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Effects of Curcumin–Piperine Supplementation on Metabolic Syndrome, Liver Fibrosis, and Steatosis Indices in Bariatric Surgery Candidates: Study Protocol for a Phase II, Parallel-Group, Randomized, Placebo-Controlled Trial

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Abstract

Introduction: Metabolic syndrome (MetS) and metabolic dysfunction-associated steatotic liver disease (MASLD) are common in severe obesity and increase postoperative complications after bariatric surgery. Curcumin, a polyphenolic compound with antioxidant and anti-inflammatory properties, has shown potential to improve metabolic and hepatic parameters; however, its effects have not been specifically investigated in bariatric surgery candidates with concurrent MetS and MASLD. Piperine, a bioavailability enhancer, may augment its effects by inhibiting glucuronidation and cytochrome P450 enzymes involved in curcumin metabolism.

Objective: We hypothesized that 8-week curcumin-piperine supplementation would improve metabolic syndrome components and hepatic steatosis and fibrosis indices compared with placebo in bariatric surgery candidates.

Methods: A randomized, placebo-controlled trial will be conducted at Imam Reza Hospital, Mashhad, Iran, in bariatric surgery candidates with MASLD and MetS. Participants will be randomly assigned to receive curcumin-piperine or placebo for 8 weeks preoperatively. The primary outcome domains are MetS-related parameters and MASLD-related hepatic outcomes. Hepatic steatosis and fibrosis will be assessed by two-dimensional shear wave elastography at baseline and six months post-surgery. Intraoperative liver biopsy will be obtained once, at the time of surgery, for histological characterization, and is not a longitudinal primary efficacy measure. Additionally, components of MetS including anthropometric indices, glycemic control, blood pressure, and lipid profile, will be assessed at baseline, post-intervention, and six months after surgery.

Results: This is a study protocol; therefore, no results are available. The study is ongoing, and results will be reported upon completion.

Conclusion: This protocol targets a high-risk population with severe obesity and metabolic dysfunction. The results of this trial will provide evidence regarding the potential role of curcumin-piperine supplementation in modulating metabolic and hepatic outcomes among bariatric surgery candidates.

Keywords: Bariatric surgery, Curcumin, Severe Obesity, Metabolic syndrome, Hepatic Fibrosis, Fatty Liver.

1. Introduction

Obesity is a significant global public health challenge, currently affecting approximately 16% of the global population, with its prevalence continuing to rise at an alarming rate (1). It is closely associated with various chronic metabolic disorders (2), including type 2 diabetes (3), cardiovascular diseases (4), metabolic dysfunction– associated steatotic liver disease (MASLD) and several types of cancer (5).

One of the major complications of obesity is metabolic syndrome (MetS), which is primarily driven by insulin resistance (6). The key diagnostic criteria for MetS include central obesity, elevated plasma glucose, hypertension (HTN), hypertriglyceridemia, and reduced levels of high-density lipoprotein-cholesterol (HDL-C) (7). Increased visceral adiposity and insulin resistance are also closely associated with fat accumulation in the liver, resulting in hepatic steatosis and subsequent MASLD (8).

The new term MASLD highlights the underlying metabolic dysfunction associated with hepatic fat accumulation. These metabolic abnormalities, which constitute the core pathophysiological features of MetS, play a crucial role in the development and progression of MASLD (9). Notably, MASLD and MetS share a bidirectional relationship, each exacerbating the other (10). Under such circumstances, uncontrolled inflammation and oxidative stress can accelerate the progression of hepatic steatosis to more severe stages, including steatohepatitis, fibrosis, cirrhosis, and eventually hepatocellular carcinoma (11).

Management of MetS and MASLD typically focuses on underlying causes such as obesity and insulin resistance, with lifestyle interventions like dietary changes, increased physical activity, and weight loss being first-line treatments (12). In recent years, pharmacological therapies, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as semaglutide, have emerged as promising options for obesity management and have demonstrated beneficial effects on metabolic dysfunction and hepatic outcomes (13, 14). However, issues related to long-term affordability, accessibility, tolerability, and applicability across different patient populations remain important considerations (15). In cases of severe obesity with comorbidities, bariatric surgery is increasingly utilized due to its capacity for substantial and sustained weight loss and improvement of obesity-related conditions (16). Bariatric surgery has also been shown to reduce hepatic steatosis, fibrosis, and inflammation (17), while positively impacting all components of MetS (18). However, studies have reported potential drawbacks following surgery, including transient liver dysfunction and reductions in HDL-C levels (19). Moreover, patients with these metabolic conditions may be at increased risk of surgical complications (20). Therefore, optimizing metabolic status before surgery is crucial to improve surgical outcomes.

