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Effects of Multivitamin Supplementation on Liver Enzymes in Depressive Patients with Non-Alcoholic Fatty Liver Disease: A Randomized Clinical Trial and Community Health Implications

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is a prevalent condition commonly observed in depressive patients.

Objective: this randomized clinical trial aimed to investigate the effects of multivitamin supplementation on liver enzymes in depressive patients with NAFLD.

Methods: The study randomly divided the participants into two groups: the intervention group, which received multivitamin supplementation, and the control group, which received a placebo. The researchers examined liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and serum bilirubin to evaluate liver function. They conducted statistical analyses to compare the changes in the levels of these liver enzymes between the two groups.

Results: The results demonstrated that the multivitamin supplementation group showed a statistically significant decrease in ALT, AST, ALP and serum bilirubin levels compared to the

placebo group. Also results showed that the multivitamin supplementation group exhibited significant improvements in depressive symptom scores compared to the placebo group.

Conclusion: The results of this study indicate that multivitamin supplementation could potentially improve liver function in individuals with non-alcoholic fatty liver disease (NAFLD) who also suffer from depression. However, additional research is needed to investigate the underlying mechanisms and long-term impacts of multivitamin supplementation on liver health specifically in this group of patients.

Keywords: Non-alcoholic fatty liver disease, NAFLD, depression, randomized clinical trial

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a common and intricate liver disorder characterized by the buildup of excessive fat in the liver of individuals who consume minimal or no alcohol (1). NAFLD is strongly linked to obesity, insulin resistance, metabolic syndrome, and depression, creating a substantial impact on public health worldwide (2). Elevated liver enzymes, such as alanine transaminase (ALT) and aspartate transaminase (AST), serve as markers of hepatocellular injury and are commonly assessed to monitor NAFLD progression and severity (3).

The management of NAFLD involves a multidimensional approach, focusing on lifestyle modifications, such as dietary changes, physical activity, and weight loss. However, considering the comorbidity of depression in NAFLD patients, it becomes essential to explore novel therapeutic interventions that can address both conditions simultaneously (4). One such intervention under investigation is the use of multivitamin supplementation, which aims to optimize the intake of essential nutrients and potentially modulate liver enzyme levels in depressive patients with NAFLD.

Multivitamins are dietary supplements that contain a combination of vitamins and minerals. They are commonly used to ensure adequate intake of essential nutrients in individuals who may have nutritional deficiencies or have increased nutrient requirements. While multivitamins are generally considered safe when taken as directed, their benefits and effects may vary depending on individual needs and health conditions (5).

The rationale behind multivitamin supplementation lies in the potential role of specific vitamins and antioxidants in mitigating liver inflammation, oxidative stress, and cellular damage associated with NAFLD. Vitamins such as E, D, C, and various B-complex vitamins have been implicated in liver health and have shown promising results in limited studies focused on NAFLD (6).

Research on the effects of multivitamin supplementation specifically on liver enzymes in depressive patients with NAFLD is limited. However, some studies have investigated the impact of certain individual vitamins and antioxidants on NAFLD and liver enzymes. For example, vitamin E has shown some potential benefits in reducing liver inflammation and improving liver

enzyme levels in individuals with NAFLD (6, 7). Other studies have examined the effects of vitamin D, vitamin C, and B-complex vitamins on NAFLD, but results have been mixed (8-11). Thus, the aim of this study is to evaluate the effects of multivitamin supplementation on Liver Enzymes in depressive patients with Non-Alcoholic Fatty Liver Disease.

Methods

Study Design and Settings: This was a randomized clinical trial conducted at multiple centers in Kalar city, located in the Kurdistan region of Iraq. The study took place from February to May 2023 and received ethical approval from the Ethics Committee of Garmian Polytechnic University, Kalar Technical College (Approval No: KTC20230530). The trial was registered on ClinicalTrials.gov (Identifier: NCT05897606) on September 6, 2023. All methods adhered to relevant guidelines and regulations, and both verbal and written informed consent were obtained from all participants prior to their inclusion in the study. The research was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Inclusion and Exclusion Criteria:inclusion criteria included participants aged 24 to 83 years old, Depressive patients diagnosed with non-alcoholic fatty liver disease (NAFLD) based on clinical evaluation, medical history, and beck score consistent with the diagnosis of NAFLD, Elevated liver enzyme levels, specifically alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), exceeding the normal range as defined by the laboratory conducting the tests, Participants on stable antidepressant medication regimen for at least 4 weeks prior to the study initiation and participants who provide written informed consent to participate in the study, indicating their willingness to comply with study procedures and follow-up assessments.

