



The effect of a high-fat diet and rosuvastatin therapy on liver steatosis in Wistar rats

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Abstract

Non-Alcoholic Fatty Liver Disease (NAFLD) is characterized by the excessive accumulation of fat in the liver and is becoming increasingly prevalent due to rising rates of obesity, diabetes, and metabolic syndrome. The progression of NAFLD from simple steatosis to steatohepatitis, fibrosis, and cirrhosis underscores the urgency for effective treatments. Rosuvastatin, a hydrophilic statin with lipid-lowering, anti-inflammatory, and antioxidant properties, is widely used to manage hyperlipidemia; however, its role in attenuating NAFLD remains debated. Aim: To evaluate the effects of a high-fat diet and rosuvastatin therapy on liver steatosis and inflammation in male Wistar rats. Fifty rats were randomly assigned into five groups: negative control (regular diet), positive control (high-fat diet), and three treatment groups receiving rosuvastatin orally at doses of 0.72 mg, 0.18 mg, and 0.09 mg following the high-fat diet. Liver function was assessed via serum transaminases (SGOT, SGPT), and histopathological analysis was performed using hematoxylin and eosin staining, with NAFLD activity score evaluation. Rosuvastatin at 0.18 mg and 0.09 mg significantly reduced steatosis and lobular inflammation without elevating SGOT and SGPT levels, whereas the high rosuvastatin dose (0.72 mg) showed minimal anti-inflammatory effect. Histopathology confirmed decreased fat accumulation and inflammation in treated groups. These findings suggest that rosuvastatin at low to moderate doses can attenuate hepatic steatosis and inflammation, potentially via activation of fatty acid oxidation pathways and suppression of pro-inflammatory cytokines. Rosuvastatin shows promise as a therapeutic agent for early NAFLD stages, offering hepatoprotective effects beyond lipid lowering. Further clinical studies are warranted to validate these findings and determine optimized dosing strategies.

Keywords: Non-alcoholic fatty liver disease, Rosuvastatin, Hepatic steatosis, Inflammation, Wistar rats, Fatty acid oxidation

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is the accumulation of fat in the liver in people who do not consume alcohol. Several metabolic disorders, such as obesity, diabetes mellitus, a high-fat diet, and dyslipidemia, cause this disorder. The initial form of NAFLD is simple hepatic steatosis, which, if left untreated, can progress to steatohepatitis, fibrosis, and even cirrhosis.¹

Wistar rats (*Rattus norvegicus*) are a frequently used experimental animal in hepatic steatosis research. Hepatic steatosis can be induced in Wistar rats by feeding them a high-fat diet. A high-fat diet can lead to the accumulation of lipids in the liver.^{2,21}

Rosuvastatin is the statin most commonly used to treat hyperlipidemia. Due to its hydrophilic nature, rosuvastatin has the advantage of having fewer tissue side effects than other statins.³ One side effect of statins is liver damage, which can occur due to

increased fat accumulation in the liver (steatosis).^{3,4}

This study aimed to assess the effects of a high-fat diet and rosuvastatin administration on liver abnormalities in Wistar rats. Liver abnormalities were evaluated using SGOT level, SGPT level, and histopathological aspects.

Methods

The study employs an experimental design with a post-control group. The study was conducted after obtaining approval from the Ethics Committee of the Faculty of Medicine, Diponegoro University, Semarang, with number 234/EC/KEPK/FK-UNDIP/VIII/2025. The study population consisted of 50 male Wistar rats, aged 2 months. The rats were acclimated for 7 days by being fed a regular diet and given mineral water to drink. The study was conducted at the Embryology Laboratory, Faculty of Veterinary Medicine, Airlangga University, from January 2025 to March 2025.