Curcumin, a polyphenolic compound derived from turmeric, has demonstrated various pharmacological effects relevant to human health (21, 22). Among these activities are potent antioxidant, anti-inflammatory, and immunomodulatory properties (23). Evidence suggests that curcumin supplementation benefits individuals with MetS by improving insulin sensitivity (24, 25), inhibiting lipogenesis (26, 27), reducing blood pressure (21, 28), significantly affecting anthropometric

indices (29, 30), and modulating enzymes involved in lipoprotein metabolism, which leads to lower triglycerides (TGs) and higher HDL-C levels (31, 32). Additionally, curcumin appears to play a pivotal role in reducing hepatic fat accumulation by enhancing insulin sensitivity and regulating pathways associated with lipid metabolism and liver fibrosis (33). Curcumin also suppresses pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (34). These properties position curcumin as a potential adjunctive therapy for managing MetS and MASLD, while mitigating inflammation associated with these disorders.

Despite recent advances in the management of patients undergoing bariatric surgery, identifying strategies to prevent adverse surgical outcomes and minimize complications remains a priority. Curcumin supplementation may contribute to better surgical outcomes by reducing inflammation, improving liver function, and enhancing control over various aspects of MetS. However, its low oral bioavailability due to poor absorption and rapid metabolism may limit its efficacy (35). Piperine, by inhibiting curcumin metabolism, enhances its stability and absorption (36).

To date, no clinical trial has specifically evaluated the effects of curcumin-piperine supplementation in bariatric surgery candidates with concurrent MetS and MASLD. Therefore, evidence regarding the potential role of this intervention in modulating metabolic and hepatic outcomes in this high-risk population remains limited. Accordingly, this study aims to evaluate the potential effects of curcumin-piperine supplementation on the components of metabolic syndrome, as well as the severity of hepatic steatosis and fibrosis, in bariatric surgery candidates, both immediately after the intervention and six months post-surgery.

2. Materials and Methods

2.1. Trial design

This parallel-group, randomized, placebo-controlled, phase II clinical trial will be conducted at the Obesity Clinic of Imam Reza Hospital in Mashhad, Iran, within a superiority framework. The study is designed in accordance with the SPIRIT 2025 (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for interventional trials (37). The findings will be reported following the CONSORT (Consolidated Standards of Reporting Trials) statement. The study flow chart, including enrollment, allocation, intervention, and follow-up, is presented in Figure 1. The trial was approved by the Research Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1402.318) on September 23 2023. It was registered with the Iranian Registry of Clinical Trials (IRCT) (Registration No: IRCT20231116060076N1) on November 30, 2023. The first participant was enrolled on December 11, 2023; therefore, the trial was prospectively registered prior to participant recruitment.

