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Fatty Liver Index and GGT/HDL-c Ratio in Patients with Metabolic Dysfunction Associated Steatotic Liver Disease Treated with Life Style Modification or Vitamin E or Pentoxifylline

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Abstract **Background:** Metabolic dysfunction associated steatotic liver disease (MASLD) is a common cause of chronic liver disease. It is becoming a major public health concern, with projections indicating a substantial increase in prevalence over the coming decades. **Objectives:** To evaluate the relationship of the Gamma Glutamyl transpeptidase (GGT) to high-density lipoprotein cholesterol (HDL-c) ratio and determine the fatty liver index (FLI) in patients with MASLD treated with pentoxifylline (PTX) and Vitamin E (VE). **Patients and Methods:** This randomized, single-blind, interventional study was conducted on 180 patients with MASLD in the Gastroenterology and Hepatology Teaching Hospital, Sulaimaniyah, Iraq, from January 2022 to June 2023. Patients were equally divided into three groups (n = 60 each): Group 1 received a placebo (control); Group 2 received VE; and Group 3 received PTX. Patients were received the treatments orally at a dose of 400 mg, twice daily for 6 months. Then, liver aminotransferase tests, haematological biomarkers, lipid profiles and FLI were measured before and after intervention. **Results:** The majority of patients were males (n = 96), with an age range of 20-40 years. All groups showed significant reductions in aminotransferase levels, lipid profile, high- sensitivity C-reactive protein (Hs-CRP), FLI, GGT/HDL-c and GGT/body mass index (BMI) ratio after 6 months of treatments with either VE or PTX. **Conclusions:** PTX and more specifically, VE reduced FLI, GGT/HDL-c and GGT/BMI ratio. They also significantly improved hepatic aminotransferase levels, lipid profiles and Hs-CRP levels.

Key Words Metabolic Associated Steatotic Liver Disease, Life Style, Pentoxifylline, Vitamin E

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as nonalcoholic fatty liver disease (NAFLD), is a highly prevalent metabolic syndrome (MS) worldwide, characterized by hepatic steatosis in conjunction with at least one cardiometabolic risk factor, such as obesity, type 2 diabetes, hypertension or dyslipidemia [1].

Steatohepatitis is the clinically severe progression of MASLD, contributing to an enormous accumulation of triglycerides (TG), liver injury, overproduction of proinflammatory cytokines and hepatocyte apoptosis [2]. In severe cases, it may contribute to hepatic cirrhosis and hepatocellular carcinoma. It is one of the most eminent causes of liver-relevant morbidity and mortality [3].

The estimated global prevalence of MASLD ranges from 15-40%, with a continued rapid increase [4]. Recently, the multifactorial hypothesis has suggested that it results from multiple causes acting together, including abnormal lipid metabolism, genetic disposition, free radicals, mitochondrial dysfunction, changes in the production of adipokines and cytokines, an imbalance of gut microbiota and stress on the endoplasmic reticulum [5]. Gamma-glutamyl transpeptidase (GGT) and high-density lipoprotein cholesterol (HDL-c) are associated with dyslipidemia, oxidative stress and obesity. Understanding the efficacy of different pharmacological agents for treating metabolic-associated steatohepatitis (MASH) is crucial [6]. No FDA-approved drugs exist for the treatment of MASLD. A variety of drugs have been tried for the treatment of MASH,

including promising drugs like vitamin E (VE) and pentoxifylline (PTX). Lifestyle modification is also considered the cornerstone of MASH treatment [7]. PTX inhibits phosphodiesterase enzymes, which are involved in peripheral and cerebrovascular disease, as well as defective regional microcirculation. It has antioxidant, antifibrotic and anti-inflammatory properties and inhibits tumour necrosis factor-alpha (TNF-α). The Fatty Liver Index (FLI) is an algorithm that combines Body Mass Index (BMI), waist circumference (WC), GGT and triglyceride (TG) levels. It has been demonstrated to be a valuable tool for predicting the presence of non-alcoholic steatohepatitis (NASH) and NAFLD [8]. VE can delay hepatic fibrosis and possibly prevent cirrhosis by modulating inflammatory response, cell injury, cellular signaling and cellular proliferation [9]. GGT was more strongly associated with the severity of Fatty Liver (FL) than alanine aminotransferase (ALT); it demonstrated a significant relationship between increased GGT and a higher degree of MASLD [10]. So, this study aimed to determine the FLI and GTT/HDL-c ratio in patients with MASLD treated with VE or PTX.