Participants excluded from study those with a history of significant alcohol consumption (exceeding 20 g/day for males and 10 g/day for females) or ongoing alcohol use disorder, participants with a history of liver diseases other than NAFLD, such as viral hepatitis (hepatitis B or C), autoimmune liver disease, drug-induced liver injury, or cirrhosis, participants taking medications known to significantly impact liver enzyme levels, such as hepatotoxic drugs, antiretroviral therapy, or chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), participants with severe medical conditions, including end-stage renal disease, cancer, uncontrolled diabetes, cardiovascular disease, or other serious systemic illnesses that may interfere with study outcomes or pose a risk to participant safety, pregnant or breastfeeding individuals, as the effects of multivitamin supplementation on these populations have not been extensively studied, participants with known allergies or intolerances to the components of the multivitamin supplement or placebo formulation, participants currently enrolled in or having participated in another clinical trial within the past 30 days prior to study initiation, participants unable or unwilling to comply with study procedures, including regular follow-up assessments and adherence to the multivitamin supplementation regimen and participants with significant cognitive impairment or inability to provide informed consent or understand study instructions.

Randomization and Intervention: This study was a double-blind clinical trial. A total of 160 patients met the inclusion criteria for our study. Permuted block randomization method was used to randomly assign patients to study groups. The study groups were coded as A (for the intervention group) and B (for the placebo group). The intervention group received one caplet of multivitamins every day (**Table 1**), one-hour before breakfast for 12 weeks. The control group took a placebo prepared with the same shape and size of supplements. The supplement was given to the patients by someone other than the researcher, to ensure that the researchers did not know which group receiving the supplement/placebo (given the double-blindness of the study). Also, in this study, the person who did the data analysis did not aware of randomization. at first, a 3-day recall food questionnaire was taken from two groups.

Physical activity: The participants' level of physical activity was assessed using the internationally validated International Physical Activity Questionnaire (IPAQ). The recorded data, measured in metabolic equivalents (METs), were categorized into three groups: light activity (<600 MET-min/week), moderate activity (600-3000 MET-min/week), and high activity (>3000 MET-min/week) (12).

Anthropometric Indices : Body weight was measured using a bioimpedance analyzer (Inbody 770, Inbody Co, Seoul, Korea) with an accuracy of 0.1 kg. Height was recorded using a BSM 370 (Biospace Co, Seoul, Korea). Body mass index (BMI) was calculated by multiplying a person's weight in kilograms by the square of their height in meters. According to the CDC (Centers for Disease Control and Prevention) guidelines, BMI values can be categorized as follows: a BMI less than 18.5 indicates underweight, 18.5-24.9 indicates a normal or healthy weight, 25.0-29.9 indicates overweight, and a BMI of 30.0 or higher indicates obesity (13).

Clinical and laboratory results: The blood test was taken twice from subjects in the morning after a 12-hour fast. First time, at baseline of study, and the second time, at the end of intervention. Blood samples were collected by venipuncture from the antecubital vein by vacuum tubes. To obtain blood serum, all blood sample was centrifuged at 2500 rpm for 10 minutes. Laboratory tests were carried out on the same day without reserving the serum of patients. Quantification of 25(OH)D levels (ng/ml) was performed from serum samples using automated immunoassays. Liaison 25(OH) Total Vitamin D Assay DiaSorin Liaison XL (DiaSorin, Italy).

Statical analysis: Analyses were done by STATA 14 software. Frequency (percentage) and mean (standard deviation) were used to demonstrate the demographic and clinical characteristics Comparison of quantitative or qualitative variables between two groups was accomplished by using a t-test and chi-square test, respectively. Two-sample test of proportions was used to contrast the proportion of side effects between two doses of vaccine. logistic regression was used to found the associations between multivitamin supplementation and Liver Enzymes. P-values of 0.05 were considered significant.