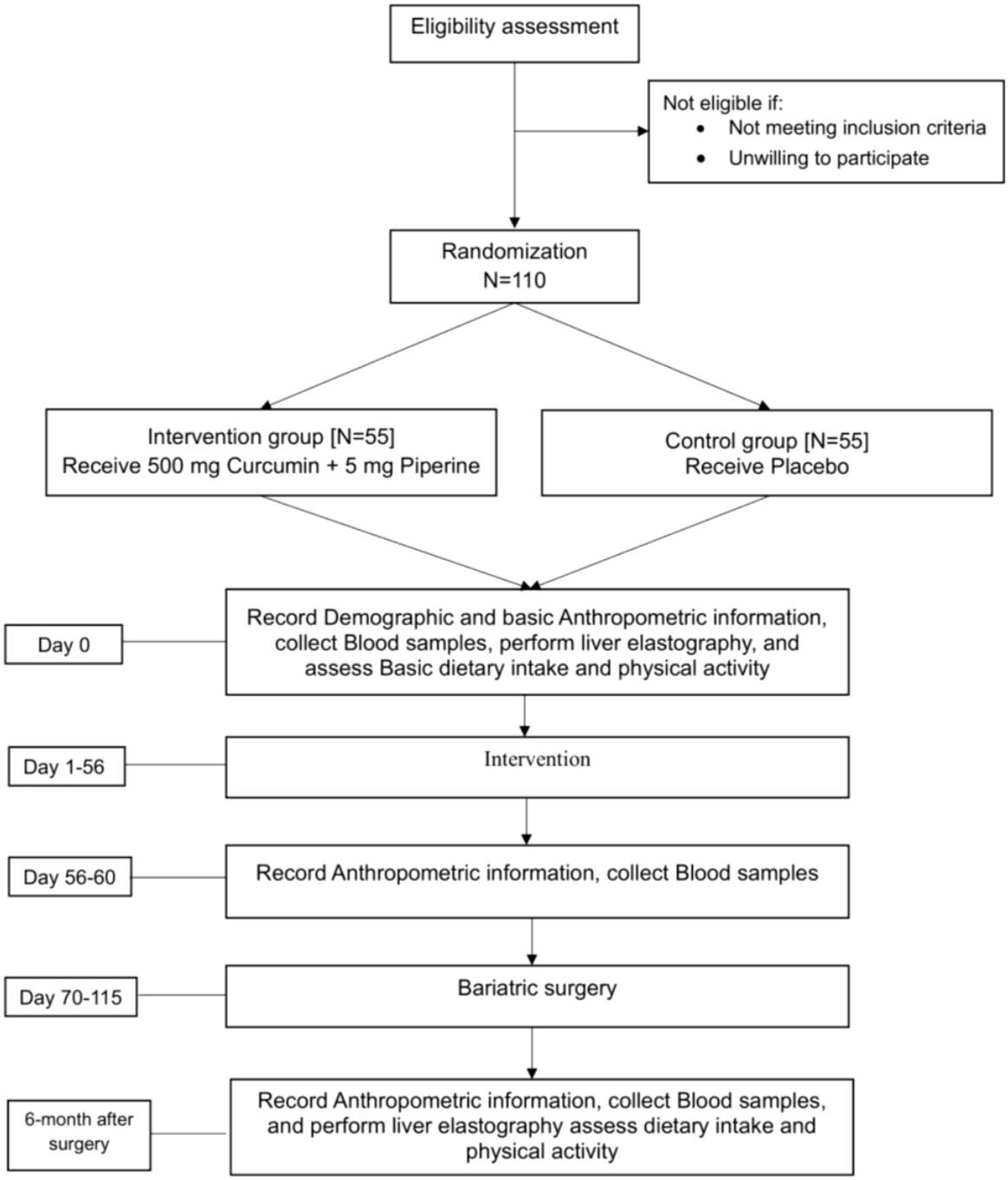

Figure1: Study flow chart

2.2. Subject and recruitment

Patients diagnosed with MetS and MASLD, who are candidates for bariatric surgery and referred to the Obesity Clinic of Imam Reza Hospital in Mashhad, Iran, will be invited to participate in this study, provided they meet the inclusion criteria. Eligible participants will be recruited using consecutive sampling until the required sample size is reached. They will receive a detailed explanation of the study, including its objectives and methodology. A trained member of the research team will obtain written informed consent from patients expressing interest in participating. Through constructive collaboration with the clinic's surgeons and nutritionists, flexible scheduling, and regular telephone follow-up, we will facilitate both recruitment and retention of participants.

To further encourage continued participation throughout the study, we will provide free assessments and supplements to eligible individuals, along with ongoing support and reminders for scheduled visits.

***Inclusion criteria*:** The inclusion criteria are as follows: 1-18 to 65 years old, 2- Diagnosis of metabolic syndrome through biochemical and clinical analyses, and diagnosis of MASLD confirmed by ultrasound by a specialist physician. 3- Willingness to participate in the study; 4- No known allergy to curcumin or turmeric

***Exclusion criteria*:** Participants will be excluded if: 1- They have used high-dose antioxidants, omega-3, probiotics, or herbal extracts (e.g., silymarin) in the past three months. 2- Diagnosed pathological conditions affecting the liver, such as viral hepatitis or a history of liver transplantation

History of chronic gastrointestinal, renal, autoimmune, psychiatric, or malignant diseases; known lactose intolerance, since the placebo capsule contains lactose; pregnancy, lactation, or intention to become pregnant during the study period.

