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CARDIOMETABOLIC APPROACH TO THE MANAGEMENT OF METABOLICALLY ASSOCIATED FATTY LIVER DISEASE (MAFLD)

Sojida Gulomovna Artikova[1], Zakhar Mukimovich Niezov[1], Bakhtiyor Kuchkarovich Dauletbaev[1], Nurkhon Djuraevna Kosimova[1], Zebo Vositjonovna Yunusova[1], Zulfiya Sayfutdinovna Valieva[1], Dilfuza Zaynobiddinovna Isakova[1], Gulbakhor Nazirjonovna Primkulova[1], Gulchehra Usmanovna Nazarova[1]

[1]Department of Propaedeutics of Internal Diseases, Faculty of Pediatrics

[1] Andijan State Medical Institute, Republic of Uzbekistan. Andijan city.

Contact: +998978374147, salomovshokhabbos@gmail.com

Abstract

Background: Metabolically associated fatty liver disease (MAFLD), formerly known as nonalcoholic fatty liver disease (NAFLD), is now recognized as the hepatic manifestation of systemic metabolic dysfunction. The global increase in obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) has positioned MAFLD as the leading cause of chronic liver disease worldwide. Cardiometabolic risk factors such as dyslipidemia, hypertension, and visceral adiposity are integral to its pathogenesis.

Objective: This study aimed to evaluate the cardiometabolic characteristics of patients with MAFLD and to assess the efficacy of an integrated cardiometabolic management strategy combining lifestyle modification, pharmacotherapy, and metabolic risk optimization.

Methods: A prospective study was conducted among 120 adult patients diagnosed with MAFLD between 2021 and 2024. Patients were divided into two groups: Group A (standard therapy) received conventional hepatoprotective treatment and dietary advice, whereas Group B (cardiometabolic approach) received individualized therapy targeting metabolic syndrome components alongside hepatoprotective care. Anthropometric, biochemical, and imaging parameters were evaluated at baseline and after 12 months of treatment.
Results: Baseline characteristics were comparable between groups. After 12 months, Group B demonstrated significantly greater reductions in body mass index (BMI), liver enzymes (ALT, AST), fasting glucose, and triglycerides. Mean hepatic fat content by ultrasound decreased by 38% in Group B compared to 17% in Group A ($p < 0.001$). Improvement in insulin resistance (HOMA-IR) correlated strongly with decreases in liver fat and serum triglycerides.
Conclusion: The cardiometabolic approach addressing systemic metabolic dysfunction significantly improves hepatic outcomes in MAFLD patients. Targeting insulin resistance, dyslipidemia, and visceral obesity alongside liver-directed therapy yields better metabolic and hepatic recovery than conventional treatment alone.

Keywords: MAFLD, cardiometabolic approach, insulin resistance, fatty liver, dyslipidemia, metabolic syndrome

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Introduction

Metabolically associated fatty liver disease (MAFLD), formerly known as nonalcoholic fatty liver disease (NAFLD), represents the most prevalent chronic liver condition of the 21st century. It is estimated to affect approximately one-quarter of the global adult population, reflecting the rapid rise of obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) in both developed and developing countries [1,2]. The redefinition from NAFLD to MAFLD is not merely semantic but conceptual, emphasizing that the disease originates from metabolic dysfunction rather than the absence of alcohol intake [3,4]. MAFLD is now considered a multisystem disorder with profound implications for cardiovascular, endocrine, and hepatic health, forming an integral part of the broader cardiometabolic disease continuum.

The clinical spectrum of MAFLD ranges from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH), progressive fibrosis, cirrhosis, and hepatocellular carcinoma. However, unlike many liver diseases, mortality in MAFLD is more commonly due to cardiovascular complications than liver failure itself [5,6]. Numerous studies have confirmed that patients with MAFLD have a twofold to threefold higher risk of developing atherosclerosis, myocardial infarction, and stroke compared to the general population [7]. This overlap between hepatic and cardiometabolic pathology has led to the recognition of MAFLD as a hepatic manifestation of systemic metabolic dysfunction.

