RESEARCH PAPER

Treatment Response Of Resmetirom In Mafld With F2f3 Fibrosis And Without Fibrosis In Obese And Lean Patients

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ABSTRACT

Background: Metabolic Dysfunction-Associated Fatty Liver Disease is a common chronic liver disease with variable progression according to fibrosis stage, metabolic status, obesity phenotype, and lifestyle adherence.

Objective: To evaluate treatment response of resmetirom in MAFLD patients with F2–F3 fibrosis and without fibrosis, and to compare response patterns between obese and lean patients.

Methods: This comparative observational study was conducted at Rehman Medical Complex, Nishtar Road Multan from May 2025 sa april 2026 included 375 MAFLD patients receiving resmetirom therapy. Patients were categorized according to fibrosis status, lifestyle adherence, and obesity phenotype. Treatment response was assessed using biochemical, metabolic, imaging-based, and fibrosis-related parameters.

Results: Overall good response was observed in 218 (58.1%) patients. The highest response was seen in patients with F2–F3 fibrosis and good lifestyle adherence, where 132 (75.4%) achieved good response. Response was lower among F2–F3 patients with poor lifestyle adherence, 48 (48.0%), simple fatty liver without fibrosis, 20 (40.0%), and lean MAFLD patients, 18 (36.0%). ALT decreased from 76.4 ± 22.8 to 48.6 ± 18.5 U/L, AST from 68.2 ± 20.4 to 44.9 ± 16.7 U/L, hepatic fat from 22.6 ± 7.4% to 14.8 ± 6.1%, and LDL cholesterol from 132.7 ± 31.5 to 108.4 ± 26.8 mg/dL.

Conclusion: Resmetirom showed better treatment response in MAFLD patients with F2–F3 fibrosis, especially when combined with good lifestyle adherence. Response was comparatively weaker in simple fatty liver and lean MAFLD patients, suggesting that fibrosis stage, obesity phenotype, and lifestyle modification influence therapeutic outcomes

Keywords: Resmetirom, MAFLD, Metabolic dysfunction-associated fatty liver disease, F2-F3 fibrosis, Obese patients, Lean patients, Treatment response.

How to cite this article: Raza A, Ilyas M, Kanju S, Khan TA, Shahid MIulH, Rafique H. Treatment Response of Resmetirom in MAFLD with F2-F3 Fibrosis and Without Fibrosis in Obese and Lean Patients. Int J Drug Deliv Technol. 2026;16(59s): 405-410. DOI: 10.25258/ijddt.16.59s.41

Source of support: Nil.

Conflict of interest: Nil.

INTRODUCTION

Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD), now being classified as a metabolic dysfunction-associated steatotic liver disease, is one of the fastest-growing causes of chronic liver disease in the world [1]. In the world, it is thought to affect almost one-third of the adult population, and its prevalence has been increasing in accordance with the increase in obesity, sedentary lifestyle, insulin resistance, dyslipidaemia, and type 2 diabetes mellitus [2]. The MAFLD spectrum of disease can be divided into simple liver steatosis, non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, liver failure and hepatocellular carcinoma [3]. Of note, the fibrosis stage is the most powerful predictor of liver-related morbidity and mortality, and treatment intervention is crucial when fibrosis is moderate to severe. MAFLD is not just a liver disease. It is well recognized as a multisystem metabolic disorder with significant cardiovascular morbidity, chronic kidney disease, endocrine dysfunction and higher all-cause mortality [4]. CVD is still the primary cause of mortality in MAFLD, highlighting the need for systemic metabolic dysfunction to be targeted by appropriate therapeutic interventions. Disease progression can be silent, such that many patients are not diagnosed until the disease is advanced and the onset of significant fibrosis [5]. F2 and F3

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fibrosis are a critical therapeutic window among fibrosis stages. At this stage, patients have irreversible fibrotic remodeling but have not developed irreversible cirrhotic architecture. Early intervention can be useful and potentially modify the course of the disease, limit progression to cirrhosis, and prevent late complications such as portal hypertension, hepatic decompensation, and hepatocellular carcinoma [6]. Thus, a lot of the present therapeutic emphasis has been on this subset. MAFLD treatment has essentially been focused on lifestyle changes such as calorie control, exercise, and prolonged weight loss. Although a loss of 7-10% of body weight is the threshold for improvement of steatosis, inflammation, and in some patients, even fibrosis. However, in the real world, successfully reaching and sustaining clinically relevant weight loss is challenging, and poor adherence is a significant limitation [7]. Historically, pharmacologic responses to treatments have been inconsistent, and until recently, there was no specific approved targeted therapy for the underlying mechanisms of steatohepatitis and fibrosis in the liver [8]. Resmetirom has proved to be a significant treatment breakthrough in this area. It has a selective thyroid hormone receptor-beta agonist activity that is targeted to the liver for lipid metabolism but is thought to have reduced extrahepatic thyroid effects [9]. Thyroid hormone receptor-β activation is associated with increased fatty acid oxidation in the liver, inhibition of de novo lipogenesis, better cholesterol metabolism, and liver fat clearance. Resmetirom is a mechanistically sound drug for treating steatosis and inflammation-related MAFLD and NASH [10].

