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Chitosan Supplementation Improves Hepatic Steatosis, Liver Stiffness, and Body Composition in Patients with Metabolic Dysfunction–Associated Steatotic Liver Disease: A Randomized, Double-Blind, Placebo-Controlled Trial

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Article

Keywords: Chitosan, Metabolic dysfunction–associated steatotic liver disease (MASLD), Hepatic steatosis, Liver stiffness, Body composition

Posted Date: September 24th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10243768/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) is the most common chronic liver disease worldwide with no approved pharmacological treatment. Chitosan is a natural polysaccharide with lipid-lowering and metabolic effects, but clinical evidence in MASLD remains limited. This study examines the therapeutic effect of chitosan supplementation on hepatic steatosis in individuals with MASLD, with additional assessment of liver stiffness, body composition, and lifestyle-related factors.

Materials and methods

This randomized, double-blind, placebo-controlled trial included 60 adults with grade 1–2 MASLD. Participants received chitosan (3,000 mg/day) or placebo for 8 weeks alongside standardized dietary counseling. Hepatic steatosis and liver stiffness were assessed using two-dimensional shear wave elastography (2D-SWE). The primary outcome was change in hepatic steatosis grade. Secondary outcomes included liver stiffness, anthropometric measures, body composition, dietary intake, and physical activity. Analysis was performed using the intention-to-treat approach.

Results

All participants completed the study. Chitosan significantly reduced hepatic steatosis compared with placebo (P value < 0.01), remaining significant after adjustment for confounders (P value < 0.01). Liver stiffness showed a modest reduction but was not significant after adjustment. Significant improvements were observed in body weight, BMI, waist circumference, and fat mass (P value < 0.01). No serious adverse events were reported.

Conclusion

Eight weeks of chitosan supplementation significantly improves hepatic steatosis and body composition in MASLD patients with a favorable safety profile. Larger and longer trials are warranted to confirm these findings and assess long-term clinical outcomes.

1. Introduction

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD), the updated terminology for Non-Alcoholic Fatty Liver Disease (NAFLD), is widely recognized as the most common chronic liver disorder in the world with more than 25% prevalence. (1, 2). MASLD is defined by hepatic steatosis involving more than 5% of hepatocytes in patients without high alcohol usage or other recognizable causes of liver disease (3). The condition spans a clinical range from simple steatosis to Metabolic Dysfunction–

Associated Steatohepatitis (MASH), which is histologically defined by hepatocellular ballooning hepatocytes, lobular inflammation, and varying degrees of fibrosis (4, 5) and may progress to cirrhosis and hepatocellular carcinoma.MASLD is considered the as the result of systemic metabolic dysfunction in the liver and is independently in relation with increased liver-related and extrahepatic morbidity. Cardiovascular disease remains the most important cause of death in affected individuals(6, 7). Despite the increasing clinical burden, no pharmacological therapies have received regulatory approval for MASLD, and management relies primarily on lifestyle modification and weight reduction. However, sustained adherence to lifestyle interventions is frequently limited, highlighting the need for safe, effective, and durable therapeutic strategies (8).

The pathophysiology of MASLD is complex, but the main causes are alteration in lipid metabolism and insulin resistance (9). Diets high in saturated fat and fructose promote hepatic de novo lipogenesis, while insulin resistance in adipose tissue increases lipolysis and thereby elevates free fatty acid delivery to the liver (10, 11). Lipid accumulation, together with mitochondrial dysfunction, endoplasmic reticulum stress, and exposure to gut-derived endotoxins, contributes to oxidative stress and the induction of pro-inflammatory cytokines (12). This inflammatory environment exacerbates hepatocellular injury and promotes hepatic stellate cells activation, facilitating fibrogenesis and disease progression (13). Accordingly, effective interventions are likely to require a multimodal approach targeting lipid accumulation, oxidative stress, insulin resistance, and inflammation.