The adjustment of the human dose of rosuvastatin to Wistar rats was carried out using a multiplication constant of 0.0185. High-intensity rosuvastatin in humans is 40 mg, so when multiplied by the constant, the dose is 0.72 mg. Moderate-intensity rosuvastatin in humans is 10 mg, so when multiplied by the constant, the dose is 0.18 mg. In this study, we added another dose below moderate intensity, namely 0.09 mg, which indicates low intensity 5,6

After acclimatization, the mice were randomly divided into five groups: negative control (C-), positive control (C+), treatment 1 (X1), treatment 2 (X2), and treatment 3 (X3). The negative control group was given a regular diet for 12 weeks. Each group consisted of 10 mice. In the negative control group (C-), the mice received a regular diet for 12 weeks; while the positive control group (C+) received a high-fat and cholic acid diet for 8 weeks, followed by a regular diet for 4 weeks. In the treatment group, the treatment was identical to that in the positive control group. However, after being given a high-fat and cholic acid diet for 8 weeks, rosuvastatin therapy was also administered during the last 4 weeks of the regular diet. Group X1 was given rosuvastatin at a dose of 0.72 mg orally for 4 weeks; group X2 was given rosuvastatin at a dose of 0.18 mg orally for 4 weeks; and group X3 was given rosuvastatin at a dose of 0.09 mg orally for 4 weeks. There were 31 rats available at the end of the study, specifically: 8 rats on C-, seven rats on C+, five rats on X1, five rats on X2, and six rats on X3.

At the end of the study, the rats were terminated. Blood was taken to separate the serum for biochemical examination of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) using a Mindray BA-88A with reagents from SGOT liquizone no Lot OTR1-2501 and SGPT liquizone no Lot ALAT - 010225 at the IDEAL Clinical Laboratory, Semarang. The liver was also used to prepare parafilm sections, and preparations were made using hematoxylin and eosin (HE) staining at the Nasional Diponegoro Laboratory's Hospital.

Non-Alcoholic Fatty Liver Disease (NAFLD) scoring is based on histopathological features using the NAFLD activity score, which evaluates the steatosis score (0-3), lobular inflammation (0-4), and hepatocyte swelling (0-2). Steatosis is confirmed if the score is

five or greater.⁷ Two anatomical pathologists conducted the NAFLD scoring examination, and the results were consistent with the kappa test.

Table 1. Non-Alcoholic Fatty Liver Disease (NAFLD) score

NAFLD activity		Score
Steatosis	<5 %	0
	5 - 33 %	1
	34 - 66 %	2
	>66 %	3
Lobular inflammation	None	0
	<2	1
	2 - 4	3
	>4	4
Balloning of hepatocytes	None	0
	Few ballooned	1
	Many balloon	2

All quantitative variables, including SGOT and SGPT levels, exhibited a normal distribution as determined by the Shapiro-Wilk test. Differences were tested using one-way ANOVA. Significant differences were found if $p < 0.05$.

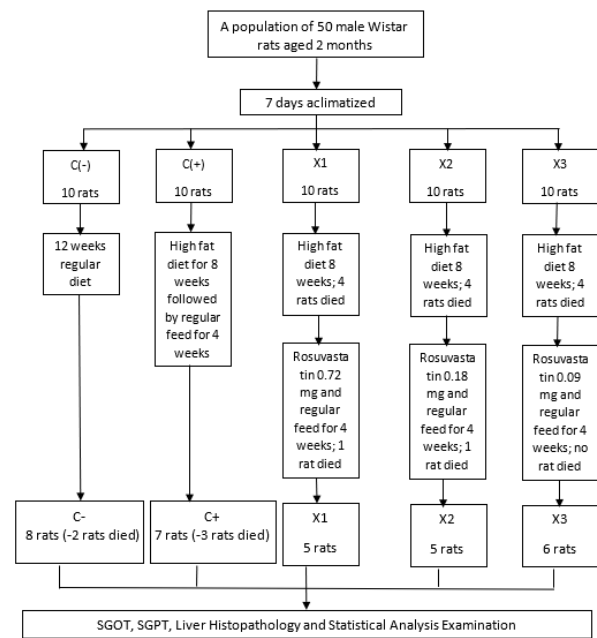


Figure 1: Research flow

Result

Liver function tests were examined using SGOT and SGPT levels. SGOT levels in the negative control group had an average value of 230.63 ± 79.63 U/L, with a range of 142-394 U/L. In contrast, the positive

control group had an average value of 158.57 ± 39.97 U/L, with a range of 96-208 U/L. SGPT levels in the negative control group had an average value of 59.14 ± 15.21 U/L, with a range of 43-85 U/L. In contrast, the positive control group had an average value of 50.29 ± 12.89 U/L, with a range of 31-67 U/L.

