinked 20% fructose for 12 weeks (Ferreira-Santos et al, 2020). This can be due to strain specificity influencing responses to high fructose consumption, involving gene regulatory pathways, dosage, duration, and preparation in metabolic tissues (Zhang et al, 2020).

Another factor that determines the weight and length gain in all groups at the end of the study might be due to the mice's growth. The mice grow slowly throughout their lives (Putra, 2016; "Life Span As Biomarker," 2016). Normal male mice aged 16 weeks have body weight average of 32.1 $\pm$ 1.4 gram (30.7 - 33.5 gram) ("Life Span As Biomarker," 2016). In our study, sedentary mice had a higher body weight, while mice with moderate- and high-intensity exercises had lower body weight.

In addition, exercise may cause a decrease in catabolic factors and an increase in muscle protein synthesis as an impact of muscle contraction during exercise, which leads to muscle mass and volume improvement. Aerobic exercise, which effectively induces hypertrophy, is highly dependent on adequate intensity, duration, and frequency to reach a large number of muscle contractions. Previous studies reported that the moderate- and high- intensity exercises are sufficient to elicit muscle hypertrophy (Osawa et al, 2014; Brightwell et al, 2019; Macedo et al, 2019).

In the final analysis of this study, it was found that moderate- and high-intensity exercises significantly reduced body weight in high fructose-induced mice. Swimming exercises were more effective in restricting weight gain, possibly due to increased caloric expenditure during a high-fructose diet.

Our findings are consistent with a previous study in obese college students that reported the higher intensity exercises significantly change body composition, including body weight (Chiu et al, 2017). This is due to the release of substances like catecholamines, growth hormone, and cortisol, which contribute to increased lipolysis (Kim et al, 2016). Exercise also promotes the conversion of white adipose tissue into brown adipose tissue, stimulating lipolysis and thermogenesis (Kim et al, 2022; Khalafi et al, 2020). The regulation of energy expenditure occurs through the upregulation of Irisin, FGF-21, and UCP1, then activating the AMPK-SIRT1-PGC-1α pathway, and promoting fat browning and thermogenesis (Khalafi et al, 2020; Albar et al, 2021). The study found moderate- and high-intensity exercise groups had higher energy loads compared to low-intensity groups, possibly due to insufficient energy for fat browning and AMPK activation (Schwalm et al, 2015) and PGC1α (Brandt et al, 2017) in an intensity-dependent manner. It was observed that higher phosphorylation levels of AMPK and acetyl CoA carboxylase were achieved after high-intensity exercise (Shwalm et al, 2015). High-intensity exercise may provide more weight loss benefits than low-intensity exercise. Low-intensity exercise may lead to greater fat utilization and oxidation (Kim et al, 2016), but the extent of fatty acid oxidation is influenced by energy expenditure, duration, type, and intensity, and cardiorespiratory fitness level (Laurens et al, 2020; Kolnes et al, 2021). High-intensity exercise promotes higher energy expenditure, potentially promoting weight loss through increased fatty acid oxidation during the recovery phase (Laurens et al, 2020).

The Lee index and BMI are anthropometric parameters commonly used as indicators of obesity in rodents (Malafaia et al, 2013). The study found significant differences in Lee index before and after intervention in low- and moderate-intensity exercises. Moderate-intensity exercise reduced the Lee index, while low-intensity exercise did not impede its increase. This supports previous studies showing moderate-intensity exercise can reduce the Lee index in obese mice (Fauzi et al, 2020; Mostarda et al, 2012).The similar results also showed that moderate-intensity exercise for 8 weeks distinctly lowered the Lee index of diet-induced obese mice compared to the untreated group (Wu et al, 2022). The Lee index can be used to measure obesity as it correlates with white adipose tissue deposits (Malafaia

et al, 2013). Indeed, exercise plays a crucial role in reducing fat mass. Previous study showed that exercise can alter body composition by decreasing fat and increasing muscle mass while maintaining stable weight (Langleite et al, 2016). This also found in another study which reported moderate-intensity exercise can reduce fat mass in adolescent obese women (Sugiharto et al, 2023). Adipose tissue stimulation enhances fat breakdown, hinders accumulation, and reduces triacylglycerol content, potentially reducing fat accumulation (Mika et al, 2019).

The study found that moderate- and high-intensity exercises had significantly lower Lee indexes compared to low-intensity exercise. This aligns with previous studies showing that high-intensity exercise reduces body weight, fat percentage, and fat mass more effectively than low-intensity exercise in obese young adults (Chiu et al, 2017). This may be due to the increased release of hormones, such as catecholamines, glucagon, growth hormone, and cortisol, which stimulate lipolytic activity in adipocytes and intramuscular stores (Muscella et al, 2020). As a result, higher intensity exercise may result in a more substantial reduction in fat mass compared to lower intensity exercise.