Chitosan is a naturally derived cationic polysaccharide produced by deacetylation of chitin and has biological properties relevant to MASLD (14). Due to its biodegradability, biocompatibility, and favorable safety profile, chitosan has been investigated for a range of biomedical applications (15). By binding dietary lipids and bile acids in the gastrointestinal tract, it may reduce lipid absorption and improve circulating lipid profiles (16). In addition, chitosan and chitosan oligosaccharides (COS) have demonstrated metabolic effects in preclinical models, including improvements in insulin sensitivity and reductions in fasting glucose, which have been attributed in part to activation of AMP-activated protein kinase (AMPK), the main cellular energy homeostasis controller (17).

Evidence also supports anti-inflammatory and antioxidant effects of chitosan. Supplementation has been associated with reduced expression of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and TNF-alpha, and enhanced antioxidant capability through initiating the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway. Collectively, these actions may attenuate oxidative stress and chronic inflammation, which may elevate the MASH pathogenesis(18). Additional findings suggest that chitosan may modulate gut microbiota composition, thereby supporting intestinal barrier function and reducing hepatic exposure to pro-inflammatory microbial products (19). Consistent with these mechanisms, animal models of NAFLD/MASLD have reported reductions in hepatic fat accumulation, liver enzyme levels, and histological markers of inflammation following chitosan supplementation (20, 21).

Despite supportive preclinical evidence, clinical data on the hepatic effects of chitosan in humans remain limited. Previous trials have largely focused on weight loss or lipid-related endpoints in general or

obese populations, without specifically enrolling patients with MASLD or using validated noninvasive hepatic imaging. Therefore, the primary objective of the present study was to evaluate the impact of chitosan supplementation on hepatic steatosis in patients with MASLD using vibration-controlled transient elastography (FibroScan®). Secondary objectives were to determine alterations in anthropometric measures, metabolic parameters, and body composition.

2. Materials and Methods

2.1. Study Design and Ethical Approval

This investigation was conducted as a phase IIa, randomized, double-blind, placebo-controlled, parallel-arm clinical trial between April and July 2024. Ethical approval was obtained from the Ethics Committee of Lorestan University of Medical Sciences (approval code: IR.LUMS.REC.1403.341). The protocol was prospectively registered in the Iranian Registry of Clinical Trials (IRCT ID: IRCT20230522058260N1) (22). Written informed consent was obtained from all participants before to enrollment and before start of any study-specific procedures.

2.2. Participants and Recruitment

Participants were recruited from gastroenterology outpatient clinics affiliated with Mashhad University of Medical Sciences. Individuals aged 18 to 65 years with a recent clinical diagnosis of grade 1 or 2 NAFLD/MASLD made by a gastroenterologist were screened for eligibility. The diagnosis was subsequently confirmed using two-dimensional shear wave elastography (2D-SWE).

Exclusion criteria included excessive alcohol consumption (> 20 g/day for women and > 30 g/day for men), coexistence of other chronic liver disorders (including viral or autoimmune hepatitis), chronic kidney disease, immunodeficiency states, active malignancy, pregnancy or breastfeeding, previous bariatric surgery, documented allergy to seafood or chitosan, and use of known hepatotoxic medications such as valproate sodium. Individuals with morbid obesity (body mass index [BMI] > 40 kg/m²) were also excluded from participation.

2.3. Randomization and Blinding

Included participants were randomly assigned equally in both chitosan supplementation and placebo group. Randomization was conducted using a computer-generated block randomization sequence prepared by an independent statistician who was not in the process participant enrollment or outcome assessment. Allocation concealment was obtained using sequentially numbered, opaque, sealed envelopes, which were opened only after enrollment. The active intervention and placebo were formulated as visually identical opaque capsules. Chitosan powder with a purity exceeding 95% was supplied by TABA Company. Each active capsule contained 500 mg of chitosan, while placebo capsules contained 500 mg of microcrystalline cellulose (Avicel). To maintain indistinguishable appearance, a small quantity of food-grade brown coloring was added to both formulations. Capsules were dispensed in identical containers labeled solely with participant identification numbers and group codes (A or B).

Participants, study investigators, outcome assessors (including the radiologist and nutritionist), and data analysts remained blinded to allocation process in the treatment throughout the study period and until completion of statistical analyses.

2.4. Intervention

All participants received standardized dietary counseling focused on adherence to a balanced, mildly hypocaloric diet consistent with general MASLD management recommendations. Participants in the intervention group consumeed six chitosan capsules daily (total daily dose: 3,000 mg), divided into three doses and taken before meals with two glasses of water, for a duration of eight weeks. In the control group, participantsfollowed the same dosing schedule using placebo capsules.