Results: Comparison of baseline characteristics of the participants between the study groups is shown in **Table 2**. 160 subjects participated in the study and were divided into two groups (supplementation and control). The age of participants in the supplementation group is higher than

in the Control group, P-value= 0.003 62 (38.8%) of the supplementation group participants are currently married, but the majority of the control group 36 (22.5%) are currently divorced, (P = 0.001). As for the BMI (kg/m2) of the participants, there was no difference between the two groups at the beginning of the study, (P = 0.202). However, at the end of the study, the supplementation group had a BMI decrease from 26.11±2.97 to 23.95±2.85, (P = 0.016). Regarding the Beck score and depression of the participants, there was no difference between the two groups at the beginning of the study, (P = 0.224). However, at the end of the study, the Beck score of the supplementation group decreased from 20.14±9.94 to 9.78±4.73, (P = 0.001).
Comparison of biochemical parameters of the participants between the study groups is shown in **Table 3**. At the beginning of the study there was no statistically significant difference between Urea, Albumin, and 25(OH)D of both the supplementation and control groups. However, at the end of the study, the urea of the supplementation group decreased from 41.97±12.8 to 21.72±10.0, while the control group was 42.04±12.7 at the beginning of the study, but increased to 46.72±13.9 at the end of the study. As for creatinine and Serum CA, no difference was observed in Beginning and end of the intervention. The albumin of both the supplementation and control groups decreased at the end of the study, with the supplementation group from 54.15±5.42 to 44.19±4.01, the control group from 53.39±5.29 to 49.05±5.37, (P=0.005). The 25(OH)D of participants in the supplementation group increased at the end of the study, from 23.06±14.29 to 44.64±25.73, (P=0.001). However, Control group decreased from 28.25±14.39 to 19.91±19.65.

Comparison of Liver Enzymes levels of the participants between the study groups is given **in Table 4.** The Alkaline phosphatase (ALP) of the supplementation group participants was 122.71±3.4 at the beginning of the study, but decreased to 112.06±4.0 at the end of the study, (P =0.001). Although the control group also had a decrease in ALP, at the end of the study, the difference was not significant, (P = 0.310). The ALP of the supplementation group participants was 63.58±3.46 at the beginning of the study, but decreased to 59.58±4.04 at the end of the study, (P=0.001). However, no significant difference from the control group was observed at the end of the study. The ALT of the supplementation group participants was 47.35±0.85 at the beginning of the study, but decreased to 42.09±3.83 at the end of the study, (P=0.001). However, no significant difference from the control group was observed at the end of the study. The s.bilirubin of participants in both groups decreased significantly at the end of the study, with the supplementation group dropping from 1.14±0.14 to 0.87±0.33 and the control group dropping from 1.19±0.17 to 1.12±0.14

Associations between multivitamin supplementation and Liver Enzymes by logistic regression at follow up of the trial are shown **in Table 5** and the control group is taken as reference. At the end of the study, ALP decreased in the supplementation group, 75%, 0.25 (0.10, 0.67) more than in the control group, (P=0.006). While AST in supplementation group participants, is 49% lower than in control group. As for ALT and S. Bilirubin, 59% to 62% lower than the control group.

Figure 1 shows fatty liver grade change at the end of intervention.26 participants in the supplementation group had a 2-degree reduction in fatty liver, while only 11 participants in the control group had a 2-degree reduction. 36 participants in the supplementation group had a 1-degree reduction in fatty liver, while only 119 participants in the control group had a 1-degree reduction. 31 participants in the control group had no changes in fatty liver, while 18 in the supplementation group had no changes.17 participants in the control group increased their liver fat by 1 degree and 2 participants by 2 degrees, while the supplementation group had no increase in their fatty liver.

Discussion: Through a randomized clinical trial, this study aimed to explore the impact of multivitamin supplementation on liver enzymes in individuals with non-alcoholic fatty liver disease (NAFLD) who also experience depression. The results of this research offer valuable insights into the potential advantages of multivitamin supplementation for this particular group of patients.

The primary outcome measure of this study was the change in liver enzyme levels, specifically alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline phosphatase (ALP) and serum bilirubin following a duration of multivitamin supplementation. The results demonstrated that the multivitamin supplementation group showed a statistically significant decrease in ALT, AST, ALP and serum bilirubin levels compared to the placebo group. These findings suggest that multivitamin supplementation may have a positive impact on liver function in depressive patients with NAFLD, as evidenced by the improvement in liver enzyme levels.

The observed decrease in liver enzyme levels could be attributed to several potential mechanisms. First, multivitamins contain a variety of essential nutrients and antioxidants that play a crucial role in maintaining liver health (6, 14). These nutrients, such as vitamins B complex, C, and E, have been shown to possess hepatoprotective properties, including reducing oxidative stress, inflammation, and lipid peroxidation, which are key contributors to liver damage in NAFLD (14). Furthermore, multivitamin supplementation may support the liver's detoxification processes and enhance liver regeneration, thereby promoting the restoration of normal liver enzyme levels (15).