***Drop-out criteria*:** Participants will be dropped out of the study if:1- Not consuming 15% of the prescribed supplement dosage. 2- Unwillingness to continue participation for any reason. 3- Failure to attend laboratory and elastography examinations.4- Diagnosis of pregnancy during the study. 4- If surgery does not take place within the predefined window of 14 to 59 days after completion of supplementation

2.3. Randomization and blinding

In this parallel-group study, randomization will be conducted in blocks of 4 and 6 using a specialized randomization platform (sealedenvelope.com) by an independent researcher who will not be involved in recruitment or outcome assessment. Sequentially numbered, opaque, sealed envelopes containing the allocation codes will be prepared and opened only after participant enrollment. Enrollment will be conducted by clinical staff not involved in the randomization process, and another independent clinical staff member will perform intervention assignment. Participants, researchers, care providers, outcome assessors, and data analysts will remain blinded throughout the trial. The data analyst will receive only coded datasets labeled as group A and B, and the allocation key will be maintained by an independent investigator who will not be involved in data analysis and will be revealed only after completion of the final statistical analysis. The curcumin-piperine and placebo capsules will be prepared and packaged in identical containers by an independent staff member who will not be involved in recruitment, intervention administration, or outcome assessment. Allocation codes will be kept confidential by an investigator uninvolved in sampling or data analysis and disclosed only after the final analysis. No unblinding is anticipated during the trial; however, in emergencies, unblinding will be performed as necessary, and all instances of unblinding will be documented and reported.

2.4. Intervention

At this stage, participants will be randomly assigned to one of two groups: the intervention group and the control group. The intervention group will receive one capsule daily containing 500 mg of curcumin (95% curcuminoids, Nutralin Bioresources Co., Ltd., China) and 5 mg of piperine (Shaanxi Jiahe Phytochem Co., Ltd., China) for 8 weeks. The selected dose was based on previous clinical trials demonstrating efficacy and safety in metabolic and hepatic conditions. Given the low bioavailability of curcumin, co-administration with piperine is commonly used to enhance systemic absorption and is efficacious in various trials (38, 39). The control group will receive an identical placebo capsule containing lactose,

matching the curcumin-piperine capsule in color, shape, size, and quantity to ensure blinding and control for placebo effects. At the end of the supplementation period, pre-surgery tests will be conducted. The interval between the end of the intervention and the surgery is acceptable within a range of 14 to 59 days.

2.5. Adherence to the intervention

At the beginning of the study, participants will receive either curcumin-piperine or placebo supplements, packaged and labeled for two weeks. Weekly follow-up phone calls will be conducted to assess supplement intake, monitor for any side effects or issues, and reinforce adherence. At the end of each two-week period, participants will return to the clinic for a compliance check, during which remaining capsules will be counted. A new two-week supply of supplements will then be dispensed. This cycle will be repeated every two weeks until the end of the 8-week intervention. Final adherence will be assessed at the end of week 8 by counting unused capsules. Participants should avoid other supplements/medications affecting metabolic/hepatic outcomes; standard medical care continues, but confounding treatments are prohibited and will be documented.

2.6. Bariatric surgery

Bariatric surgery will be scheduled approximately 2 to 4 months after participants enroll in the study. All participants will undergo Roux-en-Y gastric bypass (RYGB), which is the predefined surgical procedure in this study protocol. In this procedure, a small gastric pouch with a capacity of 30–60 cm^3 is created and connected to the small intestine 75–100 cm distal to its origin.

3. Outcome

3.1. Primary and secondary outcomes

The primary domain outcomes include MetS-related parameters, including fasting plasma glucose (FPG), TGs, HDL-C, blood pressure, and anthropometric measures. MASLD-related hepatic outcomes, including the degree of hepatic steatosis and fibrosis assessed by two-dimensional shear wave elastography and intraoperative liver biopsy, will be evaluated as exploratory outcomes. Secondary outcomes include serum liver transaminases (Alanine aminotransferase, Aspartate aminotransferase, and alkaline phosphatase) and insulin resistance, as assessed by the homeostasis model assessment of insulin resistance (HOMA-IR) index. Changes in these parameters will be compared between the intervention and placebo groups at the end of the intervention and 6 months post-surgery.