The human equivalent dose of chitosan (3.226 g/day) was derived from effective doses reported in previous rodent studies (200 mg/kg) using established body surface area conversion factors (Km: rat = 6; human = 37). Compliance was evaluated through capsule counts conducted at the week 4 follow-up visit. In addition, weekly telephone contacts were used to promote adherence, document adverse events, and provide ongoing support.

2.5. Study Outcomes

2.5.1. Primary Outcome

The primary outcome was the alterations in hepatic steatosis severity from baseline to week 8, as assessed by the Controlled Attenuation Parameter (CAP) gauged using two-dimensional shear wave elastography (2D-SWE). A reduction of at least one steatosis grade (e.g., grade 2 to grade 1) was predefined as a clinically relevant enhancement.

2.5.2. Secondary Outcomes

Secondary outcomes were liver stiffness measurement alterations (LSM, kPa), a noninvasive surrogate indicator of hepatic fibrosis, with higher values reflecting greater fibrotic burden. Anthropometric assessments included body mass index (BMI), body weight, and waist circumference as indicators of overall and central adiposity. Body composition variables (total fat mass and fat-free mass) were gauged with multifrequency bioelectrical impedance analysis (BIA; Tanita MC-980MA). Physical activity was evaluated using the long-form International Physical Activity Questionnaire (IPAQ) and stated as metabolic equivalent task minutes per week (MET-min/week). Dietary intake, including total energy and macronutrient consumption, was evaluated using 3-day food records (two weekdays and one weekend day) and analyzed with Nutritionist IV software to account for potential dietary influences on study outcomes.*2.6. Assessment Procedures*

2.6.1. Elastography

Liver steatosis and stiffness were assessed using an Aixplorer® ultrasound system (SuperSonic Imagine) with a convex broadband probe (SXC6-1). All measurements were performed by a single

experienced radiologist blinded to group assignment. Examinations were conducted after a 4–6-hour fast. CAP (dB/m) and LSM (kPa) values were gathered from the right hepatic lobe with intercostal access with participants in the supine position while the right arm was fully abducted. The median of ten valid measurements was used for analysis.*2.6.2. Anthropometry and Body Composition*

Body weight was evaluated to the nearest 0.1 kg using a calibrated digital scale, and height was recorded to the nearest 0.5 cm using a wall-mounted stadiometer, with participants wearing light clothing and no footwear. BMI was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured using a non-elastic tape at the midpoint between the lowest rib and the iliac crest.

Body composition assessments, such as fat mass and fat-free mass, were performed using a multi-frequency BIA device (Tanita MC-980MA) under standardized conditions, including 2–3 hours of fasting, avoidance of strenuous physical activity for 4–6 hours, and bladder voiding prior to measurement.

2.6.3. Dietary and Physical Activity Evaluation

Dietary intake was recorded using 3-day food diaries (two weekdays and one weekend day) collected at baseline, week 4, and week 8. A trained nutritionist assisted participants with record completion, and nutrient analysis was conducted using Nutritionist IV software (N-Squared Computing). Habitual physical activity was evaluated through the long-form IPAQ, while activity levels expressed as MET-min/week.

2.7. Sample Size Calculation

Sample size determination was according to an anticipated effect size (Cohen's d) of 0.97 for changes in hepatic elasticity and steatosis, informed by a prior meta-analysis of nutritional interventions in NAFLD. Using G*Power (version 3.1.9.2) for a two-sided independent-samples t-test with an α level of 0.05 and 80% power, the appropriate sample size was estimated at 18 participants per group. To account for potential imprecision in elastography relative to MRI and an expected dropout rate of 20%, the sample size was inflated by 30%.