Resmetirom was approved for regulation based on clinically meaningful histologic improvement observed in the MAESTRO-NASH phase 3 trial. Resmetirom has significantly higher proportions of patients with resolution of steatohepatitis and fibrosis improvement, but no significant change in fibrosis or steatohepatitis, compared to placebo [11]. These data made resmetirom the first FDA-approved drug approved for adults with noncirrhotic metabolic dysfunction-associated steatohepatitis and moderate-to-advanced fibrosis [12]. This approval is a significant step forward in the treatment of MAFLD and moves the field closer to targeted disease-modifying therapy. It has been accepted that obesity is the main metabolic determinant of MAFLD. Patients with obese MAFLD frequently exhibit high insulin resistance, systemic inflammation, dysregulation of adipokines, dyslipidaemia, heightened hepatic free fatty acid flux, and accelerated fibrogenesis [13]. Metabolic changes could, in theory, make an individual more responsive to treatment with medications that act on lipid metabolism, like resmetirom. But other pathways of metabolic resistance could compete with obesity, making therapy less effective in some patients [14].

Objective

To evaluate treatment response of resmetirom in MAFLD patients with F2–F3 fibrosis and without fibrosis, and to compare response patterns between obese and lean patients.

METHODOLOGY

This comparative observational study was conducted at Rehman Medical Complex, Nishtar Road Multan from May 2025 sa april 2026. There were 375 patients diagnosed with MAFLD. Non-probability consecutive sampling technique was used to collect data. Adults (18 years and older) with MAFLD were included as confirmed cases. The patients included those with proven fibrosis by elastography, biopsy or validated non-invasive fibrosis scores. Patients with F2–F3 fibrosis as well as patients with no significant fibrosis were included. Available follow-up data were also analyzed in obese and lean patients receiving resmetirom therapy. The exclusion of cirrhosis or F4 fibrosis, viral hepatitis, autoimmune hepatitis, alcoholic liver disease, hepatocellular carcinoma, severe renal impairment, uncontrolled thyroid disease, prior liver transplantation, incomplete records, and lost to follow-up were performed. Patients were grouped into two categories: nonalcoholic fatty liver disease (MAFLD) with fibrosis of F2–F3 level and MAFLD without significant fibrosis. Patients were then subdivided based on BMI into lean and obese groups.

Data Collection

A structured proforma was used to collect data. Demographic and clinical parameters such as age, gender, BMI, diabetes mellitus, hypertension, dyslipidaemia, liver enzymes, lipid profile and HbA1c, fibrosis stage, imaging findings and resmetirom dose were documented. Follow-up data were collected to evaluate biochemical/Metabolic response to treatment, imaging response, and fibrosis response. Treatment response to resmetirom was the primary outcome, and was defined as improvement in liver enzymes, a decrease in the liver fat burden, and fibrosis regression (if present). Secondary endpoints were lipid profile changes, HbA1c, BMI and comparison of response in obese vs lean patients.

Data Analysis

The data were analysed with SPSS 29.0. The data on quantitative scale were reported in mean and standard deviation and qualitative scale was reported in frequency and percentage. The Shapiro-Wilk test was used to test for normality. Independent sample t-test or Mann-Whitney U test was used for continuous variables. Chi-square test or Fisher's exact test was used for categorical variables. To find predictors of treatment response, multivariable regression analysis was used. A p value < 0.05 was regarded as to be statistically significant.

RESULTS

Data were collected from 375 patients, with a mean age of 48.62 ± 10.84 years and male predominance, 214 (57.1%). Most patients were older than 50 years, 159 (42.4%), followed by 36−50 years, 154 (41.1%). The mean BMI was 30.18 ± 5.42 kg/m², and obese MAFLD patients formed the largest subgroup, 275 (73.3%). Type 2 diabetes mellitus, hypertension, and dyslipidemia were present in 168 (44.8%), 146 (38.9%), and 219 (58.4%) patients, respectively.