Patients and Methods Study Design and Setting

This computer-based randomized, single-blind, interventional study recruited 180 patients with MASLD from January 2022 to June 2023 at the Gastroenterology and Hepatology Teaching Hospital, Sulaimaniyah, Iraq, using consecutive sampling method. Patients were blind to the received treatment in each group.

Inclusion Criteria

Patients aged 18 years or older and had evidence of MASLD, characterized by persistently elevated ALT levels (>45 IU/L for males and >30 IU/L for females) and ultrasound findings showing fatty infiltration.

Exclusion Criteria

Pregnant patients and those with a history of alcohol dependence, receiving drugs known to induce FL (e.g., Amiodarone, Tamoxifen, Methotrexate, Steroids, etc.) and with a history of hypersensitivity to PTX, methylxanthines or VE.

Study Protocol

A standard questionnaire collected patients' sociodemographic data (age, gender and smoking status). Anthropometric measurements, including body weight and height were also determined to find BMI (kg/m^2). Then, transabdominal ultrasonography was performed on the patients to confirm FL using a Samsung-V7. All participants were asked to attend the hospital after overnight fasting and 10 mL blood was taken for laboratory investigations, including ALT, aspartate transferase (AST), GGT, total cholesterol (TC), TG, LDL, HDL-c and high-sensitivity C-reactive protein (Hs-CRP) using Cobas c 311/501 analyzer. FLI was determined to provide a quantitative estimate of liver steatosis that ranging from 0-100. FLI <30 rules out steatosis, while FLI ≥60 suggests hepatic steatosis [11]. The participants were randomly divided into three age- and gender-matched groups of 60 each to receive either starch (placebo/control group), VE (group 2/intervention) or PTX (group 3/intervention). All treatments were administered orally at a dose of 400 mg in a capsule, twice daily. Additionally, patients were advised for lifestyle modification followed up every week for 6 months to ensure compliance, drug adherence and to report any side effects.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Science (SPSS, IBM, Chicago, USA, version 27). A one-way analysis of variance (ANOVA) was conducted to determine correlations of variables within and between the treatment groups. An important difference was considered at p≤0.05, while a highly significant difference was set at p≤0.001.

RESULTS

Most patients in all groups were aged 20-40 years old (n = 89, 49.5%), males (n = 96, 53.3%) and non-smokers (n = 160, 88.9%) (Table 1).

Aminotransferase levels, lipid profiles and FLI were significantly (p≤0.001) reduced in all groups (control, VE and PTX) after 6 months of treatment compared to the baseline (Figure 1, 3 and 5). Similarly, a highly significant reduction (p≤0.001) was found for Hs-CRP, GGT/HDL-c and GGT/BMI ratio in all groups after 6 months of treatment compared to the baseline (Figure 2, 4 and 6). However, HDL-c levels were significantly (p≤0.001) increased in all groups after 6 months of treatment compared to the baseline (Figure 1, 3 and 5). After 6 months of intervention, the reduction in ALT, AST, GGT, GGT/HDL-c and GGT/BMI ratios was significantly (p≤0.05) changed in the treated

Table 1: Sociodemographic characteristics of the Study Patients

Variable		Treatment Group						Total
		Control		Vitamin E		Pentoxifylline		
		No.	%	No.	%	No.	%	No. (%)
Age Group (Years)	20-40	33.0	55.0	24.0	40.0	32.0	53.3	89 (49.5)
	41-60	27.0	45.0	32.0	53.3	24.0	40.0	83 (46.0)
	>60	0.0	0.0	4.0	6.7	4.0	6.7	8.0 (4.5)
Gender	Male	32.0	53.3	36.0	60.0	28.0	46.7	96 (53.3)
	Female	28.0	46.7	24.0	40.0	32.0	53.3	84 (46.7)
Smoking Status	Yes	4.0	6.7	8.0	13.3	8.0	13.3	20 (11.1)
	No	56.0	93.3	52.0	86.7	52.0	86.7	160 (88.9)
Total		60	100	60	100	60	100	180