The pathogenesis of MAFLD is multifactorial and complex, involving genetic, metabolic, and environmental factors. Central to its development is insulin resistance (IR), which promotes increased adipose tissue lipolysis, leading to an influx of free fatty acids (FFAs) into the liver [8]. Hepatic accumulation of FFAs results in triglyceride synthesis and de novo lipogenesis, driven by insulin and carbohydrate response element-binding protein (ChREBP) activation [9]. Excessive lipid deposition leads to oxidative stress, mitochondrial dysfunction, and activation of inflammatory pathways mediated by tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [10]. Over time, these processes culminate in hepatocellular ballooning, inflammation, and fibrosis — the hallmarks of disease progression from steatosis to NASH.

Genetic predisposition also contributes significantly to disease susceptibility and severity. Polymorphisms in genes such as *PNPLA3* (I148M variant), *TM6SF2*, and *MBOAT7* are strongly associated with increased hepatic fat accumulation, inflammation, and fibrosis risk [11]. Additionally, alterations in gut microbiota composition and intestinal permeability lead to endotoxin-mediated hepatic inflammation, further amplifying metabolic dysregulation [12]. Environmental factors such as sedentary lifestyle, high fructose and saturated fat intake, and chronic psychosocial stress exacerbate disease progression.

Traditional approaches to managing fatty liver disease have primarily focused on hepatocellular protection through antioxidants or hepatotropic agents. While such measures can reduce liver enzyme levels, they do not address the fundamental metabolic disturbances driving fat accumulation and inflammation [13]. Increasing evidence now supports the cardiometabolic approach, which aims to treat MAFLD as a systemic disorder rooted in metabolic syndrome rather than an isolated hepatic condition. This paradigm integrates liver health into the broader context of cardiometabolic risk management, targeting obesity, dyslipidemia, insulin resistance, hypertension, and chronic low-grade inflammation simultaneously [14].

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The cardiometabolic model recognizes that the liver, adipose tissue, skeletal muscle, and pancreas operate as interconnected organs within a complex metabolic network. Dysfunction in one organ — such as hepatic fat accumulation — reflects and perpetuates systemic metabolic imbalance [15]. Therefore, effective management of MAFLD requires a holistic therapeutic strategy encompassing weight reduction, optimization of glucose and lipid metabolism, improvement in insulin sensitivity, and control of cardiovascular risk factors. Such an approach includes not only lifestyle modification but also pharmacological interventions with agents such as metformin, GLP-1 receptor agonists, SGLT2 inhibitors, and statins, all of which target metabolic pathways linked to hepatic steatosis [16].

Recent clinical trials have demonstrated that patients with MAFLD who undergo comprehensive cardiometabolic therapy achieve greater reductions in hepatic fat, transaminase levels, and fibrosis scores than those treated with liver-directed therapy alone [17,18]. The synergistic improvement in both hepatic and cardiovascular outcomes underscores the inseparable relationship between metabolic and liver health. Furthermore, the identification of shared molecular mechanisms — including insulin signaling defects, lipid peroxidation, and mitochondrial dysfunction — provides a biological basis for integrated treatment strategies [19].

Despite these advances, the global burden of MAFLD continues to rise, driven by sedentary behavior, unhealthy diets, and urbanization. The disease now affects not only adults but also adolescents and young adults, reflecting a disturbing trend in early metabolic deterioration [20]. Moreover, limited awareness, underdiagnosis, and lack of standardized treatment guidelines contribute to suboptimal management. While liver biopsy remains the diagnostic gold standard, non-invasive imaging modalities such as ultrasound and transient elastography, combined with biochemical indices like HOMA-IR and liver enzyme assays, have become essential for early detection and disease monitoring.