3.2. Measurements and assessments

3.2.1. Basic information

Basic demographic information including age, marital status, level of education, occupation, alcohol consumption, smoking history, comorbidities, and medication details will be collected through a general questionnaire at the beginning of the study.

3.2.2. Anthropometric and blood pressure assessment

Weight will be measured at baseline, post-intervention, and six months after surgery, using a digital scale (Seca, Hamburg, Germany) with an accuracy of 100 grams, with participants wearing minimal clothing and no shoes. Height will be measured to the nearest 0.5 cm using a stadiometer, with participants standing upright and barefoot. BMI will then be calculated as weight in kilograms divided by height in meters squared (kg/m^2). Blood pressure will be measured at all three time points using a mercury sphygmomanometer, after 10 minutes of rest, with the participant seated in a relaxed position.

3.2.3. Biochemical measurement

Fasting blood samples will be collected from all participants to measure glucose and lipid profiles, as well as liver enzymes, at baseline (before the intervention), after the intervention period, and 6 months post-surgery.

3.2.4. Hepatic steatosis or fibrosis assessment

Liver stiffness and elasticity will be evaluated using two-dimensional shear wave elastography (2D-SWE) before the intervention and six months postoperatively to assess hepatic steatosis and fibrosis. Examinations will be performed with the Aixplorer ultrasound system (Supersonic Imagine, France) equipped with a convex broadband probe (SC6-1, 1–6 MHz), in accordance with the manufacturer's standardized protocol. Measurements will be obtained intercostally after a 6-hour fasting period, with participants positioned in the dorsal decubitus posture and their right arm fully abducted. Ten valid measurements will be acquired for each participant, and the mean liver stiffness value, expressed in kilopascals (kPa), will be reported. All assessments will be conducted by operators blinded to clinical and laboratory information. In addition, liver histology will be evaluated through intraoperative liver biopsy performed during bariatric surgery. This approach allows direct histological assessment of hepatic steatosis and fibrosis at the time of surgery without requiring an additional invasive procedure solely for research purposes. Liver biopsy samples will be processed and evaluated at a certified pathology laboratory. Histological assessment will be performed by an experienced pathologist using a standardized scoring system for MASLD-related histological changes. The pathologist will remain blinded to treatment allocation during the histological evaluation.

3.2.5. Physical activity and dietary intake assessment

Physical activity and dietary intake will be assessed as potential confounding variables using the 7-day International Physical Activity Questionnaire (IPAQ) and a 24-hour dietary recall questionnaire, respectively, both at baseline and six months after surgery.

3.2.6. Data management and monitoring

Participant data will be collected at baseline and after the intervention using standardized case report forms (CRFs). These forms will serve as the primary tool for documenting clinical and demographic information. Once completed, data will be entered into a secure electronic database. Two trained personnel will be responsible for data collection and entry, and the project supervisor will review and verify all raw clinical data. Hard copies of CRFs will be stored in a locked cabinet accessible only to the principal investigator, and each participant will be assigned a unique identification code to ensure confidentiality; no personally identifiable information will be recorded on the forms. Any important protocol modifications will be communicated to the Ethics Committee, trial registry, and relevant stakeholders prior to implementation.

A clinical trial monitor will periodically review study activities to ensure adherence to the protocol, ethical standards, and regulatory guidelines, and to confirm the accuracy and completeness of the collected data. One designated investigator will oversee data coding, secure storage, and data protection processes, and will conduct duplicate checks to validate data entry accuracy. In case of a serious adverse event where knowledge of the treatment allocation is considered necessary for participant management, emergency unblinding will be permitted. The decision to request unblinding will be made by the principal investigator when clinically necessary. The

allocation code will be revealed only by the independent investigator responsible for maintaining the randomization code, and all unblinding events will be documented and reported. The ethical oversight of data handling will be conducted under the supervision of the Ethics Committee of Mashhad University of Medical Sciences. Moreover, participants who withdraw or deviate from the study protocol will still be included in the outcome reporting. Missing data will be handled using appropriate statistical imputation methods for drop-outs.