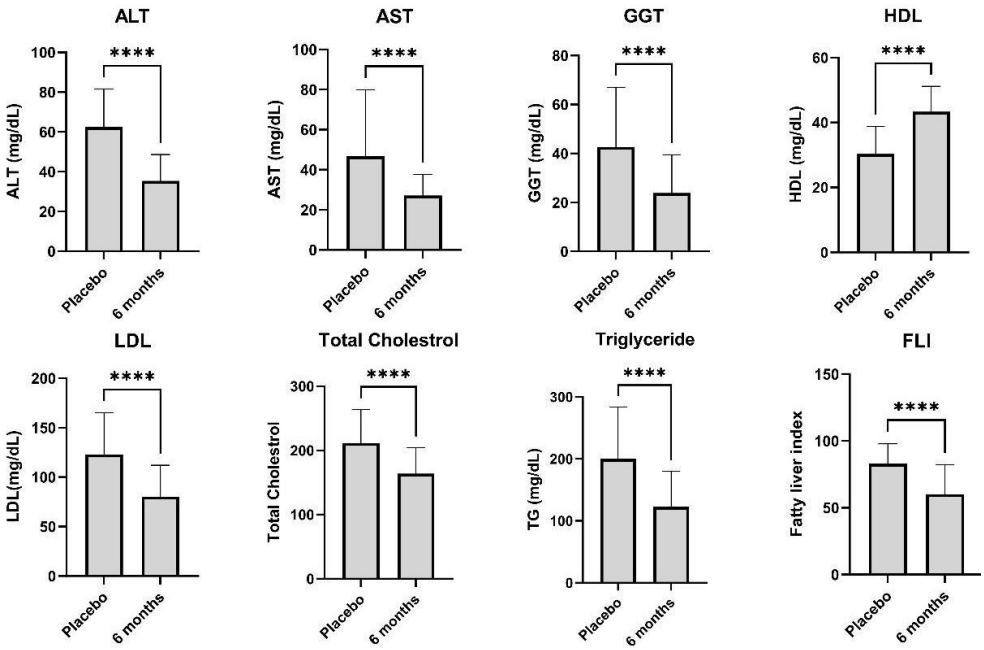

Figure 1: Liver Enzymes and Lipid Profile of Control Group Before and After Six Months

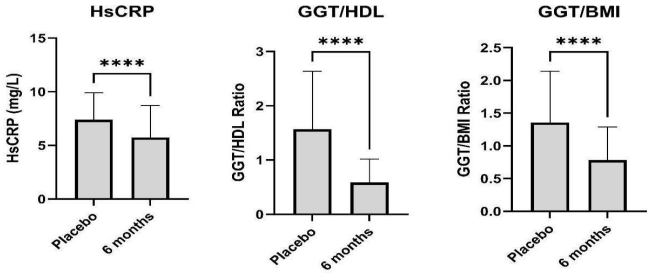

Figure 2: Associations of GGT/HDL-c, GGT/BMI Ratio and Hs-CRP in the Control Group