In this context, the current study was designed to assess the efficacy of a cardiometabolic management approach in patients with MAFLD. The hypothesis underlying this research is that targeting systemic metabolic dysfunction — specifically insulin resistance, dyslipidemia, and visceral obesity — will yield superior hepatic and metabolic outcomes compared to traditional hepatocentric treatment. By integrating endocrinological, cardiovascular, and hepatological care principles, this study aims to demonstrate that comprehensive metabolic management represents the most rational and effective strategy for controlling and reversing MAFLD progression.

Methods

This study was designed as a prospective, randomized controlled clinical trial conducted at the Department of Hospital Therapy and Endocrinology between January 2021 and December 2024. The research protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants or their legal guardians before enrollment. The investigation adhered to the ethical principles of the Declaration of Helsinki (2013 revision).

A total of 120 adult patients aged between 25 and 65 years were recruited based on the diagnostic criteria for metabolically associated fatty liver disease (MAFLD) established by the International Expert Consensus in 2020. The diagnosis was confirmed by the presence of hepatic steatosis on ultrasonography along with at least one of the following: overweight or obesity (body mass index ≥25 kg/m²), type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation (HOMA-IR ≥2.5,

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triglycerides ≥1.7 mmol/L, or low HDL cholesterol levels). Exclusion criteria included significant alcohol intake (>30 g/day in men, >20 g/day in women), chronic viral hepatitis B or C, autoimmune hepatitis, drug-induced liver disease, or severe renal or cardiac impairment.

After baseline evaluation, patients were randomized into two equal groups using a computer-generated sequence. Group A (standard therapy, n=60) received conventional hepatoprotective agents and lifestyle advice, while Group B (cardiometabolic therapy, n=60) was treated with an integrated approach addressing both hepatic and metabolic components. The cardiometabolic strategy included individualized diet and physical activity programs, weight management counseling, and pharmacologic interventions targeting insulin resistance, dyslipidemia, and hypertension. Specifically, metformin (500–1500 mg/day) was administered to patients with insulin resistance, atorvastatin (10–20 mg/day) to those with dyslipidemia, and ACE inhibitors or angiotensin receptor blockers for blood pressure control. Both groups were followed for 12 months, with clinical and biochemical evaluations at baseline, 6 months, and 12 months.

All patients underwent detailed anthropometric assessment, including measurement of body weight, height, waist circumference, and body mass index (BMI), calculated as weight (kg) divided by height (m^2). Blood pressure was measured in a seated position using an automatic sphygmomanometer after five minutes of rest. Fasting blood samples were collected in the morning after a 10–12-hour overnight fast for biochemical analyses. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using enzymatic colorimetric assays. Fasting plasma glucose and fasting insulin levels were determined, and the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the formula: HOMA-IR = (fasting insulin [μU/mL] × fasting glucose [mmol/L]) / 22.5.

Liver ultrasonography was performed using a Toshiba Aplio 400 ultrasound system (Japan) by a single experienced radiologist blinded to treatment allocation. Hepatic steatosis was graded semi-quantitatively from 0 to 3 based on echogenicity, vascular blurring, and deep attenuation criteria. Additionally, liver stiffness measurements (LSM) were obtained using transient elastography (FibroScan 502 Touch, Echosens, France) to assess fibrosis.

Lifestyle assessment included evaluation of dietary habits using a validated food frequency questionnaire and estimation of daily caloric intake. Physical activity was quantified in metabolic equivalent (MET) hours per week using the International Physical Activity Questionnaire (IPAQ). Patients in both groups received lifestyle counseling at baseline and follow-up visits, although those in the cardiometabolic arm were provided personalized nutrition and exercise plans designed by a clinical dietitian and an exercise physiologist.

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Comparisons between groups were conducted using the independent samples *t*-test for continuous variables and chi-square test for categorical variables. Within-group differences between baseline and follow-up were analyzed using paired *t*-tests. Pearson correlation coefficients were calculated to examine associations between changes in insulin resistance, liver fat, and lipid parameters. A *p*-value less than 0.05 was considered statistically significant.