The rosuvastatin treatment group was divided into three groups, namely the rosuvastatin 0.72 mg group, the rosuvastatin 0.18 mg group, and the rosuvastatin

0.09 mg group. In the rosuvastatin 0.72 mg therapy group, SGOT levels averaged 219.60 ± 28.82 U/L, while SGPT levels averaged 49.80 ± 3.70 U/L. In the rosuvastatin 0.18 mg therapy group, SGOT levels averaged 193.60 ± 49.67 U/L, while SGPT levels averaged 49.20 ± 20.52 U/L. In the 0.09 mg rosuvastatin therapy group, SGOT levels averaged 233.0 ± 119.82 U/L, while SGPT levels averaged 58.00 ± 29.34 U/L. (Table 2)

Table 2. Characteristics of transaminase enzyme data in each group

Variable	Mean \pm SD (U/L)	Minimum - Maximum (U/L)	Normality test
Negative control			
- SGOT level	230.63 ± 79.63	142-394	0.33
- SGPT level	59.14 ± 15.21	43-85	0.38
Positive control			
- SGOT level	212.0 ± 78.59	130-37	0.82
- SGPT level	50.29 ± 12.89	31-67	0.74
Rosuvastatin 0,72 mg			
- SGOT level	219.60 ± 28.82	193-268	0.2
- SGPT level	49.80 ± 3.70	45-55	0.98
Rosuvastatin 0,18 mg			
- SGOT level	193.60 ± 49.67	156-278	0.09
- SGPT level	49.20 ± 20.52	35-81	0.06
Rosuvastatin 0,09 mg			
- SGOT level	233.0 ± 119.82	104-392	0.41
- SGPT level	58.00 ± 29.34	30-96	0.15

* Normality test with the Shapiro-Wilk test, normal if $p > 0,05$

Normality tests were performed using the Shapiro-Wilk test, and the data distribution was normal ($p > 0.05$) in all groups. (Table 2) A one-way ANOVA test revealed no significant difference ($p > 0.05$) between SGOT and SGPT levels in all groups (Figures 2 and 3).

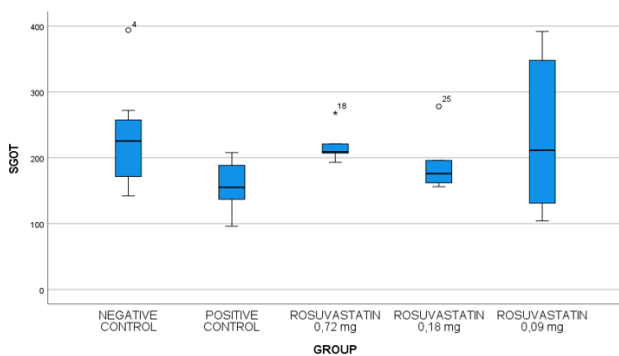


Figure 2: Boxplot of differences in SGOT levels between groups

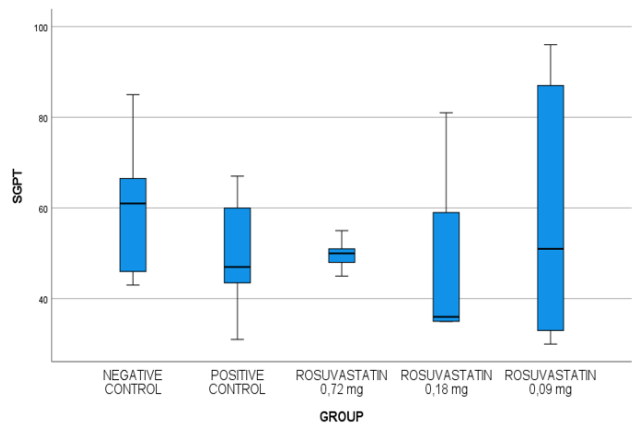


Figure 3: Boxplot of differences in SGPT levels between groups

Histopathological examination was performed using hematoxylin and eosin staining of the liver. The NAFLD score was measured by assessing the status of steatosis, inflammation, and hepatocyte ballooning. Two pathologists made observations, and the inter-

rater Cohen's kappa test showed a value below 0.2, indicating agreement between the two pathologists. (Table 3)