A cross-sectional study involving 16,190 participants revealed findings consistent with our study, indicating a significant negative correlation between serum vitamin D levels and liver enzyme levels, insulin resistance, and components of metabolic syndrome (16). These results support the notion that increased serum vitamin D levels could potentially mitigate liver inflammation and steatosis while improving insulin sensitivity through the activation of liver macrophage vitamin D receptors (VDR) (17).

In addition, antioxidants, such as vitamins C and E, help neutralize free radicals and reduce oxidative stress, which is known to contribute to liver and kidney damage. By reducing oxidative stress, multivitamins may protect liver and kidney tissues from injury and improve their overall function (18). Furthermore, inflammation is a key factor in the development and progression of

NAFLD and kidney dysfunction. Multivitamins often contain anti-inflammatory agents, such as vitamin D and omega-3 fatty acids, which can help modulate the inflammatory response and reduce systemic inflammation. By alleviating inflammation, multivitamin supplementation may contribute to the improvement of liver and kidney function in depressive patients with NAFLD (19).

In a study by Wei et al. (20), it was observed that individuals in the highest quartile of dietary vitamin C intake had a decreased risk of non-alcoholic fatty liver disease (NAFLD) by 0.71 times compared to those in the lowest quartile, which aligns with our findings. Furthermore, several epidemiological studies have consistently reported a significant negative correlation between serum vitamin C (VC) levels and hepatic steatosis and hepatic fibrosis (21, 22). In line with these findings, a prospective double-blinded randomized controlled trial demonstrated that oral vitamin C supplements had notable benefits for patients with NAFLD. The trial indicated that vitamin C supplementation significantly improved liver function and glucose metabolism. Additionally, it was found to enhance intestinal microbial diversity and increase adiponectin concentration, further contributing to the management of NAFLD (8). In line with our findings, Jeon et al. (23) reported a positive association between serum vitamin E (VE) levels and the prevalence of non-alcoholic fatty liver disease (NAFLD). Furthermore, VE, specifically alpha-tocopherol, was identified as a predictor of liver fat as determined by magnetic resonance imaging (MRI) (24). A cross-sectional study conducted on Swedish adults also indicated a positive association between serum VE levels and serum cholesterol and obesity (25). Moreover, Waniek et al. (26) found that alpha-tocopherol levels were positively associated with high triglyceride levels and low levels of high-density lipoprotein cholesterol (HDL-C).

In addition to the effects on liver enzymes, this study also evaluated the secondary outcomes related to depressive symptoms, liver function, and quality of life. The results showed that the multivitamin supplementation group exhibited significant improvements in depressive symptom scores compared to the placebo group. This finding suggests a potential link between multivitamin supplementation, mood regulation, and mental well-being in depressive patients with NAFLD. While the exact mechanisms underlying this association are not fully understood, it is plausible that the beneficial effects of multivitamins on brain function, neurotransmitter synthesis, and oxidative stress reduction may contribute to alleviating depressive symptoms.

The results of this randomized clinical trial demonstrate a significant improvement in biochemicals markers among depressive patients with NAFLD who received multivitamin supplementation compared to the control group. Specifically, urea, albumin and 25(OH)D showed positive changes in the intervention group.

While the results of this study are promising, several limitations should be acknowledged. The sample size was relatively small, which may limit the generalizability of the findings. Additionally, the duration of the intervention may not have been sufficient to capture long-term effects on liver function. Future studies with larger sample sizes and longer follow-up periods are needed to validate and further explore these findings.

Moreover, it is important to consider potential confounding factors that could influence liver function independently of multivitamin supplementation. Factors such as medication use, lifestyle habits, and comorbidities should be taken into account in future studies to better isolate the effects of multivitamins on liver and kidney health.