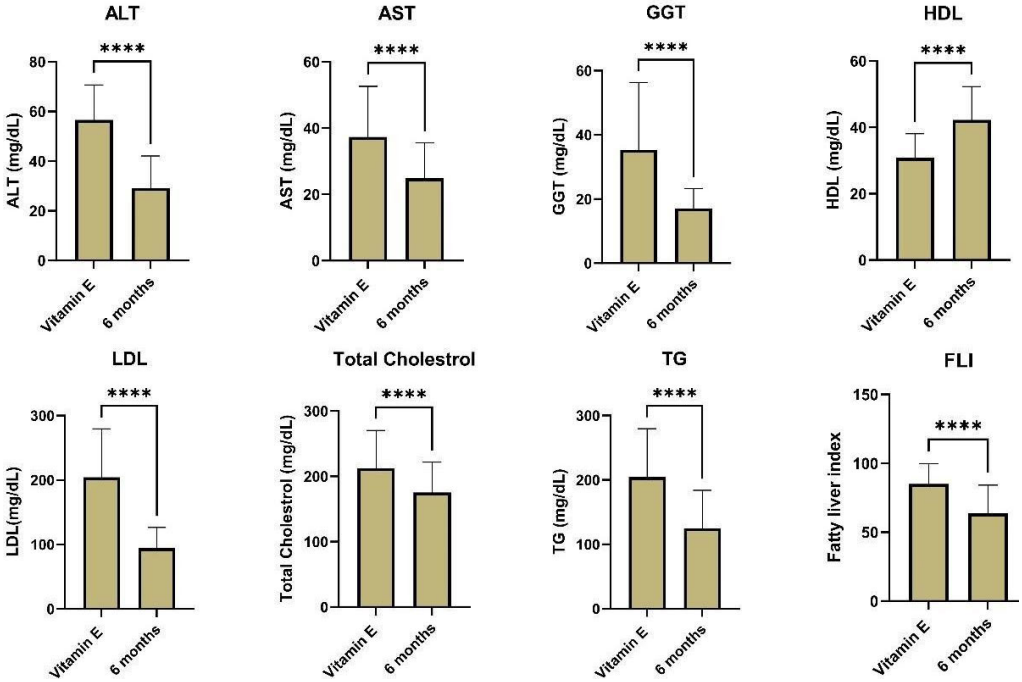

Figure 3: Liver Enzymes and Lipid Profile of Vitamin E Group at the Baseline and After Six Months of Treatment

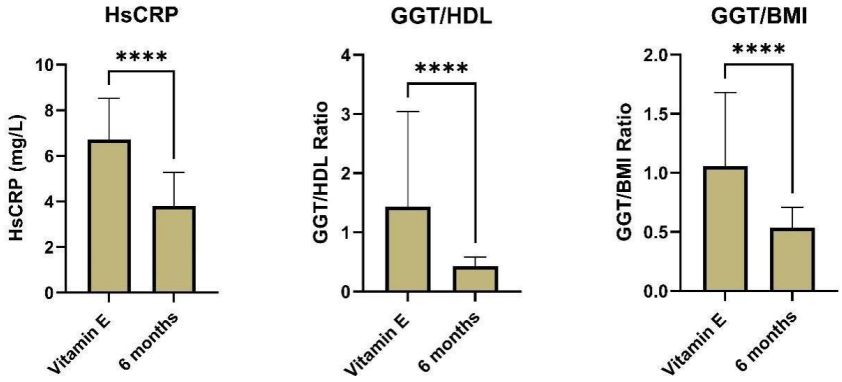

Figure 4: Associations of GGT/HDL-c, GGT/BMI Ratio and Hs-CRP in the Vitamin E Group

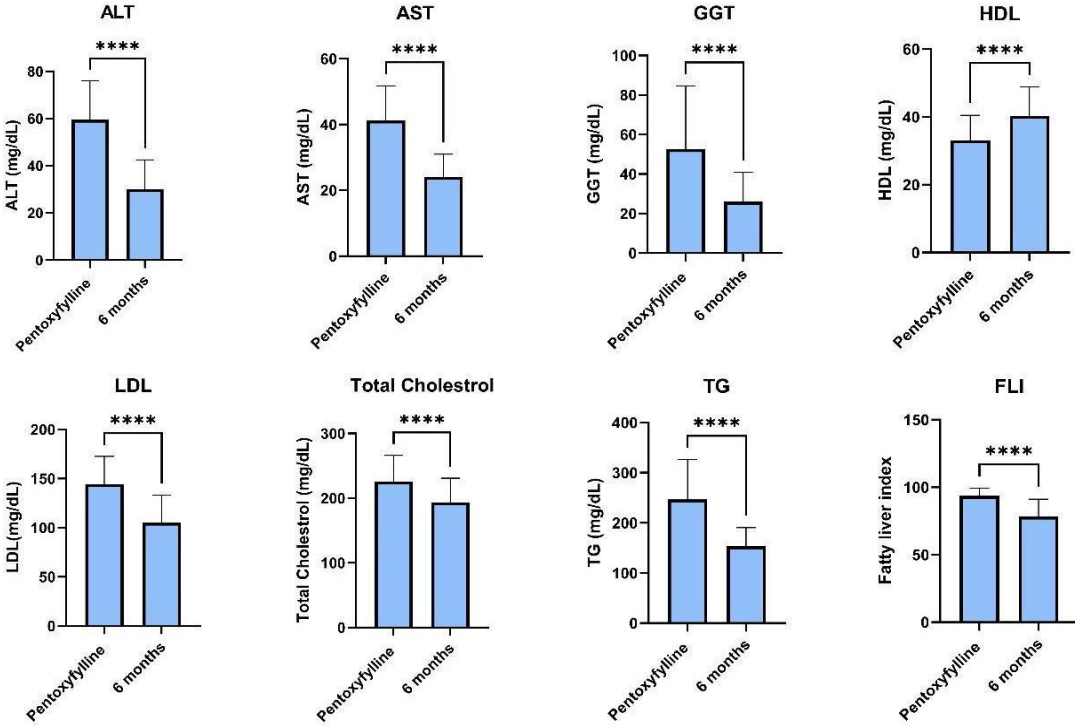

Figure 5: Liver Enzymes and Lipid Profile of the PTX Group at the Baseline and After Six Months of Treatment