Alterations in BMI were correlated with lipid profile and oxidative stress level (Novelli et al, 2007; Epingeac et al, 2019). Our study indicated that exercise did not affect the BMI alteration at the end of the period, except in the low-intensity exercise group, which was unable to maintain the BMI and even increased in the end period. A previous study showed that moderate- and high-intensity groups significantly influence BMI, energy expenditure, VO2 max, and fat mass (Berge et al, 2021).

The post-exercise Lee index and BMI of the low-intensity exercise group were the highest among others. It might be because the low-intensity exercise group had the lowest post-exercise body length compared to all groups. All adult mice experience growth in biological processes and structures until three months old, causing increased body length (Laboratory, TJ, 2016). At the time of sexual maturation, they do not undergo epiphyseal fusion and have persistent linier growth into adulthood, but continues to slow, obtaining very low rates (Lui & Baron, 2011).

The low-intensity exercise group had the lowest post-exercise body length, which may be due to hormonal and mechanical stimulation factors. Disruption of GH and Growth Hormone Receptor (GHR) genes can result in decreased body length (List et al, 2019; Duran-Ortiz et al, 2021). Previous evidence reported that exercise can stimulate GH release via the JAK-STAT5 signaling pathway (Consitt et al, 2008). Modified factors of the GH secretion in response to exercise are very diverse, including cardiorespiratory fitness, exercise volume and intensity (Sabag et al, 2021). Exercise that obtains a threshold of exercise intensity can rise GH production in linier dose-dependent manner (Ferlazzo et al, 2020). High-intensity exercise was adequate to increase GH secretory rate but did not differ from moderate-intensity exercise (Deemer et al, 2018). Prior research found that high-intensity exercise enhanced GH concentrations while low-intensity exercise failed to induce any significant increases in GH levels (Kliszczewicz et al, 2021). Another study stated that exercise with moderate-intensity could significantly enhanced GH secretion (Yousefi et al, 2022). Growth hormone has both direct and indirect effects on bone growth, development, and metabolism. Many of the activities of growth hormone are mediated through insulin-like growth factor I (IGF-I) (Hall & Hall, 2021). Exercise increases IGF-I levels in the bloodstream, regardless of GH levels, IGF-1 is a crucial metabolic biomarker with anabolic and insulin-sensitizing effects (Hejazi, 2017). In diabetic rats, swimming exercise with a load of 5% of body weight, performed five days a week for six weeks, restored bone length by stimulating the GH/IGF-1 axis (Gomes et al, 2006). On the other hand, low-intensity exercise did not significantly increase IGF-1 levels (Kliszczewicz et al, 2021). Swimming exercise with 9% body weight load causes greater muscle contractions than low-intensity exercise, causing chondrocyte proliferation and hypertrophy, increasing bone size and length compared to low-intensity exercise (Purwatiningrum, 2006; Mizuno et al, 2018).

High fructose solution was implemented in this study in order to induce renal damage due to its high expression of fructokinase (Diggle et al, 2009). A high-fructose diet causes renal morphological alteration through an increase in alpha-smooth muscle actin (α-SMA), inflammation, glomerulosclerosis, and necrosis gene expressions, leading to a reduction in the glomerular filtration rate (GFR) and higher urea and creatinine levels in the blood (Elsisy, El-Magd, & Abdelkarim, 2021).

In current study, exercise was expected to ameliorate the kidney impairment as high fructose induced. In this study, found that all groups experienced morphological damage accompanied by impaired kidney function. Serum creatinine is one of the good parameters for measuring kidney function (Gowda et al, 2010) with the normal SCr levels are 0.6–1.3 mg/dL (Gounden, Bhatt, & Jialal, 2022).

This study revealed that exercise groups significantly lower SCr levels in fructose-induced mice, indicating exercise can prevent increased SCr levels due to fructose administration. This study supports previous research showing that exercise can reduce SCr levels in fructose-induced mice (Hu et al, 2020). This can be seen in decreased SCr levels if mice undergo physical exercise in the form of swimming at various intensities. This finding aligns with the theory that exercise can enhance the secretion of PGC-1α (Fauzi et al, 2022) by activating AMPK, thereby facilitating the processes of fat browning and lipolysis (Albar et al (2021) This process prevents the increase in triglycerides and lipid accumulation in the kidneys (Salim, Kurnia, & Bintarti, 2018), thus causing inhibition of the secretion of inflammatory mediators that can trigger inflammation and damage in the kidneys (Myers, Kokkinos, & Nyelin, 2019). Therefore, physical exercise is able to prevent damage in the kidneys characterized by a

decrease in SCr levels.