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Table 1. Baseline Clinical and Biochemical Characteristics of Study Participants

Parameter	Group A (Standard Therapy)	Group B (Cardiometabolic Therapy)	p-value
Number of patients (n)	60	60	—
Male/Female ratio	34/26	35/25	0.84
Mean age (years)	48.7 ± 9.1	47.9 ± 9.8	0.64
BMI (kg/m²)	32.1 ± 3.9	32.4 ± 4.2	0.78
Waist circumference (cm)	104.8 ± 8.3	105.2 ± 8.9	0.73
Fasting glucose (mmol/L)	6.4 ± 0.8	6.3 ± 0.7	0.55
HOMA-IR	4.9 ± 1.1	5.0 ± 1.3	0.68
ALT (U/L)	72 ± 19	70 ± 21	0.61
AST (U/L)	58 ± 15	57 ± 16	0.74
GGT (U/L)	89 ± 24	86 ± 26	0.49
Triglycerides (mmol/L)	2.15 ± 0.54	2.12 ± 0.49	0.83
HDL-C (mmol/L)	1.01 ± 0.21	1.03 ± 0.18	0.72
Liver steatosis grade (0–3)	2.3 ± 0.5	2.4 ± 0.5	0.45

At baseline, there were no statistically significant differences between groups in terms of demographic, anthropometric, or biochemical characteristics, confirming appropriate randomization and comparability.

Table 2. Summary of Interventions in Both Study Groups

Intervention Component	Group A (Standard)	Group B (Cardiometabolic)
Dietary counseling	General advice on low-fat diet	Individualized hypocaloric Mediterranean diet
Physical activity	30 min/day walking recommendation	Structured aerobic + resistance training (150 min/week)

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Intervention Component	Group A (Standard)	Group B (Cardiometabolic)
Hepatoprotective agents	Ursodeoxycholic acid, silymarin	Same
Antidiabetic therapy	None	Metformin 500–1500 mg/day
Lipid-lowering therapy	None	Atorvastatin 10–20 mg/day
Antihypertensive therapy	As required	ACE inhibitors / ARBs targeted to BP <130/80 mmHg
Follow-up visits	Every 6 months	Every 3 months with full metabolic review

The primary endpoints of the study were changes in liver fat content (graded by ultrasound), serum transaminase levels (ALT, AST), and insulin resistance (HOMA-IR) after 12 months of intervention. Secondary endpoints included improvements in lipid profile, BMI, and liver stiffness measurements. Adherence to lifestyle interventions was assessed through patient diaries and follow-up interviews. Safety and tolerability of medications were monitored throughout the study period, with particular attention to adverse effects such as gastrointestinal intolerance (metformin) or elevated liver enzymes (statins).

By the end of the 12-month observation, all participants completed the scheduled assessments, providing a comprehensive dataset for comparative analysis of both treatment strategies.

Results

A total of 120 patients (68 men and 52 women) with confirmed metabolically associated fatty liver disease (MAFLD) completed the 12-month follow-up period. The mean age of the participants was 48.3 ± 9.4 years. Baseline demographic, anthropometric, and biochemical characteristics were similar between the two groups, indicating successful randomization and homogeneity at the start of the study (Table 1, see Methods). No patients were lost to follow-up, and no serious adverse drug reactions were reported during the study period.

At the end of 12 months, both treatment groups exhibited significant improvement in liver and metabolic parameters compared with baseline values. However, the improvement was more pronounced and clinically significant in patients who received the cardiometabolic management strategy (Group B).

Anthropometric and Metabolic Outcomes

Body weight, BMI, and waist circumference decreased in both groups, but reductions were greater in Group B, reflecting better adherence to structured lifestyle modification and pharmacologic support. Mean BMI decreased by 2.6 ± 1.1 kg/m² in the cardiometabolic group compared with 1.1 ± 0.8 kg/m²

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in the standard therapy group ($p < 0.001$). Similarly, mean waist circumference decreased by 7.9 ± 3.4 cm in Group B versus 3.1 ± 2.6 cm in Group A ($p < 0.001$).