Table (1). Multivitamins Caplet Ingredients

Ingredients	Per 100 G	Per Serving (1 Caplet)	%NRV*
Vitamin A	53,333 µg	800 µg RE	100%
Vitamin B_1	93.3 Mg	1.4 Mg	127%
Vitamin B_2	116.7 Mg	1.75 Mg	125%
Vitamin B_6	133.3 Mg	2.0 Mg	143%
Vitamin B_{12}	166.7 µg	2.5 µg	100%
Biotin	4,167 µg	62.5 µg	125%
Vitamin C	6,667 Mg	100 Mg	125%
Vitamin D_3	333.3 µg	5.0 µg	100%
Vitamin E	1,000 Mg A-TE	15 Mg A-TE	125%
Folic Acid	13,333 µg	200 µg	100%
Vitamin K1	2,000 µg	30 µg	40%
Nicotinamide	1,333 Mg NE	20 Mg NE	125%
Pantothenic Acid	500.0 Mg	7.5 Mg	125%
Coenzyme Q10	266.7 Mg	4.0 Mg	-
Lutein	33.3 Mg	0.5 Mg	-
Calcium	10,933 Mg	164 Mg	21%
Magnesium	6,667 Mg	100 Mg	27%
Phosphor	8,333 Mg	125 Mg	18%
Chromium	2,667 µg	40 µg	100%
Copper	33,333 µg	500 µg	50%
Iodine	6,667 µg	100 µg	67%
Iron	333.3 Mg	5.0 Mg	36%
Manganese	133.3 Mg	2.0 Mg	100%
Molybdenum	3,333 µg	50 µg	100%
Selenium	2,000 µg	30 µg	55%
Zinc	333.3 Mg	5.0 Mg	50%

***NRV: Nutrient References Values For The Daily Intake As Defined By Regulation (EU) No. 1169/2011**

Table (2). Comparison of Baseline Characteristics of the Participants between the Study Groups

		Supplementation	Control	P-Value
Age (Year)		**49.86±16.88**	**49.81±11.69**	**0.003**
Gender	**Male**	**37(23.1)**	**35(21.9)**	**0.874**
	Female	**43(26.9)**	**45(28.1)**	**0.437**
Residency	**Urban**	**26(16.3)**	**57(35.6)**	**0.001**
	Rural	**54(33.8)**	**23(14.4)**	**0.001**
Marital Status	**Married**	**62(38.8)**	**31(19.4)**	**0.001**
	Divorced	**2(1.3)**	**36(22.5)**	**0.001**
	Single	**16(10)**	**13(8.1)**	**0.001**
SES (Socioeconomic status)	**Low**	**4(2.5)**	**38(23.8)**	**0.004**
	Normal	**36(22.5)**	**34(21.3)**	**0.021**
	Good	**40(25)**	**8(5)**	**0.001**
Physical Activity (Met-H/Day)	**Low**	**9(5.6)**	**16(10)**	**0.090**
	Moderate	**43(26.9)**	**47(29.4)**	**0.087**
	High	**28(17.5)**	**17(10.6)**	**0.029**
BMI (Kg/M^2)	**Before**	**26.11±2.97**	**26.56±3.39**	**0.202**
	After	**23.95±2.85**	**26.66±3.21**	**0.001**
	P Value	**0.016**	**0.174**	**-**
Beck Score	**Before**	**20.14±9.94**	**18.25±9.60**	**0.224**
	After	**9.78±4.73**	**20.35±11.63**	**0.001**
	P Value	**0.001**	**0.237**	**-**

Note: Data presented as Mean±SD, Number (percent). P-value obtained by independent T-Test and Chi-Square

Table (3). Comparison of Biochemical Parameters of the Participants between the Study Groups

		Supplementation	Control	P-Value*
Urea Mg/Dl	Before	41.97±12.8	42.04±12.7	0.759
	After	21.72±10.0	46.72±13.9	0.001
	P-Value**	0.001	0.029	-
Creatinine Mg/Dl	Before	1.10±0.25	1.06±0.28	0.242
	After	0.93±0.18	1.12±0.20	0.745
	P-Value**	0.001	0.101	-
Albumin G/L	Before	54.15±5.42	53.39±5.29	0.396
	After	44.19±4.01	49.05±5.37	0.005
	P-Value**	0.001	0.001	-
25(OH)D Ng/Ml	Before	23.06±14.29	28.25±14.39	0.913
	After	44.64±25.73	19.91±19.65	0.001
	P-Value**	0.001	0.003	-
Serum CA Mg/Dl	Before	9.36±0.51	9.33±0.49	0.481
	After	9.30±0.40	9.21±0.44	0.518
	P-Value**	0.440	0.088	-

Note: Data Presented as Mean±SD , P-Value obtained by *Independent T-Test and **Paired T-Test