Our study revealed a significant difference in SCr levels among exercise groups where moderate-intensity having the lowest levels. High-intensity exercise had smaller decreases, possibly due to the intensity of the exercise. The load given to each group is 3% of body weight for low-intensity, 6% of body weight for moderate-intensity group, and 9% of body weight for high- intensity group (Albar et al, 2021). During the study, high-intensity exercise group experienced more stress exposure because received a greatest load among others. The intensity of exercise plays a crucial role in determining whether it elicits distress or eustress (Pranoto et al, 2020). The study highlights the importance of considering factors like frequency, intensity, duration, and type of exercise for optimal results (Rejeki, Rahim, & Prasetya, 2018). Excessive physical stress can disrupt physiological processes, leading to oxidative stress, which can harm organs like the kidneys (Gyurászová et al, 2020). Previous research shows that swimming exercises can cause oxidative stress, causing increased levels of malondialdehyde and serum alanine aminotransferase (ALT), biomarkers of oxidative stress (Dewi, Hairrudin, & Normasari, 2016).

Low-intensity exercise groups had the highest SCr levels despite lower stress exposure. This is due to the high fructose intake, which hinders the kidneys' ability to handle lipid accumulation. Previous studies have shown that moderate- and high-intensity exercises reduce body fat and weight more effectively than low-intensity exercise (Chiu et al, 2017), resulting in lower SCr levels. Low-intensity exercise burns less fat than the moderate- and high-intensity exercises (Maillard, Pereira, & Boisseau, 2018). Therefore, low-intensity exercise did not ameliorate the SCr levels despite receiving less stress exposure.

Our study found that moderate-intensity exercise is more effective in preventing increased SCr levels and reducing stress exposure compared to high-intensity exercise. Physical activity carried out with the proper intensity can be a stimulator for the body (Pranoto et al, 2020). High-intensity exercise increases ROS production, disrupts oxidation-antioxidation balance, increases inflammatory mediators, and increases injury risk (Lu et al, 2021). In contrast, moderate-intensity exercise, when combined with resting periods, offers maximum benefits (Cerqueira et al, 2020). Balancing exercise intensity and recovery is crucial for optimal benefits and risks. Therefore, moderate-intensity exercise is more optimal to prevent chronic inflammation and oxidative stress, thereby preventing kidney damage which is characterized by a decrease in SCr levels.

Our study indicated that exercise can improve SCr levels, but the IGS and interstitial fibrosis remain unsignificant among groups. These mean that chronic swimming exercise, 10-15 min/day, 3 times/week with various intensities, did not affect histological changes in the kidney. This is similar with previous study demonstrated that IGS score of diabetic fatty rats which underwent treadmill (10-60 min/day, 5 days/week) for 8 weeks was not significantly difference although kidney restoration was found through reduction of albumin excretion, normalize of creatinine clearance, upregulation of Nitrite Oxide Synthase (NOS) expression, and suppression of NADP oxidase (Ito et al, 2015). Another study corroborated our result found that swimming exercise (3 days a week for 45 minutes) in 5 weeks did not ameliorate the renal histology of adenine-induced CKD rats (Ali et al, 2014).

Indeed, there are studies that demonstrate the positive effects of exercise on renal protection and oxidative stress. Hu et al. (2020) found that treadmill exercise in high fructose-fed rats attenuated glomerulosclerosis and renal fibrosis by enhancing renal fatty acid metabolism and restoring lipogenesis enzyme expression in the kidney (Hu et al, 2020). Another study reported that moderate-intensity exercise reduced glomerulosclerosis, tubular injury, and collagen deposition through antioxidant and anti-inflammatory mechanisms, podocyte protection, and induction of autophagy (Salem & Farid, 2021). These findings suggest that the type, frequency, and duration of exercise, as well as the animal strain used, can influence the histological changes in the kidney.