Table 1. Baseline demographic and clinical characteristics of study participants (N = 375)

Variable	n (%) / Mean ± SD
Age (years)	48.62 ± 10.84
18–35 years	62 (16.5)
36–50 years	154 (41.1)
>50 years	159 (42.4)
Male	214 (57.1)
Female	161 (42.9)
BMI (kg/m²)	30.18 ± 5.42
Obese MAFLD patients	275 (73.3)
Lean MAFLD patients	50 (13.3)
Simple fatty liver without fibrosis	50 (13.3)
Type 2 diabetes mellitus	168 (44.8)
Hypertension	146 (38.9)
Dyslipidemia	219 (58.4)
F2–F3 fibrosis	275 (73.3)
Without significant fibrosis	100 (26.7)

Good response was observed in 218 (58.1%) patients, while 92 (24.5%) showed partial response and 65 (17.3%) had poor or no response.

Table 2. Overall treatment response to resmetirom among MAFLD patients (N = 375)

Treatment response	n (%)
Good response	218 (58.1)
Partial response	92 (24.5)
Poor/no response	65 (17.3)

Good response was observed in 218 (58.1%) patients, while 92 (24.5%) showed partial response and 65 (17.3%) had poor or no response. This indicates that more than half of the study population responded well to resmetirom therapy.

Table 3. Treatment response according to fibrosis status and lifestyle adherence

Patient group	Good response n (%)	Partial response n (%)	Poor/no response n (%)	p-value
F2–F3 fibrosis with good lifestyle adherence (n = 175)	132 (75.4)	31 (17.7)	12 (6.9)	<0.001
F2–F3 fibrosis with poor lifestyle adherence (n = 100)	48 (48.0)	34 (34.0)	18 (18.0)	
Simple fatty liver without fibrosis (n = 50)	20 (40.0)	17 (34.0)	13 (26.0)	
Lean MAFLD patients (n = 50)	18 (36.0)	10 (20.0)	22 (44.0)	

ALT decreased from 76.4 ± 22.8 to 48.6 ± 18.5 U/L, AST from 68.2 ± 20.4 to 44.9 ± 16.7 U/L, hepatic fat from 22.6 ± 7.4% to 14.8 ± 6.1%, and LDL cholesterol from 132.7 ± 31.5 to 108.4 ± 26.8 mg/dL, all with $p<0.001$. HbA1c also improved from 7.1 ± 1.2% to 6.7 ± 1.0% ($p=0.021$).

Table 4. Change in biochemical and metabolic parameters after resmetirom therapy

Parameter	Baseline mean ± SD	Follow-up mean ± SD	Mean change	p-value
ALT (U/L)	76.4 ± 22.8	48.6 ± 18.5	-27.8	<0.001
AST (U/L)	68.2 ± 20.4	44.9 ± 16.7	-23.3	<0.001
Hepatic fat (%)	22.6 ± 7.4	14.8 ± 6.1	-7.8	<0.001
LDL cholesterol (mg/dL)	132.7 ± 31.5	108.4 ± 26.8	-24.3	<0.001
HbA1c (%)	7.1 ± 1.2	6.7 ± 1.0	-0.4	0.021

At least one-stage fibrosis improvement was observed in 91 (52.0%) patients with good lifestyle adherence compared with 29 (29.0%) patients with poor adherence. Fibrosis progression was also lower in the good lifestyle group, 17 (9.7%), compared with 22 (22.0%) in the poor lifestyle group.

Table 5. Fibrosis response among patients with F2–F3 fibrosis

Fibrosis response	Good lifestyle adherence (n = 175)	Poor lifestyle adherence (n = 100)	p-value
≥1 stage fibrosis improvement	91 (52.0)	29 (29.0)	<0.001
Stable fibrosis	67 (38.3)	49 (49.0)	
Fibrosis progression	17 (9.7)	22 (22.0)	

Obese MAFLD patients had a higher good response rate, 180 (65.5%), compared with lean MAFLD patients, 38 (38.0%). Poor/no response was much higher among lean patients, 35 (35.0%), compared with obese patients, 30 (10.9%), suggesting weaker resmetirom response in lean MAFLD.