Table 3: Inter-observer Cohen's kappa assessment between 2 observers regarding steatosis value

Cohen's kappa		Steatosis Observer 1			Total
		0	1	2	
Steatosis Observer 2	0	22	1	0	23
	1	1	3	0	4
	2	0	3	1	4
Total		23	7	1	31

Cohen's kappa value between 2 observers is 0.613

Table 4. Inter Cohen kappa assessment between 2 observers regarding the lobular inflammation value

Cohen's kappa		Lobular Inflammation Observer 1		Total
		0	1	
Lobular Inflammation Observer 2	0	22	1	23
	1	2	6	4
Total		23	7	31

Cohen's kappa value between 2 observers is 0.737

Table 5. Inter Cohen kappa assessment between 2 observers regarding the ballooning hepatocytes value

Cohen's kappa		Balloon Hepatocytes Observer 1			Total
		0	1	2	
Balloon Hepatocytes Observer 2	0	22	1	0	23
	1	1	3	0	4
	2	0	3	1	4
Total		23	7	1	31

Cohen's kappa value between 2 observers is 0.85

In the negative control group, histopathological features such as steatosis, lobular inflammation, and ballooning of hepatocytes were largely absent; this contrasts with the features in the group given a high-fat diet.

In the positive control group, the steatosis score was 1.14 ± 0.69 ; the inflammatory status was 0.71 ± 0.48 ; and hepatocyte ballooning was scored 2. (Table 6, Figure 4).

Table 6: Characteristics of the NAFLD score in each group

	Steatosis	Lobular inflammation	Balloon hepatocytes
Negative control	0	0	0.25 ± 0.46
Positive control	1.14 ± 0.69	0.71 ± 0.48	2 ± 0
Rosuvastatin 0.72mg	0.5 ± 0.5	0.4 ± 0.41	2 ± 0
Rosuvastatin 0.18mg	0	0	1.9 ± 0.22
Rosuvastatin 0.09mg	0	0	1.9 ± 0.20

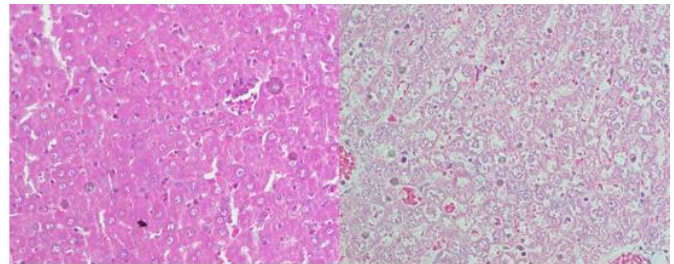


Figure 4: Differences in histopathological features in groups of rats given a regular diet/ C- (left) and a high-fat diet/ C+ (right)

Adding rosuvastatin therapy after a high-fat diet can reduce steatosis and lobular inflammation, but not hepatocyte ballooning. Rosuvastatin 0.18 mg and 0.09 mg can prevent steatosis and lobular inflammation, reducing the score to 0 (Table 4 and Figure 5).

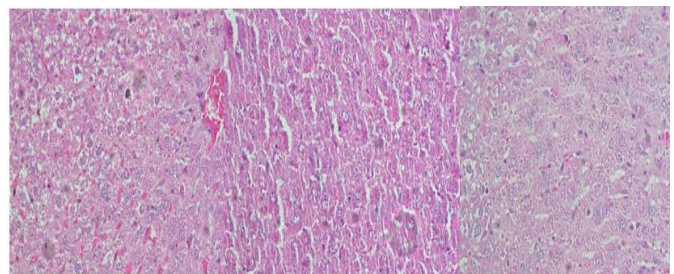


Figure 5: Differences in histopathological features in groups of rats given a rosuvastatin 0.72mg (left), a rosuvastatin 0.18mg (middle), and a rosuvastatin 0.09mg (right)