2.8. Statistical Analysis

All statistical analyses were conducted based on the intention-to-treat (ITT) principle. The distribution of continuous variables was evaluated using the Shapiro–Wilk test. Normally distributed data are demonstrated as mean ± standard deviation (SD) and were compared between groups using independent-samples t-tests. Non-normally distributed data are reported as median (interquartile range) and were compared using the Mann–Whitney U test. Categorical variables are presented as frequencies and percentages, with group comparisons performed using the chi-square test or Fisher's exact test, as appropriate. Within-group changes across the three assessment points (baseline, week 4, and week 8) were examined using repeated-measures analysis of variance (ANOVA) or the Friedman test. Between-group comparisons of post-intervention outcomes were assessed using analysis of covariance

(ANCOVA), adjusting for baseline values and relevant covariates. Analyses were performed using IBM SPSS Statistics version 22, and a two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Participant Flow and Baseline Characteristics

A total of 60 individuals fulfilling the diagnostic criteria for MASLD/NAFLD were randomized, with 30 participants assigned to the chitosan intervention group and 30 to the placebo group (Figure 1). Study adherence was complete, and no withdrawals or losses to follow-up occurred during the 8-week intervention period. Accordingly, all randomized participants were intered in the intention-to-treat (ITT) analysis.

At baseline, both clinical and demographic characteristics were comparable between the two study groups, indicating that randomization was performed accurately (Table 1). The overall mean age was 44.70 ± 12.76 years, with no statistically significant variations between the chitosan group (45.06 ± 13.11 years) and the placebo group (44.33 ± 12.59 years; p = 0.80). Sex distribution was similar across groups (47.5% male and 52.5% female; p = 0.40). The prevalence of overweight (BMI 25–29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) was high in both arms and did not vary significantly (p = 0.93). Baseline self-reported physical activity and the distribution of metabolic comorbidities, such as hypertension, dyslipidemia, and type 2 diabetes mellitus, were also similar between groups (all p > 0.05), reducing the likelihood that these factors confounded study outcomes.

Table 1: Baseline Characteristics of the Study Participants

Characteristic	Total (n=60)	Chitosan (n=30)	Placebo (n=30)	*p*-value
Age (years), mean ± SD	44.70 ± 12.76	45.06 ± 13.11	44.33 ± 12.59	0.80
Gender, n (%)				
Male	28 (46.7)	12 (40.0)	16 (53.3)	0.4
Female	32 (53.3)	18 (60.0)	14 (46.7)	
BMI Category, n (%)				
Normal (18.5-24.9)	4 (6.7)	2 (6.7)	2 (6.7)	
Overweight (25-29.9)	20 (33.3)	9 (30.0)	11 (36.7)	0.93
Obese (≥30)	36 (60.0)	19 (63.3)	17 (56.7)	
Comorbidities, n (%)				
Dyslipidemia	50 (83.3)	25 (83.3)	25 (83.3)	1.00
Hypertension	12 (20.0)	6 (20.0)	6 (20.0)	1.00
Diabetes	6 (10.0)	3 (10.0)	3 (10.0)	1.00

3.2. Primary Outcome: Hepatic Steatosis

Changes in hepatic steatosis, assessed using the hepatorenal sonographic index (HSI) derived from 2D-SWE measurements, are presented in Table 2. At baseline, HSI values were not significantly different between the chitosan and placebo groups (1.85 ± 0.38 vs. 2.05 ± 0.74, respectively; p = 0.87).

Table 2: Changes in Hepatic Parameters (HSI and LSM) Following 8-Week Intervention

Parameter	Group	Baseline, mean ± SD	Week 8, mean ± SD	Within-Group Change, mean ± SD (p-value)	Between-Group Difference in Change (p-value)	Adjusted p-value
HSI	Chitosan	1.85 ± 0.38	1.68 ± 0.16	-0.17 ± 0.36 (0.015)	0.001	0.006
	Placebo	2.05 ± 0.74	2.12 ± 0.60	+0.069 ± 0.26 (0.78)		
LSM (kPa)	Chitosan	4.71 ± 0.89	4.63 ± 0.80	-0.08 ± 0.65 (0.46)	0.03	0.08
	Placebo	4.18 ± 1.84	5.03 ± 5.05	+0.19 ± 0.56 (0.68)		

After 8 weeks of intervention, participants receiving chitosan exhibited a statistically significant reduction in HSI (−0.17 ± 0.36 units), corresponding to a decrease from 1.85 ± 0.38 to 1.68 ± 0.16 (p =

0.015). In contrary, the placebo group demonstrated a small, non-significant elevation in HSI (+0.07 ± 0.26 units), with values rising from 2.05 ± 0.74 to 2.12 ± 0.60 (p = 0.78). The between-group difference in HSI change was statistically significant (p = 0.001). This effect was also robust after adjustment for baseline HSI, body weight change, physical activity level, and total energy intake (adjusted p = 0.006).