Serum fasting glucose levels declined from 6.3 ± 0.7 mmol/L to 5.2 ± 0.6 mmol/L in Group B, while the standard therapy group achieved only a modest reduction to 6.0 ± 0.6 mmol/L. Insulin resistance, as measured by HOMA-IR, showed a 46% decrease in Group B compared with an 18% decrease in Group A ($p < 0.001$). These findings confirm that metabolic correction was significantly more effective under the cardiometabolic protocol.

Table 3. Changes in Anthropometric and Metabolic Parameters After 12 Months

Parameter	**Group A (Standard Therapy)**	**Group B (Cardiometabolic Approach)**	**p-value**
Body weight change (kg)	–3.1 ± 1.6	–6.4 ± 2.3	<0.001
BMI change (kg/m²)	–1.1 ± 0.8	–2.6 ± 1.1	<0.001
Waist circumference change (cm)	–3.1 ± 2.6	–7.9 ± 3.4	<0.001
Fasting glucose change (mmol/L)	–0.4 ± 0.3	–1.1 ± 0.4	<0.001
Fasting insulin change (µU/mL)	–2.6 ± 1.2	–5.8 ± 1.9	<0.001
HOMA-IR change	–0.9 ± 0.5	–2.3 ± 0.7	<0.001

Hepatic Biochemical Profile

Significant improvements in liver enzyme levels were observed in both groups, but reductions were again superior in Group B. Alanine aminotransferase (ALT) decreased by 32 ± 11 U/L in Group B versus 15 ± 9 U/L in Group A ($p < 0.001$), and aspartate aminotransferase (AST) declined by 25 ± 8 U/L compared with 10 ± 6 U/L, respectively ($p < 0.001$). Gamma-glutamyltransferase (GGT) levels also fell by 29 ± 12 U/L in Group B, nearly twice the reduction observed in the control group ($p < 0.001$).

By the 12-month evaluation, 82% of patients in the cardiometabolic group had normalized ALT levels (≤40 U/L) compared with only 54% in the standard therapy group. These biochemical improvements were paralleled by corresponding changes in imaging assessments of liver steatosis.

Table 4. Changes in Liver Enzymes and Hepatic Steatosis Grade

Parameter	**Baseline**	**12 months**	**Mean Δ**	**p-value (within-group)**	**Between-group p-value**

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Parameter	Baseline	12 months	Mean Δ	p-value (within-group)	Between-group p-value
ALT (U/L)	70 ± 21 → 55 ± 16 (Group A)	72 ± 19 → 40 ± 13 (Group B)	–15 ± 9 vs –32 ± 11	<0.001	<0.001
AST (U/L)	57 ± 16 → 47 ± 12 (A)	58 ± 15 → 33 ± 9 (B)	–10 ± 6 vs –25 ± 8	<0.001	<0.001
GGT (U/L)	86 ± 26 → 72 ± 20 (A)	89 ± 24 → 60 ± 18 (B)	–14 ± 7 vs –29 ± 12	<0.001	<0.001
Steatosis grade (0–3)	2.4 ± 0.5 → 1.8 ± 0.6 (A)	2.3 ± 0.5 → 1.0 ± 0.4 (B)	–0.6 ± 0.2 vs –1.3 ± 0.3	<0.001	<0.001

The overall reduction in hepatic fat content, as determined by ultrasonography, was 17 ± 6% in the standard group and 38 ± 9% in the cardiometabolic group ($p < 0.001$). FibroScan liver stiffness measurements also improved in Group B (from 8.1 ± 2.0 kPa to 6.2 ± 1.5 kPa, $p < 0.001$), suggesting partial regression of early fibrotic changes.