Discussion

Non-Alcoholic Fatty Liver Disease (NAFLD) constitutes an escalating global health concern, driven by the increasing incidence of obesity and metabolic syndrome.^{1,2} This study examines the impact of a high-fat diet followed by rosuvastatin

therapy on liver steatosis in Wistar rats, employing both biochemical and histopathological evaluations.³ Fat consumed during the diet is transported to the liver by lipoproteins. Fat accumulation in the liver occurs when fatty acid synthesis and uptake exceed cholesterol oxidation and secretion.^{3–5}

An eight-week regimen of a high-fat, cholic acid-enriched diet effectively induced hepatic steatosis and lobular inflammation. Notably, rosuvastatin therapy at low (0.09 mg) and moderate (0.18 mg) doses, administered post high-fat diet exposure, significantly ameliorated liver steatosis and inflammation, while transaminase levels (SGOT and SGPT) remained within normal parameters.

Liver transaminase enzyme levels, both SGOT and SGPT, will increase if hepatocytes are damaged. Cell membrane damage that occurs during steatosis will cause an increase in SGPT in the early stages. As stressors continue, mitochondria in the cells will release SGPT.⁶ Early steatosis will not show any obvious clinical signs or symptoms. Laboratory tests for SGOT and SGPT may not increase in cases of early steatosis.^{6,7} Cross-sectional studies in healthy volunteers showed that a high-fat diet did not increase transaminase activity (ALT/AST), while a high sucrose diet significantly increased transaminase and triglyceride levels.⁶ This is consistent with this study, which showed no difference between SGOT and SGPT levels in groups fed a regular diet and a high-fat diet.

Our histopathological examination between the regular and high-fat diet groups showed differences in NAFLD scores. Velázquez stated that a high-fat diet can lead to increased inflammation, steatosis, and ballooning of hepatocytes.⁸ In this study, a high-fat diet for 8 weeks followed by a regular diet for 4 weeks caused hepatocyte ballooning, but had little effect on steatosis and lobular inflammation. This contrasts with Velázquez's study, which found an increase in all three features—steatosis, lobular inflammation, and hepatocyte ballooning—followed by a high-fat diet for 16 weeks.⁸

Rosuvastatin is a hydrophilic statin often used to reduce LDL levels in the blood.⁹ It is more commonly used than other statins due to its potent effects and minimal tissue side effects. In addition to lowering cholesterol, statins also have pleiotropic effects that

are beneficial to the body, such as anti-inflammatory and antioxidant effects. The effect of rosuvastatin on fatty liver disease remains controversial. Inhibition of the HMG-CoA enzyme reduces cholesterol secretion, particularly in very low-density lipoproteins, and leads to intrahepatic lipid accumulation¹⁰

The present study demonstrates that administering rosuvastatin at dosages of 0.18 mg and 0.09 mg effectively reduces steatosis in liver cells by eliminating lipid accumulation within the liver. These findings challenge prior assertions that statins contribute to increased hepatic lipid deposition. Mechanistically, rosuvastatin enhances fatty acid oxidation not only through mitochondrial pathways but also by activating the PPAR α receptor, akin to the action of fibrate-class drugs.¹¹ Activation of PPAR α upregulates genes that facilitate the oxidation of fatty acid chains present in liver triglycerides, with peroxisomes degrading long-chain and branched-chain fatty acids that cannot be efficiently oxidized within mitochondria. This process reduces hepatic lipid accumulation and mitigates lipotoxicity¹²

Moreover, rosuvastatin attenuates pro-inflammatory responses through the activation of antioxidant pathways, thereby supporting hepatic protection. These effects align with recent meta-analyses and experimental evidence indicating that statins, particularly rosuvastatin, can reduce liver fat accumulation and lower the risk of NAFLD without increasing adverse hepatic events for most patients. Notably, systematic reviews in 2024 indicate that statin therapy contributes to histological improvement and decreases aminotransferase levels in NAFLD subjects, potentially modifying the disease's progression. Our data further oppose earlier concerns that statins exacerbate hepatic injury or promote steatosis, as supported by robust animal and clinical trials in the current literature.^{14–17}