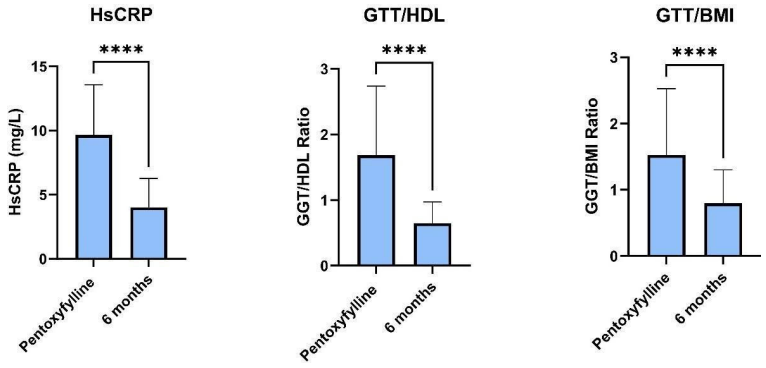

Figure 6: Associations of GGT/HDL-C, GGT/BMI Ratio and Hs-CRP in the PTX Group

groups compared to the placebo. At the same time, the values mentioned above were non-significantly ($p \geq 0.05$) reduced in the PTX group compared to placebo (Figure 7).

DISCUSSION

MASLD has surpassed alcoholic hepatitis to become the most prevalent chronic liver disease, affecting more than a

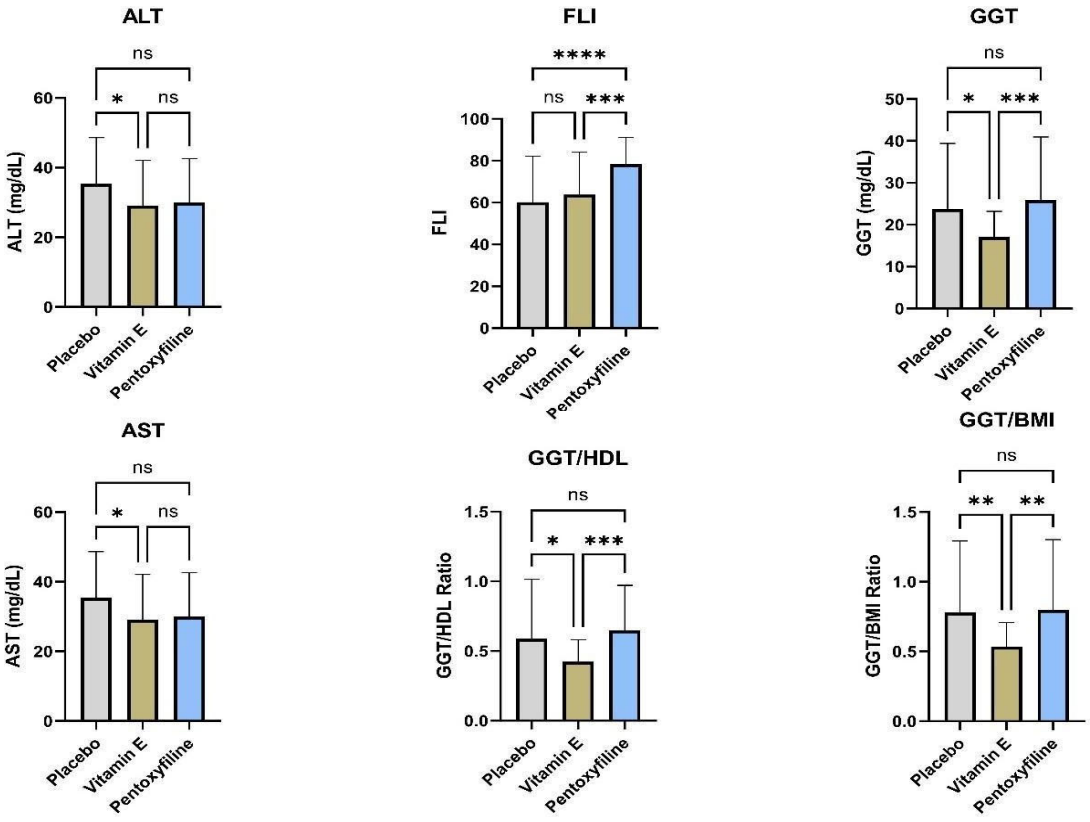

Figure 7: Comparison Among the Control, Vitamin E and PTX Groups After Six Months of Treatment