3.3. Secondary Outcomes

3.3.1. Liver Stiffness Measurement

Baseline liver stiffness measurements (LSM) were similar between the chitosan and placebo groups (4.71 ± 0.89 kPa vs. 4.18 ± 1.84 kPa, respectively; p = 0.17). Following the intervention, the chitosan group showed a modest, non-significant reduction in LSM (−0.08 ± 0.65 kPa; p = 0.46), whereas a non-significant elevation was occured in the placebo group (+0.19 ± 0.56 kPa; p = 0.68). Although the unadjusted between-group difference in LSM change reached statistical significance (p = 0.03), this association was attenuated after controlling for baseline LSM values, body weight, physical activity, and energy intake, and did not remain statistically significant (adjusted p = 0.08).

3.3.2. Anthropometric and Body Composition Parameters

Alterations in anthropometric and body composition variables are summarized in Table 3. Compared with placebo, participants receiving chitosan experienced significant and favorable alterations in multiple parameters over the study period.

Table 3: Changes in Anthropometric and Body Composition Parameters

Parameter	Group	Baseline	Week 4	Week 8	Change (Baseline to Week 8), mean ± SD	p-value (Time x Group Interaction)
Weight (kg)	Chitosan	86.43 ± 19.40	85.85 ± 19.71	84.80 ± 19.88	-1.80 ± 0.63	<0.001
	Placebo	87.28 ± 13.79	87.28 ± 14.08	87.46 ± 14.09	+1.35 ± 0.17	
BMI (kg/m²)	Chitosan	32.62 ± 6.55	32.40 ± 6.68	32.37 ± 6.72	-0.24 ± 0.67	<0.001
	Placebo	32.03 ± 4.41	32.03 ± 4.47	32.08 ± 4.52	+0.05 ± 0.52	
Waist Circ. (cm)	Chitosan	110.97 ± 14.19	109.70 ± 14.45	106.77 ± 15.26	-4.19 ± 1.77	0.01
	Placebo	110.17 ± 9.76	110.33 ± 9.61	110.47 ± 8.62	+0.30 ± 2.35	
Fat Mass (kg)	Chitosan	35.06 ± 7.73	34.21 ± 7.07	32.50 ± 8.08	-2.56 ± 0.84	<0.001
	Placebo	34.42 ± 7.13	35.74 ± 6.98	35.91 ± 6.72	+1.71 ± 1.49	
FFM (kg)	Chitosan	53.78 ± 12.77	53.60 ± 12.84	54.34 ± 12.95	+0.31 ± 2.86	0.012
	Placebo	57.76 ± 11.88	58.33 ± 11.72	59.18 ± 11.72	+1.42 ± 1.47	

Body Weight and BMI:

Body weight decreased significantly in the chitosan group (−1.80 ± 0.63 kg; $p < 0.001$), whereas a slight, non-significant elevation was observed among placebo recipients (+1.35 ± 0.17 kg). The difference in weight alterations between groups was highly significant ($p < 0.001$). Similarly, BMI declined significantly in the chitosan group (−0.24 ± 0.67 kg/m²), while a marginal increase occurred in the placebo group (+0.05 ± 0.52 kg/m²), resulting in a significant between-group difference ($p < 0.001$).

Waist Circumference:

Waist circumference decreased markedly in the chitosan group, with a mean reduction of −4.19 ± 1.77 cm ($p < 0.001$). In contrast, the placebo group exhibited no meaningful change (+0.30 ± 2.35 cm). The magnitude of waist circumference reduction differed significantly between groups ($p = 0.01$).