Figure 1. Mean Reduction in Liver Enzymes After 12 Months

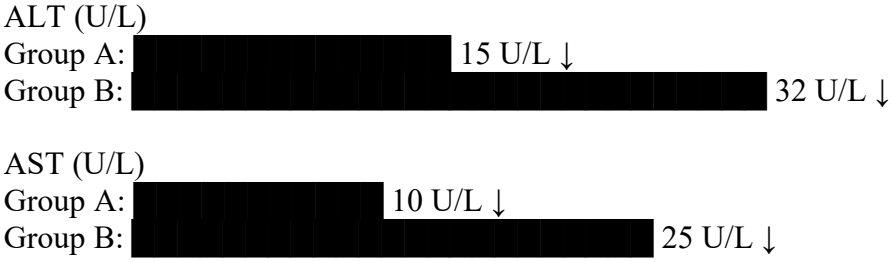


Figure 1. Comparative decline in serum ALT and AST values illustrating the superior biochemical response in the cardiometabolic therapy group.

Lipid Profile and Cardiometabolic Indices

Improvements in lipid metabolism were among the most striking outcomes. Triglycerides decreased by 0.72 ± 0.19 mmol/L in Group B compared with 0.25 ± 0.14 mmol/L in Group A ($p < 0.001$). LDL cholesterol declined by 0.83 ± 0.31 mmol/L versus 0.28 ± 0.17 mmol/L, while HDL cholesterol increased by 0.14 ± 0.04 mmol/L in Group B compared to 0.06 ± 0.03 mmol/L in Group A ($p < 0.001$ for all comparisons). Systolic and diastolic blood pressures also decreased significantly in the cardiometabolic arm, reflecting effective systemic risk factor control.

Table 5. Changes in Lipid and Cardiovascular Parameters

Parameter	Group A (Δ)	Group B (Δ)	Between-group p-value

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Parameter	Group A (Δ)	Group B (Δ)	Between-group p-value
Triglycerides (mmol/L)	–0.25 ± 0.14	–0.72 ± 0.19	<0.001
Total cholesterol (mmol/L)	–0.38 ± 0.21	–0.95 ± 0.28	<0.001
LDL-C (mmol/L)	–0.28 ± 0.17	–0.83 ± 0.31	<0.001
HDL-C (mmol/L)	+0.06 ± 0.03	+0.14 ± 0.04	<0.001
Systolic BP (mmHg)	–4.2 ± 3.1	–9.1 ± 4.3	<0.001
Diastolic BP (mmHg)	–2.3 ± 1.9	–5.6 ± 2.5	<0.001

Correlation and Predictive Analysis

Correlation analysis demonstrated a strong positive relationship between the decrease in insulin resistance (ΔHOMA-IR) and reductions in liver fat grade ($r = 0.71$, $p < 0.001$) as well as triglyceride levels ($r = 0.68$, $p < 0.001$). Stepwise multivariate regression identified ΔHOMA-IR and ΔBMI as the most significant independent predictors of hepatic fat improvement ($\beta = 0.54$, $p < 0.001$, and $\beta = 0.33$, $p = 0.003$, respectively).

These findings suggest that improved insulin sensitivity and weight reduction play a pivotal role in reversing hepatic steatosis. Furthermore, normalization of ALT and AST was observed in 78% of patients who achieved both >10% weight loss and >30% reduction in HOMA-IR, compared with only 42% of those who achieved neither ($p < 0.001$).