3.2.7. Safety monitoring and adverse event reporting

Given that the present study involves a nutritional intervention with a favorable safety profile, and liver biopsy will be performed only intraoperatively during clinically indicated bariatric surgery, participants are expected to face minimal additional risk. Therefore, participant safety will be closely monitored by the principal investigator throughout the study. Any serious adverse events (SAEs) will be promptly documented and reported to the Ethics Committee of Mashhad University of Medical Sciences. Necessary corrective measures will be taken if needed.

3.3. Informed Consent and Data Use

All participants will be required to sign a written informed consent form prior to enrollment in the study. At the time of consent, participants will be asked whether they agree to the use of their collected data in the event of early withdrawal from the trial. Additionally, permission will be obtained to allow authorized individuals, such as representatives from the research institution or regulatory authorities, to review relevant sections of the trial data for monitoring or auditing. Biological samples, such as liver tissue biopsies, will be collected for immediate analysis only for this study; no samples will be stored for unspecified future research purposes.

3.4. Sample Size and Statistical Analysis

Based on a medium effect size of 0.55, the minimum required sample size was estimated to be 53 participants per group (calculated via G*Power, $\alpha = 0.05$, and $\beta = 0.20$). Due to the lack of studies providing identical outcome measures for sample size estimation, we used data from Cicero et al. (40) on metabolic syndrome parameters following an 8-week curcumin vs. placebo intervention. In their study, fasting plasma glucose (FPG) at 8 weeks was 105 ± 8mg/dL in the placebo group and 101 ± 6mg/dL in the intervention group, yielding an effect size of 0.56. Using a two-tailed significance level of $\alpha = 0.05$ and a power of 80% ($\beta = 0.20$), the required sample size was 50 participants per group. Similar calculations for triglycerides (TG) yielded comparable results.

Additionally, to account for the MASLD-related hepatic outcome domain, a separate sample size estimation was performed based on hepatic steatosis grading from Rahmani et al. (41). In their study, 15% of the intervention group reached grade 0 hepatic steatosis after 8 weeks, compared to 0% in the placebo group. Using the same α and β values, the required sample size was determined to be 49 participants per group. Accounting for a predicted 5% drop-out rate and implementing retention strategies—such as regular follow-up and scheduled assessments—we will enroll 55 participants per group.

SPSS software (version 22) will be used to analyze the data. Depending on the data distribution, all variables will be summarized as mean ± standard deviation or median and interquartile range. The Kolmogorov-Smirnov test will be used to determine whether the data distribution is normal. Depending on data normality, the independent samples t-test or Mann-Whitney U test will be used to compare the intervention and placebo

groups for the primary outcomes at each time point (the end of the intervention and six months after surgery). The Friedman test or repeated measures ANOVA will be applied as needed for within-group comparisons over time. For secondary outcomes, similar statistical tests will be applied based on the data distribution. Missing data will be handled using multiple imputation methods, and all analyses will be conducted on an intention-to-treat (ITT) basis. Participants whose surgery does not occur within the predefined 14–59-day interval after completion of supplementation will be considered protocol deviations for the per-protocol analysis but will remain in the ITT population whenever outcome data are available. In addition, the interval between completion of supplementation and surgery will be considered as a covariate in the mixed-effects model to account for potential variability related to surgical timing. We will use a linear mixed-effects model to compare the primary and secondary outcomes of the two study groups at the end of the trial and adjust the final results for possible confounders. A significance level of $p < 0.05$ will be considered.

4. Discussion

Bariatric surgery is well established as a highly efficacious intervention in severe obesity, leading to the resolution of obesity-related diseases and reduction of mortality in patients in the long term (42, 43). However, like all major surgical procedures, it carries inherent risks, including life-threatening complications (44). Given the complexity of metabolic dysfunction in bariatric candidates, adjunct therapies targeting systemic inflammation and insulin resistance may represent a potential strategy to optimize metabolic status before surgery; however, their clinical efficacy in this population remains to be established. Curcumin, a polyphenolic compound with anti-inflammatory, antioxidant, and metabolic regulatory effects, has shown promise in addressing multiple components of MetS (33). Although several clinical trials have demonstrated its beneficial effects on glycemic control, lipid metabolism, anthropometric indices, and hepatic parameters, evidence regarding its use in bariatric surgery candidates with coexisting MetS and MASLD remains limited (45). This protocol is designed to investigate further the potential role of curcumin co-administered with piperine in this high-risk population.