quarter of people globally. GTT, routinely used to assess hepatocyte damage, is an established predictor of MASLD. In contrast, lower HDL-c levels are a risk factor for MS. The GGT/HDL-c ratio is crucial for investigating the association between the GGT/HDL-c ratio and MASLD [12].

The current study showed that the majority of patients were aged 20-40 years old (49.5%), which means that MASLD is more common among young adults, which might be related to the wrong lifestyle, including poor physical activity, poor diet, stress, sleeplessness, alcoholism and environmental conditions. Regarding the gender distribution among patients, males were slightly more predominant (53.3%), indicating that the disease affected males more frequently than females. That might be because sex chromosomes and hormones influence MASLD development and progression, as estrogen typically protects against, whereas androgens promote, MASLD [13].

Smoking is a known risk factor for MASLD, which is characterised by fat build-up in the liver and possible progression to more severe liver inflammation. This study shows that most patients were non-smokers (88.9%), which is contrary to that of Jung *et al.* [14], which showed that smoking contributes to the development of MASLD.

Regarding the biochemical parameters among groups at baseline and after 6 months of treatment, there was a highly significant reduction in aminotransferase levels ($p<0.0001$) in all groups compared to baseline. This outcome is comparable to Fouda *et al.* [9], which showed that ALT and AST levels were significantly reduced in the VE (400 IU twice daily) and PTX-treated groups (400 mg twice daily) after three months. Ahmed *et al.* showed that ALT, AST and GGT levels were significantly reduced in patients treated with PTX (400 mg, three times daily) for 6 months. Serum activities of ALT, AST and GGT assessed liver function response. The potential components of anti-TNF agents targeting the second hit in the pathogenesis of MASH include those that improve necrosis, inflammation and fibrogenesis caused by several proinflammatory adipocytokines, including TNF-α. So, VE and PTX effectively improve liver transaminases and inflammatory markers in MASH patients. Additionally, oxidative stress is a significant contributor to the second hit in the pathogenesis of MASLD/MASH, which VE can control to reduce hepatic inflammation [15]. It is also an essential micronutrient that protects cellular structural integrity against damage from lipid peroxidation and oxygen-free radicals [15].

This study found significant reductions in TC, LDL-c and TG, accompanied by a considerable elevation of HDL-c ($p<0.0001$) in the intervention groups compared to the control group after 6 months of treatment. These outcomes are comparable to those of Ahmed *et al.*, who showed a significant effect of PTX (400 mg thrice daily) for 6 months on these values. However, Ashraf *et al.* [15] showed a substantial reduction in TG with VE (800 IU daily) for 3 months with a non-significant effect in TC.

In this study, there is a highly significant reduction in FLI ($p<0.0001$) in all groups after 6 months compared to baseline, which is comparable to the findings reported by

Ashraf *et al.* [15] and Ahmed *et al.* who showed a significant reduction of FLI in VE-treated patients (800 IU daily) for 3 months and PTX-treated patients (1200 mg daily) for 6 months.

Moreover, we found a highly significant reduction in Hs-CRP levels in all groups after 6 months compared to baseline, which is comparable to the findings of Saboori *et al.* [16], who showed a considerable reduction in Hs-CRP in VE-treated patients (1200 IU daily) over 3 months. Hs-CRP is the most sensitive of the acute-phase reactants and its concentration increases rapidly during inflammatory processes [17]. Furthermore, this study observed a highly significant reduction of GGT/HDL-c and GGT/BMI ratios in all groups after 6 months compared to baseline. In this regard, Feng *et al.* [4] significantly reduced the GGT/HDL-c ratio. GGT was more strongly associated with FL severity than classical inflammatory markers, such as ALT. An increase in GGT can indicate steatosis in liver cells, while a single decrease in HDL-c is associated with dyslipidaemia and insulin resistance (IR). HDL-c has anti-inflammatory, antioxidant and antithrombotic properties and low HDL is associated with dyslipidaemias, atherogenic indices, insulin resistance (IR) and obesity [4].