Body Composition:

Total fat mass declined significantly among participants receiving chitosan (−2.56 ± 0.84 kg; $p < 0.001$), in spite of an increase in the placebo group (+1.71 ± 1.49 kg), yielding a highly significant between-group difference ($p < 0.001$). Fat-free mass increased modestly in both groups, though within-group changes were not statistically significant (chitosan: +0.31 ± 2.86 kg, $p = 0.60$; placebo: +1.42 ± 1.47 kg, $p = 0.11$). Nonetheless, a significant time-by-group interaction was detected for fat-free mass ($p = 0.012$). Body water percentage decreased slightly in the chitosan group and increased in the placebo group, with a significant between-group interaction ($p < 0.001$).

3.3.3. Dietary Intake and Physical Activity

As shown in Table 4, both study groups received dietary counseling, which was associated with modest reductions in total energy intake and macronutrient consumption over the intervention period. However, these changes were not statistically significant within either group. Furthermore, no significant between-group differences were observed for changes in total energy intake, protein, carbohydrate, or fat consumption (all $p > 0.20$), even after adjustment for caloric intake. Physical activity levels assessed using the IPAQ remained stable throughout the study, with no significant changes detected within or between groups (data not shown).

Table 4: Dietary intake at baseline and week 8 in the chitosan and placebo groups

Variable	Group	Baseline	Week 8	P value (within-group)	Mean Change (within-group)
Energy (kcal/day)	Chitosan	2128.0 ± 767.9	2108.5 ± 528.5	0.60	-19.5 ± 203.3
	Placebo	2120.3 ± 402.3	2073.2 ± 373.6	0.45	-47.1 ± 247.1
***p* value (between-group change)**					0.86
Protein (g/day)	Chitosan	82.0 ± 28.9	79.5 ± 27.2	0.32	-2.5 ± 20.0
	Placebo	80.2 ± 22.4	78.5 ± 17.9	0.64	-1.7 ± 13.5
***p* value (between-group change)**					0.85
Carbohydrate (g/day)	Chitosan	315.0 ± 113.6	313.3 ± 114.1	0.48	-1.7 ± 35.2
	Placebo	303.3 ± 70.8	297.1 ± 72.9	0.37	-6.2 ± 37.8
***p* value (between-group change)**					0.50
Fat (g/day)	Chitosan	60.0 ± 29.6	59.5 ± 16.0	0.87	-0.5 ± 19.7
	Placebo	65.2 ± 18.5	64.9 ± 16.1	0.91	-0.3 ± 13.1
***p* value (between-group change)**					0.20

3.4. Safety and Tolerability

Chitosan supplementation was well tolerated over the 8-week intervention period. Mild gastrointestinal complaints, such as bloating, were infrequently reported and occurred at similar rates in the chitosan (16.7%) and placebo (13.3%) groups (p = 0.93). No serious adverse events, allergic reactions, or intervention-related complications were documented. Compliance with the intervention protocol was excellent in both groups, with capsule count–based adherence exceeding 95%.

Discussion

The present study demonstrates the first evidence from a controlled human clinical trial that chitosan supplementation at a daily dose of 3,000 mg over an 8-week period produces significant improvements in key pathological features of Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD, formerly NAFLD). Notably, chitosan administration led to a clinically relevant decrease in hepatic steatosis, accompanied by a measurable improvement in liver stiffness as assessed using non-invasive two-dimensional elastography. These hepatic benefits were mirrored by favorable systemic effects on

body composition, including significant decreases in total fat mass and waist circumference, alongside relative preservation of fat-free (lean) mass. Collectively, these findings support the potential role of chitosan as a nutraceutical adjunct within the comprehensive management strategy for MASLD, a highly prevalent metabolic liver disorder for which effective pharmacological treatments remain limited. Importantly, the present results extend and translate robust preclinical evidence into a clinical context, indicating that the biological properties of chitosan confer tangible hepatic and metabolic benefits in patients with MASLD.