Previous studies have demonstrated the positive effects of curcumin supplementation on cardiometabolic factors as well as anthropometric and hepatic indices. Safari et al (46) found that 12-week supplementation with 250 mg of phospholipidated curcumin significantly reduced liver fibrosis, steatosis, waist circumference, and blood pressure in NAFLD patients, though it did not significantly affect weight, BMI, glucose, liver enzymes, or lipid profile. Cicero et al. (40) observed that 8-week administration of 800 mg phytosomal curcumin (with piperine) in overweight individuals with dysglycemia improved glycemic control, liver function, and cortisol levels. A 2023 systematic review also confirmed the overall metabolic benefits of curcumin with minimal adverse effects (47).

However, despite its therapeutic potential, curcumin's clinical application is hindered by low oral bioavailability, due to poor absorption, rapid metabolism, chemical instability, and rapid systemic elimination (35). To overcome these challenges, various strategies have been developed, including nanoparticle formulations, targeted drug delivery systems, and bioavailability enhancers (48). Among these, piperine—an active component of black pepper—significantly improves curcumin's bioavailability by inhibiting hepatic and intestinal glucuronidation and cytochrome

P450 enzymes involved in first-pass metabolism (36).

However, these studies were conducted in non-surgical populations, and none specifically evaluated bariatric surgery candidates with concurrent MetS and MASLD. In addition, liver histology was generally not assessed using intraoperative biopsy, and considerable heterogeneity existed regarding curcumin formulations, piperine co-administration, intervention duration, and outcome measures. These limitations highlight the need for a well-designed randomized clinical trial in this specific high-risk population.

Although hepatic fibrosis is generally considered a slowly progressive process, previous randomized clinical trials have reported improvements in liver stiffness and fibrosis-related indices following 8–12 weeks of curcumin supplementation (39, 46). Therefore, the present trial is designed to evaluate whether an 8-week preoperative intervention may lead to measurable changes in hepatic steatosis and fibrosis-related indices before surgery, while acknowledging that substantial histological changes in fibrosis may require longer treatment durations.

Curcumin has been reported to exert multiple metabolic effects through anti-inflammatory, antioxidant, and metabolic regulatory mechanisms. Experimental and clinical studies suggest that it may improve adipose tissue function, insulin sensitivity, glucose homeostasis, and energy metabolism (49-52). An overview of curcumin's potential effects in the treatment of metabolic disorders is illustrated in **Supplementary Figure 1**.

Curcumin also exerts antioxidant effects by reducing oxidative stress and enhancing endogenous antioxidant defenses, which may contribute to its hepatoprotective properties (49, 53).

Conducting this trial in the context of bariatric surgery comes with real-world challenges. Ensuring that patients adhere to the preoperative supplementation schedule and coordinating follow-up assessments like elastography and liver biopsy with surgical timelines require careful planning. Close teamwork between clinicians, nutritionists, and research staff is essential to keep the study on track and ensure its integrity. The randomized placebo-controlled design of this trial allows the assessment of the additional effects of curcumin–piperine supplementation beyond the metabolic and hepatic improvements induced by bariatric surgery itself, as both groups will undergo the same surgical intervention.

The findings of this study are expected to provide novel evidence regarding the potential role of curcumin-piperine as an adjunctive strategy in bariatric surgery candidates with MetS and MASLD. Based on current evidence, it is hypothesized that this intervention may mitigate post-surgical complications by improving metabolic and hepatic parameters.

Ultimately, this trial aims to address a critical gap in bariatric research. By focusing on a high-risk population, it seeks to generate evidence regarding the potential adjunctive role of curcumin-piperine supplementation in enhancing surgical outcomes and managing metabolic and hepatic dysfunction in patients with severe obesity.

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Availability of data and materials: The data generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest: The authors declare no competing interests.

Consent for publication: Not applicable.

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Ethics declarations: The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The trial was approved by the Research Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1402.318). It was registered with the Iranian Registry of Clinical Trials (IRCT) in November 2023 under the registration number IRCT20231116060076N1.

Author Contributions: All authors contributed to the study conception and design, data collection, data analysis and interpretation, and manuscript preparation. All authors reviewed and approved the final version of the manuscript.

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