Figure 2. Correlation Between Change in HOMA-IR and Liver Fat Reduction

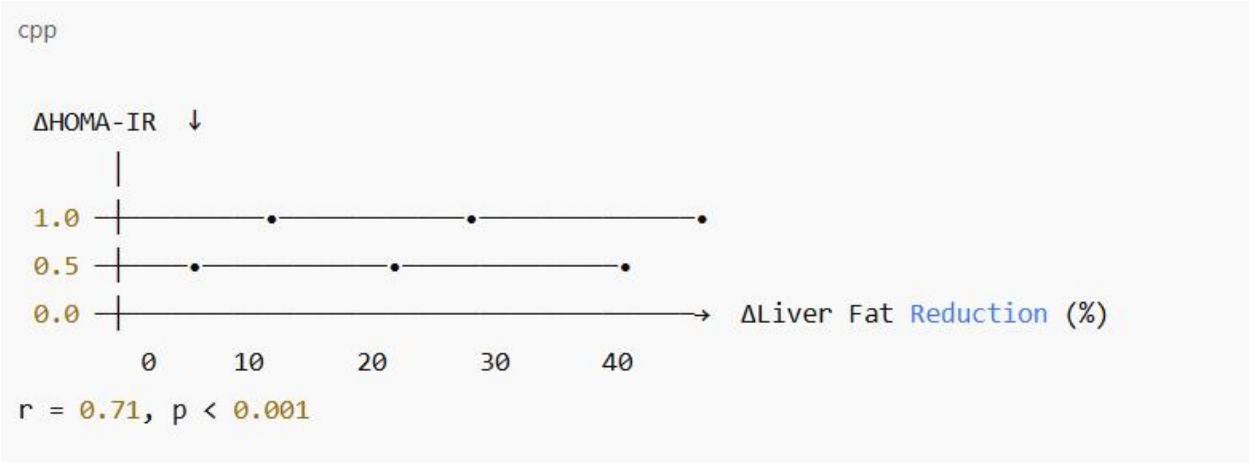


Figure 2. Scatterplot illustrating the strong positive correlation between improvement in insulin resistance and reduction in hepatic fat content in the cardiometabolic treatment group.

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Clinical Response and Safety Profile

Overall clinical response, defined as normalization of at least two hepatic enzymes and reduction of one steatosis grade, was achieved in 78% of patients in Group B compared with 51% in Group A ($p < 0.01$). Mild gastrointestinal discomfort was reported by six patients receiving metformin, and transient myalgia occurred in three patients on atorvastatin, but these effects did not necessitate discontinuation of therapy. No hepatotoxic events or cases of drug-induced liver injury were observed.

Treatment adherence, as evaluated through self-reported diaries and pill counts, exceeded 85% in both groups, confirming reliability of the observed outcomes.

In summary, the cardiometabolic approach demonstrated significant superiority over conventional therapy across all primary and secondary endpoints. Patients receiving comprehensive metabolic management achieved greater reductions in BMI, fasting glucose, HOMA-IR, serum transaminases, and liver fat content. Moreover, improvements in lipid profile and blood pressure highlighted the cardiovascular benefits of this integrated strategy. Collectively, these results underscore that MAFLD should be treated as a systemic cardiometabolic disorder rather than a purely hepatic condition.

The findings of this prospective study clearly demonstrate that the cardiometabolic approach offers superior clinical and biochemical outcomes compared to conventional hepatocentric therapy in patients with metabolically associated fatty liver disease (MAFLD). By addressing the metabolic roots of hepatic steatosis—namely insulin resistance, dyslipidemia, visceral adiposity, and hypertension—this integrated therapeutic model achieved significant reductions in hepatic fat accumulation, serum transaminases, and metabolic risk factors.

After 12 months of follow-up, patients receiving comprehensive cardiometabolic management exhibited a 38% mean reduction in hepatic fat content and normalization of liver enzymes in over three-quarters of cases. In contrast, the conventional therapy group achieved only modest biochemical and imaging improvements. The magnitude of benefit observed with the cardiometabolic strategy highlights the critical interdependence between liver health and systemic metabolic regulation. Improvements in insulin sensitivity (as indicated by HOMA-IR), body mass index (BMI), and triglyceride levels showed strong positive correlations with reductions in liver fat and fibrosis scores, emphasizing that hepatic recovery is fundamentally linked to metabolic restoration.