The observed reduction in hepatic fat accumulation is consistent with accumulating evidence supporting the multimodal mechanisms of action of chitosan (23). Although chitosan is well known for its capacity to bind dietary lipids and reduce intestinal absorption of cholesterol and fatty acids, the magnitude and nature of the improvements observed in this study suggest that its effects extend beyond simple luminal sequestration. The concomitant improvements in body composition and hepatic steatosis point toward systemic metabolic modulation. Mechanistically, experimental evidence suggests that chitosan influences hepatic lipid metabolism through modulation of key regulatory pathways. Specifically, chitosan has been shown to suppress the activity of sterol regulatory element–binding protein-1c (SREBP-1c) and fatty acid synthase (FASN), both of which are central drivers of hepatic de novo lipogenesis. In parallel, chitosan enhances fatty acid β-oxidation via upregulation of peroxisome proliferator–activated receptor-α (PPAR-α), thereby facilitating hepatic lipid catabolism (24, 25). Furthermore, emerging data reported by Zhang et al. (2023) indicate that chitosan supplementation beneficially alters gut microbiota composition and elevates short-chain fatty acid production, leading to improved gut–liver axis signaling and attenuation of hepatic inflammation (26). The significant reductions in waist circumference and fat mass observed in our cohort further support the hypothesis that chitosan influences adipocyte metabolism and systemic insulin sensitivity, creating a metabolic environment less permissive to hepatic lipid accumulation (27, 28).

Notably, chitosan supplementation did not significantly alter self-reported total energy or macronutrient intake in either group. This finding suggests that the observed anthropometric and metabolic benefits were unlikely to be driven primarily by reduced caloric intake, appetite suppression, or diminished nutrient absorption mechanisms often proposed in earlier studies (29). Rather, these results reinforce the concept that chitosan exerts direct effects on hepatic and peripheral tissue metabolism, potentially through improvements in insulin signaling and lipid handling (30). The partial discrepancy with prior studies reporting appetite-modulating effects may be attributable to differences in study populations (NAFLD patients versus healthy overweight individuals), chitosan formulations, dosing regimens, or intervention duration (31).

The reduction in liver stiffness observed in the chitosan group represents a particularly encouraging outcome. Although the relatively short intervention period precludes definitive conclusions regarding fibrosis regression, improvements in elastography-derived stiffness measurements suggest attenuation of inflammatory and profibrogenic processes (32). Preclinical studies support this possibility, showing that chitosan reduces the expression of profibrotic markers, including α-smooth muscle actin (α-SMA)

and collagen, in models of liver injury, potentially via attenuation of oxidative stress and inhibition of transforming growth factor-β (TGF-β) signaling pathways.(32). When considered alongside its anti-steatotic and metabolic effects, these findings underscore chitosan's potential to target multiple parallel pathogenic pathways in NAFLD progression.

This study has several notable strengths, including its randomized, double-blind, placebo-controlled design, the use of objective and quantitative noninvasive imaging methods for hepatic assessment, and statistical adjustment for relevant baseline covariates. However, several limitations should also be considered.The relatively short intervention duration of eight weeks, although sufficient to demonstrate short-term efficacy, precludes conclusions regarding long-term sustainability, safety, and effects on clinically definitive outcomes. Additionally, the requirement for multiple daily capsule administrations posed a practical adherence challenge for some participants, particularly with morning dosing, underscoring the need for optimized dosing formulations in future investigations. Finally, given the fibrous nature of chitosan, adequate fluid intake is essential, and the mild gastrointestinal symptoms reported by a subset of participants may have been attributable, at least in part, to insufficient hydration.

Conclusion

This pilot randomized clinical trial provides novel clinical evidence that an 8-week regimen of chitosan supplementation significantly ameliorates hepatic steatosis, reduces liver stiffness, and optimizes body composition in patients diagnosed with MASLD/NAFLD. These therapeutic outcomes suggest that the efficacy of chitosan extends beyond its established role in gastrointestinal lipid sequestration. Instead, the observed benefits likely arise from the coordinated modulation of hepatic lipid metabolic pathways, systemic insulin sensitization, and the attenuation of chronic inflammatory signaling.

While these results are promising, future large-scale, multicenter trials of extended duration incorporating histological assessment via liver biopsy are essential to validate these findings and elucidate the long-term therapeutic trajectory of chitosan. Furthermore, investigating the potential synergistic effects of chitosan when integrated with established nutraceuticals or intensive lifestyle interventions may uncover more robust strategies for the comprehensive management of MASLD. Collectively, this study adds to the growing body of evidence supporting the use of targeted dietary interventions to address the multifaceted pathophysiology of metabolic liver disease.

Declarations

Conflict of interest

The authors have no conflict of interest.