In the current study, significant reductions in ALT and AST were comparable in the VE and PTX groups. However, the decrease in VE was more critical than that of the control and PTX groups after 6 months of treatment. This is comparable to Fouda *et al.* [9], who demonstrated that the changes induced by VE supplementation (400 mg twice daily) were more pronounced and significant. VE is an effective chain-breaking antioxidant that has been shown to delay the pathogenesis of MASLD, suppress peroxidation and limit the expression of transforming growth factor-beta, which is linked to hepatic fibrosis and hepatocyte apoptosis by stimulating hepatic stellate cells [18].

In this study, the reduction of GGT in the control group and PTX was comparable; however, the reduction in the VE group was higher than in the control and PTX groups. Similarly, Papatheodoridi and Cholongitas reported that patients treated with PTX for 6 months showed a marked reduction in GGT [19]. We found that the reduction of FLI in the VE and control groups was comparable and more significant than in the PTX group. In this respect, Ahmed *et al.* demonstrated a substantial reduction in FLI in patients treated with PTX (400 mg, administered three times daily) for six months. Additionally, significant reductions in the GGT/HDL-c ratio were comparable in the control and PTX groups. Still, the reduction was higher in VE than in the control and PTX groups after 6 months. Similarly, Ahmed *et al.* demonstrated that patients treated with PTX for 6 months exhibited a significant reduction in the GGT/HDL ratio.

GGT is a surface enzyme that cleaves extracellular glutathione (GSH), thereby maintaining GSH homeostasis and playing a crucial role in mitigating the effects of oxidative stress. Elevated GGT activity is associated with MS, cardiovascular risk factors, systemic inflammation and oxidative stress. Serum GGT activity is widely used as a sensitive indicator of FL disease, hepatic inflammation and hepatitis. Oxidative stress upregulates intracellular GGT levels; therefore, intracellular GGT levels can be considered a biomarker for oxidative stress associated with GSH metabolism. In contrast, lower HDL-c levels are a risk factor for MS [4].

In this study, the significant reduction in the GGT/MBI ratio was comparable in the placebo and PTX groups; however, in VE, this reduction was more pronounced than in the other groups. Derakhshandeh-Rishehri *et al.* [20] showed that VE supplementation can significantly decrease GGT levels without significant effects on BMI. The obesity epidemic is closely associated with the rising prevalence and severity of MASLD; it has been linked not only with simple steatosis but also with advanced diseases, such as MASH, MASH-related cirrhosis and hepatocellular carcinoma [21]. This study's limitations were the small sample size, the nature of the study and the single-centred design. Also, the study reliance on indirect markers rather than direct liver fat or fibrosis measurements.

CONCLUSIONS

GGT/HDL-c ratio was strongly associated with MASH. Lifestyle modification significantly lowered liver enzymes, lipid profile, BMI and FLI. VE and PTX treatment for 6 months significantly reduced ALT, AST and GGT levels, improved lipid profile and inflammatory marker (Hs-CRP) and showed a more significant GGT/HDL-c ratio and FLI reduction. However, VE significantly reduced the GGT/HDL-c and GGT/BMI ratio among treated patients more than PTX.

Recommendations

Future work should include longitudinal study including larger sample size from multicenters, as well as conducting more direct liver assessments, such as using FibroScan or MRI-based fat measurement, with longer patients' follow-up period. Also, studies comparing combination therapy, dose-response and better placebo-controlled designs are strongly recommended. Additionally, future research should also measure physical activity, diet adherence and weight-loss percentage more carefully.

Acknowledgement

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Ethical Considerations

The research protocol was reviewed and approved by the Institutional Review Board (IRB) of Gastroenterology and Hepatology Teaching Hospital and the Ethics Committee of the College of Pharmacy, University of Sulaimani, Sulaimaniyah, Iraq (No. PH124/24 on May 12, 2022). The study adhered to the ethical guidelines of the Declaration of Helsinki, 2008. Written informed consent was obtained from

all participants before the study and they were assured of the confidentiality and anonymity of their responses.

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