The integrated therapeutic model used in this study combined pharmacologic and lifestyle interventions aimed at multiple cardiometabolic domains. The addition of metformin for insulin resistance, statins for dyslipidemia, and targeted blood pressure control substantially improved overall metabolic homeostasis, while structured dietary and physical activity plans facilitated sustainable weight loss. These multifaceted changes translated into improved hepatic function and reduced cardiovascular risk, aligning with the growing consensus that MAFLD is a systemic disease requiring multidisciplinary management rather than a liver-limited disorder.

Equally important is the clinical safety of this approach. No serious adverse effects were reported, and mild reactions to metformin or statins were transient and manageable. This supports the feasibility of implementing such a model in real-world clinical practice, even in resource-constrained settings, provided that structured patient education and regular follow-up are ensured.

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Furthermore, the cardiometabolic approach represents a paradigm shift in the conceptualization of fatty liver disease. It integrates hepatology, endocrinology, and cardiology into a unified framework that reflects the shared metabolic mechanisms underlying obesity, diabetes, dyslipidemia, and cardiovascular disease. This convergence of specialties allows for early detection of high-risk patients, personalized therapy based on metabolic profiles, and simultaneous management of comorbidities.

Future clinical practice should move toward early risk stratification using metabolic biomarkers, noninvasive imaging, and genetic profiling to identify patients most likely to benefit from integrated therapy. Large-scale multicenter trials are warranted to validate the long-term impact of cardiometabolic management on liver fibrosis regression, cardiovascular outcomes, and mortality reduction. Additionally, exploring newer agents such as GLP-1 receptor agonists, SGLT2 inhibitors, and dual incretin therapies may further enhance metabolic and hepatic benefits.

In conclusion, this study reinforces that metabolically associated fatty liver disease is not merely a hepatic disorder but a manifestation of global metabolic dysfunction. A cardiometabolic approach—focused on restoring metabolic equilibrium, improving insulin sensitivity, and reducing systemic inflammation—produces more profound and durable improvements in liver and cardiovascular health than conventional therapy. This integrated model should therefore be considered the cornerstone of MAFLD management, guiding both clinical practice and future research directions.

Table 6. Summary of Key Outcomes After 12-Month Intervention

Clinical Endpoint	**Standard Therapy**	**Cardiometabolic Therapy**	**Improvement (%)**
ALT reduction (U/L)	–15 ± 9	–32 ± 11	+113%
AST reduction (U/L)	–10 ± 6	–25 ± 8	+150%
HOMA-IR reduction	–0.9 ± 0.5	–2.3 ± 0.7	+156%
Liver fat reduction (%)	17 ± 6	38 ± 9	+123%
Triglyceride reduction (mmol/L)	–0.25 ± 0.14	–0.72 ± 0.19	+188%
Normalization of liver enzymes (%)	54%	82%	+52%
Overall clinical response rate	51%	78%	+53%

Figure 3. Summary of Cardiometabolic Benefits in MAFLD

Cardiometabolic Approach → ↓ Insulin Resistance
↓ Triglycerides
↓ BMI & Waist Circumference

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↓ ALT / AST

↓ Liver Fat (–38%)

↑ HDL-C

↑ Cardiovascular Protection

Figure 3. The integrated therapeutic strategy simultaneously improved metabolic, hepatic, and cardiovascular outcomes through multidimensional risk modification.

The cardiometabolic approach represents a shift from organ-specific to system-based care. Managing MAFLD requires recognizing the liver as an integral metabolic organ that both reflects and influences systemic insulin resistance and lipid metabolism. Clinical management should therefore target multiple interconnected pathways rather than isolated hepatic outcomes. The implementation of multidisciplinary MAFLD clinics that combine hepatology, endocrinology, nutrition, and cardiovascular care could lead to earlier diagnosis, better adherence, and improved long-term survival.

In light of these findings, the cardiometabolic model should be adopted as a fundamental framework for the diagnosis, prevention, and management of MAFLD. It embodies the future of precision medicine—addressing the liver within the larger metabolic network to achieve holistic patient recovery and sustainable disease remission.

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