In the context of steatohepatitis, the accumulation of mitochondrial cholesterol and the dysfunction of peroxisomes contribute to oxidative stress and hepatocellular injury. Statins facilitate the dissolution of cholesterol crystals, which are the primary lipotoxic agents, within the lipid droplets of hepatocytes, thereby mitigating inflammation and fibrosis. This therapeutic effect is further supported by the restoration of Kupffer cell crown-like

structures and the upregulation of paraoxonase 1 (PON1), a hepatic antioxidant enzyme associated with enhanced oxidative status and diminished inflammatory signaling^{18,19}

Our study found that the administration of rosuvastatin at doses of 0.18 mg and 0.09 mg effectively eliminates lobular inflammation in the liver of Wistar rats, whereas a higher dose of 0.72 mg results in only minimal inflammation. This pronounced anti-inflammatory effect is mediated through the suppression of key pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF- α), interleukin 6 (IL-6), and tumor growth factor beta 1 (TGF- β 1).

Beyond their classical lipid-lowering properties, statins exert broad pleiotropic actions that complement these anti-inflammatory benefits. These include reducing the production of adhesion molecules and acute phase reactants, as well as enhancing endothelial function by increasing eNOS phosphorylation and nitric oxide bioavailability. The resulting improvement in microvascular architecture and function further supports hepatic repair and metabolic stabilization, underscoring the multifaceted therapeutic potential of rosuvastatin in mitigating liver inflammation and promoting liver health.¹⁹

Substantial evidence from experimental models and clinical studies highlights the efficacy of statins in mitigating hepatic lipotoxicity, resolving cholesterol crystal-induced inflammation, and ameliorating fibrosis. Statins are capable of nearly dissolving hepatic cholesterol crystals, reducing NLRP3 inflammasome activation in Kupffer cells, and decreasing crown-like structures associated with inflammation and fibrosis in NAFLD/NASH. Furthermore, statin therapy enhances hepatic and adipose microvascular function by improving the health of liver sinusoidal endothelial cells, preventing microcirculatory dysfunction, and promoting endothelial nitric oxide synthase (eNOS) phosphorylation, which results in reduced portal pressure and the prevention of endothelial dysfunction.²⁰

The translational implications of these findings are significant. Rosuvastatin may serve as a novel, safe, and effective intervention for non-alcoholic fatty liver

disease (NAFLD), particularly in patients with concurrent cardiovascular risk factors. Given the favorable profile observed at low and moderate doses, therapy can be tailored to balance lipid-lowering and hepatic outcomes. However, caution is advised with higher statin doses, as recent evidence suggests potential mitochondrial effects and hepatic stress at excessive exposures. Future research should prioritize long-term, multicenter studies to elucidate optimal dosing, the durability of benefits, and the mechanistic pathways underlying statin effects in metabolic liver disease.²⁰

This study acknowledges certain limitations. The absence of direct assessment following the initial high-fat diet constrains the understanding of acute changes preceding the introduction of rosuvastatin. Furthermore, the reduced number of animals and brief intervention periods may lead to an underestimation of the long-term effects and safety profile. While rodent models offer mechanistic insights, they may not fully replicate the heterogeneity of human NAFLD, thereby necessitating clinical validation.

Our findings robustly support existing literature, indicating that statins—particularly hydrophilic agents such as rosuvastatin—can mitigate hepatic lipid accumulation and inflammation without routinely causing liver injury at therapeutic doses.

This challenges earlier retrospective reports suggesting increased liver toxicity associated with statin use, a perspective now reconsidered in light of recent prospective data and controlled studies. Given the potential for dose-related differences, careful selection and titration of statins should inform clinical decisions in the management of NAFLD.^{12,16,17}

Conclusion

A high-fat diet administration can increase hepatic steatosis. Rosuvastatin administration as a lipid-lowering drug can reduce NAFLD score by lowering steatosis and lobular inflammation. A limitation of this study is the lack of direct examination of the high-fat diet group immediately after 8 weeks of high-fat diet administration.

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