Exercise is known to elicit a stress response in the human body (Hackney, 2006). Stress reactions to exercise can vary widely depending on intensity, duration, type of exercise, age, gender, and training status (Athanasiou, Bogdanis, & Mastorakos, 2023). Individuals' physiological condition and training background significantly impact their response to exercise stress. Exercise intensity and duration impact neuroendocrine stress response, hypothalamic-pituitary-adrenal (HPA) axis activation, sympathetic nervous system stimulation. (Hackney, 2006). Specifically, the cortisol response of the HPA axis during endurance exercise is typically observed at intensities above 60% of VO2 max (Duclos & Tabarin, 2016). This highlights that the hormonal and physiological responses to exercise are influenced by the intensity at which it is performed. High-intensity exercise increases HSL phosphorylation in adipose tissue (Liu et al, 2020), causing prolonged lipolysis and influenced by hormones like catecholamines and glucagon (Muscella et al, 2020; Kim et al, 2015). The type, duration, and intensity of exercise, along with the presence of specific hormones, all contribute to exercise-induced lipolysis.

Exercise disrupts the balance between oxidation and reduction in the body, causing oxidative stress. Exercise load influences oxidative stress, with markers increasing when intensity exceeds the lactate threshold (Kawamura & Muraoka, 2018). Exercise enhances antioxidant defenses and mitigates stress through NRF2/KEAP1 pathways (Alves et al, 2020). Sclerosis and fibrosis in kidneys are manifestations of inflammation. Exercise has anti-inflammatory function by modulating the profile of proinflammatory cytokines (Salem & Faried, 2021). However, there are instances where exercise may not eliminate existing inflammation. Previous research showed that exercise can reduce C-reactive protein (CRP) instead

of IL-6 levels (Salem & Faried, 2021). These support our study that exercise had no effect on renal histological alterations caused by excessive fructose intake. This is because the inflammatory process persists due to its lack of direct effect on other proinflammatory cytokines.

Oxidative stress and high fructose induction contribute to inflammatory processes, as exercise increases ROS and antioxidants (Sener et al, 2020; Choi & Cho, 2007). Moderate-intensity exercise may increase SOD but not decrease MDA (Choi & Cho, 2007), causing redox imbalances which serves as the underlying basis for the consistency of IGS and interstitial fibrosis in all groups in this study. Exercise did not significantly repair kidney damage, suggesting the need for optimized exercise interventions for diverse populations.

It's important to note that this research highlights the significance of exercise intensity concerning kidney health. The results indicate that moderate-intensity exercise has a more favorable impact on kidney function compared to high-intensity exercise, which seems to exert additional stress on the organ (Rivera, Röling, & Kappes, 2023). The importance of identifying and understanding sports motivation and individual identity in the context of this research can inform how we comprehend behavior and health related to physical activity. This underscores the importance of a holistic approach to understanding and maintaining body health, which includes a combination of a healthy diet and regular physical activity, as discussed in previous research (Leunda-Goni, Jauregui, & Figueras, 2023). While physical exercise plays a crucial role in managing health issues such as obesity, inflammation, and metabolic disorders, it should not be forgotten that diet plays a significant role in achieving these health goals (Álvarez-Herrero, Martinez-Roig, & Urrea-Solano, 2022). Not everyone needs to engage in high-intensity exercise to reap health benefits, and even moderate-intensity exercise can have a significant impact. Increasing daily physical activities like walking, cycling, or swimming regularly can help maintain a healthy weight and minimize the risks associated with obesity-related health problems (Donate et al, 2023).

Moderate-intensity exercise can improve renal function, despite glomerulosclerosis and interstitial fibrosis, restoring renal dysfunction earlier than morphological damage. This could be related to scar tissue formation in the glomeruli and renal interstitium through various highly complex mechanisms that require a considerable amount of time, as does the healing process (Farris & Colvin, 2012; Schlondoroff, 2008). Furthermore, in the current study, renal morphological damage was only observed in one kidney. It is plausible that improvements in blood creatinine levels due to exercise might be compensated by the other kidney.

The study's limitations include limited blood collection, lack of measurements, and biochemical analysis, requiring further investigation to evaluate kidney damage and inflammatory responses in relation to exercise intensity. Further studies are needed to reveal mechanisms of exercise intensity on metabolic homeostasis in high carbohydrate-related diseases.

Conclusion

Exercise affects anthropometric parameters and SCr levels, with moderate- intensity exercise being more effective in preventing renal damage. Further investigation is needed to understand pathways, molecular interactions, and potential mediators contributing to these changes. This knowledge can guide the development of optimized exercise interventions for diverse populations.

Conflict of Interest

The authors declare that they have no conflict of interest.

Financial Support

This study received financial support from an internal research grant provided by the Faculty of Medicine Universitas Airlangga, Indonesia, grant number: 1303/UN3.1.1/PT/2022.

Acknowledgments

We would like to express our sincere gratitude to Universitas Airlangga, Indonesia, for their invaluable support in the successful completion of our research. This assistance played a pivotal role in facilitating data collection, analysis, and the overall execution of the project.

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