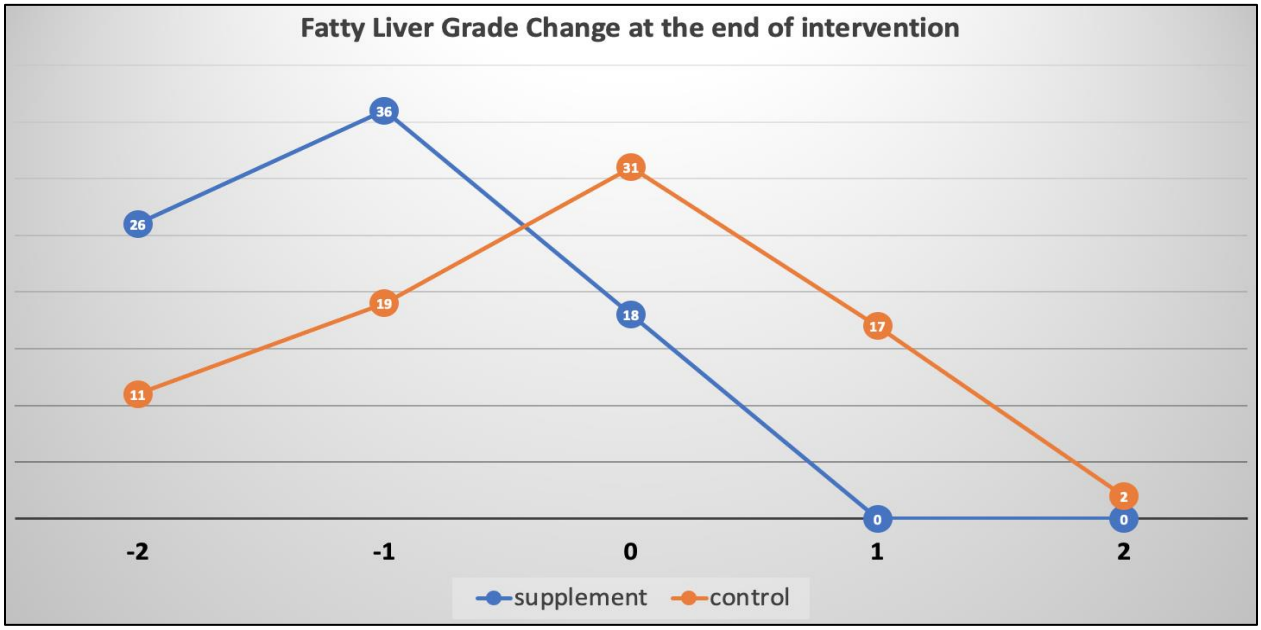
Table (4). Comparison of Liver Enzymes levels of the participants between the study groups

		Supplementation	Control	P-Value*
ALP	Before	122.71±3.4	121.26±2.5	0.003
	After	112.06±4.0	120.88±2.3	0.001
	P-Value**	0.001	0.310	-
AST	Before	63.58±3.46	68.70±2.54	0.001
	After	59.58±4.04	69.27±3.86	0.001
	P-Value**	0.001	0.245	-
ALT	Before	47.35±0.85	47.15±1.13	0.199
	After	42.09±3.83	46.63±1.91	0.001
	P-Value**	0.001	0.056	-
S. Bilirubin	Before	1.14±0.14	1.19±0.17	0.037
	After	0.87±0.33	1.12±0.14	0.001
	P-Value**	0.001	0.008	-

Note: Data Presented as Mean±SD , P-Value obtained by *Independent T-Test and **Paired T-Test

Table (5). Associations between multivitamin supplementation and Liver Enzymes by logistic regression at follow up of the trial

	Control	Supplementation	P-Value
	Adjusted OR (95% CI)		
ALP	Ref.	0.25 (0.10, 0.67)	0.006
AST	Ref.	0.51 (0.35, 0.75)	0.001
ALT	Ref.	0.41 (0.25, 0.66)	0.001
S. Bilirubin	Ref.	0.38 (0.21, 0.73)	0.001



*Adjusted for Kilocalories S_ALP_1st AST_1st ALT_1st

Figure (1), fatty liver grade change at the end of intervention

Conclusion: The results of this randomized clinical trial suggest that multivitamin supplementation has a favorable effect on liver enzyme levels, depressive symptoms, liver function, and quality of life in depressive patients with NAFLD. These findings support the

potential use of multivitamin supplementation as an adjunctive therapy in the management of NAFLD in this specific patient population. Further research is needed to elucidate the underlying mechanisms, optimize the formulation and dosage of multivitamin supplements, and determine the long-term benefits and safety of such interventions. Ultimately, the integration of multivitamin supplementation into the clinical care of depressive patients with NAFLD may hold promise for improving liver health and mental well-being.

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