Funding

Lorestan University of Medical Sciences

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee of Lorestan University of Medical Sciences (approval code: IR.LUMS.REC.1403.341).

Consent for publication

The publisher has the authors' permission to publish research findings.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data are available from the corresponding author upon reasonable request.

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Figures

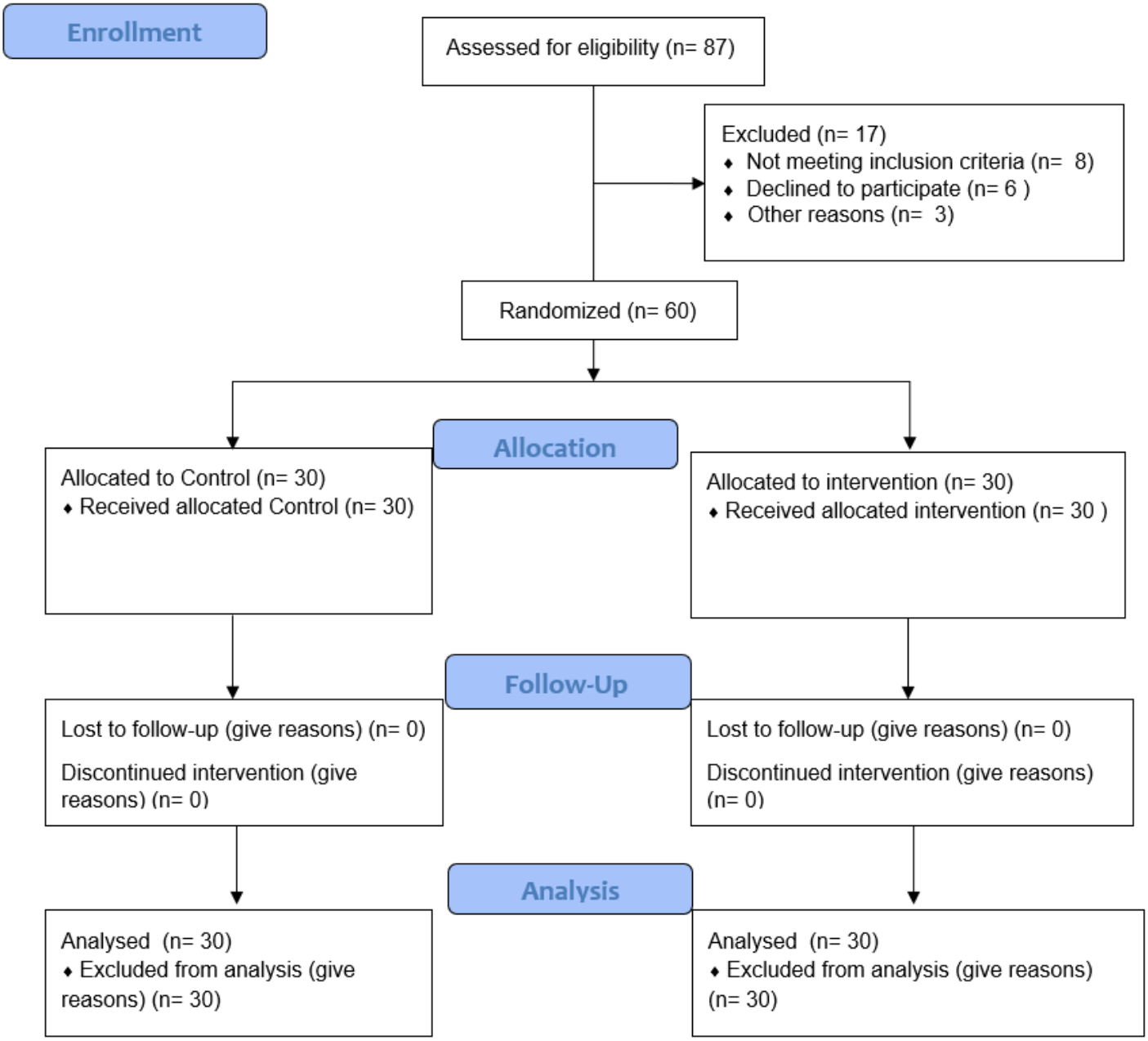


Figure 1

CONSORT flow diagram