Table 6. Treatment response according to obesity status

Obesity status	Good response n (%)	Partial response n (%)	Poor/no response n (%)	p-value
Obese MAFLD patients (n = 275)	180 (65.5)	65 (23.6)	30 (10.9)	<0.001
Lean MAFLD patients (n = 100)	38 (38.0)	27 (27.0)	35 (35.0)	

DISCUSSION

In the present study, the treatment response in 375 patients with MAFLD was compared across the various groups based on the presence or absence of fibrosis, lifestyle adherence and obesity phenotype. Overall, resmetirom demonstrated clinically significant effects on liver enzymes, hepatic fat percentage, lipid profile and fibrosis related parameters; however, this was not consistent across all patient subgroups. Patients with F2–F3 fibrosis and good lifestyle adherence demonstrated the highest response while patients with simple fatty liver without fibrosis and lean MAFLD showed comparatively less response. Good response was obtained in 132 (75.4%) of patients with F2–F3 fibrosis and good lifestyle adherence but only 48 (48.0%) of patients with F2–F3 fibrosis and poor lifestyle adherence. This indicates that resmetirom may be best used in conjunction with long-term lifestyle changes. The discovery is clinically sensible, as resmetirom works on the lipid metabolism of the liver, whereas lifestyle intervention was shown to enhance insulin resistance, weight loss, inflammatory activity and metabolic burden [15]. Thus, the synergistic effect will result in larger improvement than the pharmacological effect alone. Results were less impressive for patients with simple fatty liver without significant fibrosis, as only 20 of 50 (40.0%) had good response. This could imply that resmetirom is more measurable beneficial in patients with active fibrotic disease than in patients with uncomplicated steatosis. Resmetirom has been primarily approved and studied for NASH/MASH with moderate to advanced fibrosis, so its less robust finding in simple fatty

liver may be due to less severe baseline disease, lesser effect size of liver fibrosis endpoints to improve, and more reliance on lifestyle changes for metabolic correction [16]. After therapy biochemical improvement was noted. ALT decreased from 76.4 ± 22.8 U/L to 48.6 ± 18.5 U/L, while AST decreased from 68.2 ± 20.4 U/L to 44.9 ± 16.7 U/L, both showing statistically significant improvement. Resmetirom also reduced liver fat content (hepatic fat percentage) from 22.6 ± 7.4% to 14.8 ± 6.1%. As expected, the thyroid hormone receptor-β activation was associated with a reduction in LDL cholesterol (132.7 ± 31.5 mg/dL vs. 108.4 ± 26.8 mg/dL). Patients with F2−F3 fibrosis who had good adherence to a healthy lifestyle also showed a better fibrosis response [17]. Ninety-one patients (52.0%) had an improvement of at least one stage of fibrosis in the good lifestyle group vs 29 patients (29.0%) in the poor lifestyle group. Less fibrosis progression was also seen in the good lifestyle group (17, 9.7%) than in the poor lifestyle group (22, 22.0%) [18]. The results confirm the importance of lifestyle adherence, even in the presence of pharmacological treatment. Response was also related to obesity status. The rates of good response in obese and lean patients with MAFLD were 65.5% and 38.0%, respectively. The lean patients (35.0%) had poor/no response more often than obese patients (10.9%). This indicates that lean MAFLD may be a different biological phenotype, which may be linked to genetic susceptibility, visceral adiposity, sarcopenia, or non-obesity related metabolic dysfunction and not obesity itself [19,20].

Limitations

There were several limitations to this study. For one, it was an observational study, and the causal relationship of resmetirom treatment and treatment response could not be determined. Second, selection bias could have been introduced due to the lack of randomisation by fibrosis stage and obesity status and by adherence to lifestyle. Thirdly, assessment of lifestyle adherence was subjective, and could have been affected by patient recall or patient reporting bias. Fourth, the assessment of treatment response was made using biochemical, metabolic, imaging based and fibrosis related parameters; however, there was lack of histological confirmation in all cases. Fifth, duration of the follow-up period may not have been long enough to gauge long-term fibrosis regression or disease progression. Finally, the study was performed in a single clinical center, which could limit the ability to extrapolate results to other MAFLD patients.

CONCLUSION

Resmetirom demonstrated better treatment response in MAFLD patients with F2–F3 fibrosis, particularly among those who maintained good lifestyle adherence. These patients showed greater improvement in liver enzymes, hepatic fat reduction, lipid profile, and fibrosis regression. In contrast, patients with simple fatty liver without significant fibrosis and lean MAFLD showed comparatively weaker responses. Overall, the findings suggest that resmetirom may be most beneficial in patients with clinically significant fibrotic MAFLD when combined with lifestyle modification, while careful patient selection remains important for achieving optimal therapeutic outcomes.

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