Iran Red Crescent Med J. 2017 April; 19(4):e43193. doi: 10.5812/ircmj.43193.

Published online 2017 January 8. **Research Article**

Effects of Turmeric on Homocysteine and Fetuin-A in Patients With Nonalcoholic Fatty Liver Disease: A Randomized Double-Blind Placebo-Controlled Study

Aida Ghaffari,[1] Maryam Rafraf,[2,*] Roya Navekar,[3] Bita Sepehri,[4] Mohammad Asghari-Jafarabadi,[5,6] Seyyed-Mostafa Ghavami,[7] and Nahid Manafi[8]

[1]Student's Research Committee, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Community Nutrition, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Department of Gastroenterology and Hepatology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Road Traffic Injury Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[6]Department of Statistics and Epidemiology, Faculty of Health, Tabriz University of Medical Sciences, Tabriz, Iran
[7]Department of Radiology, Faculty of Paramedical, Tabriz University of Medical Sciences, Tabriz, Iran
[8]Sanjesh Laboratory

[*]*Corresponding author*: Maryam Rafraf, Tabriz University of Medical Sciences, Atar Neyshapoori Av., Golgasht St., Tabriz, Iran. Tel: +98-9143145786, Fax: +98-411 33340634, E-mail: rafrafm@tbzmed.ac.ir

Received 2016 October 19; **Revised** 2016 December 07; **Accepted** 2017 January 09.

Abstract

Background: Elevated levels of homocysteine (Hcy) and fetuin-A are important risk factors for cardiovascular diseases in patients with a nonalcoholic fatty liver disease (NAFLD). There is limited evidence regarding the effects of turmeric on NAFLD.
Objectives: This study aimed at investigating the effects of turmeric supplementation on serum levels of Hcy and fetuin-A in patients with NAFLD.
Methods: In this double-blind, randomized, controlled clinical trial, 46 NAFLD patients (21 males and 25 females; age range, 20 - 60 years) with body mass index ranged 24.9 - 40 kg/m^2 were recruited from Sheikh-ol-Raees clinic in Tabriz City, Iran during Nov 2014-May 2015. The participants were allocated into the two groups using the block randomization method. The intervention and control groups received 3g of turmeric (n = 23) and placebo (n = 23), daily for 12 weeks. Fasting blood samples were collected at baseline and at the end of the trial for biochemical analysis.
Results: Turmeric supplementation significantly decreased serum levels of Hcy, compared with the placebo group at the end of the study (by 27.83%, P = 0.034). No significant difference was observed between the two groups in serum levels of fetuin-A after the intervention (P > 0.05). Serum levels of glucose, insulin and homeostasis model assessment for insulin resistance were declined significantly in the turmeric group (by 1.22%, 17.69% and 19.48%, P = 0.039, P = 0.013 and P = 0.001, respectively) compared to the placebo.
Conclusions: Turmeric consumption had beneficial effects on serum Hcy levels and may be useful in management of this risk factor in NAFLD patients.

Keywords: Turmeric, Homocysteine, Fetuin-A, Nonalcoholic Fatty Liver

1. Background

Nonalcoholic fatty liver disease (NAFLD) is a common liver disorder without history of significant consumption of ethanol (1). The spectrum of NAFLD ranges from simple steatosis (deposition of triglyceride as lipid droplets in the cytoplasm of hepatocytes) to the nonalcoholic steatohepatitis and end-stage liver disease (2). The prevalence of this disorder is 20% - 40% in Western countries and 10% - 30% in Asian countries, and it is rising over time in relation to increase of obesity. Nonalcoholic fatty liver disease is associated with components of the metabolic syndrome and is considered as an independent risk factor for cardiovascular disease (CVD) (3). Several highly interrelated factors such as hyperhomocysteinemia contribute to the enhanced risk of CVD in persons with NAFLD (4). Homocysteine (Hcy), a sulfur containing amino acid, is derived from the metabolism of methionine (5). It increases susceptibility of low-density lipoprotein cholesterol (LDL-C) to oxidation, and platelet aggregation and activates the coagulation factors and finally directs injury of the endothelium (6). Moreover, hyperhomocysteinemia plays a role in the development of liver steatosis and accelerated progression to liver fibrosis in chronic hepatitis C. These evidences suggest a possible role of hyperhomocysteinemia in the liver steatosis-atherosclerosis connection (7).

Another risk factor for development of NAFLD is high serum levels of fetuin-A. It is a glycoprotein completely produced in the liver and is secreted into circulation. Fetuin-A induces insulin resistance in liver and skeletal muscle by inhibition of insulin receptor in these target tissues (8). Higher levels of fetuin-A are associated with obesity, insulin resistance, NAFLD, myocardial infarction and ischemic stroke in general population (9-12). In addition, circulating fetuin-A is independently related with endothelial dysfunction and subclinical atherosclerosis in NAFLD (8).

In recent years, much research has been focused on functional natural compounds to reverse the risk factors of CVD (13). In this context, one of the most investigated and relatively well-recognized agents with minimal side effects is turmeric. Turmeric, the rhizome of Curcuma longa L., is a perennial member of the Zingiberaceae family, and cultivates mainly in India, and Southeast Asia. The primary active compound responsible for the yellow color named curcumin. Several studies have demonstrated its antioxidant, hepatoprotective and antiatherosclerotic activities (14). Recently, the effect of the parent plant turmeric and/or curcumin on cardiovascular systems has received much attention (15). Ramaswami et al. showed that curcumin effectively blocked the detrimental effect of Hcy on the vascular system in porcine coronary arteries and thus could be used in patients with hyperhomocysteinemia, and to prevent cardiovascular diseases (14). In another study, curcumin treatment appeared to be effective in reducing serum fetuin-A levels in rat fed a high-fat diet (HFD) (16).

Although some studies have already demonstrated the beneficial effects of curcumin on Hcy and serum fetuin-A levels (14, 16), no clinical trials have been conducted to assess the effects of whole turmeric in NAFLD patients. Because turmeric is commonly used in food, we conducted a study to evaluate the efficacy of turmeric supplementation on serum levels of Hcy and fetuin-A in patients with NAFLD.

2. Methods

2.1. Subjects

A total of 204 patients recruited from Sheikh-ol-Raees clinic in Tabriz, Iran, were screened based on a transabdominal ultrasonography to diagnose NAFLD (Figure 1). One hundred forty-two patients did not meet all inclusion criteria or met exclusion criteria and 16 people refused to participate and all excluded. A total of 46 NAFLD patients (21 males and 25 females; age range, 20-60 years) with body mass index (BMI) ranged 24.9 - 40 kg/m^2 were included in the study. This study was approved by the ethics committee of Tabriz University of Medical Sciences and was registered on the Iranian registry of clinical trials with the identification IRCT201406183664N12. Written informed consent was obtained from all participants. Subjects with the history of thyroid disorders, severe anemia, cancer, biliary and kidney stone, viral hepatitis and other hepatic diseases, being postmenopause, pregnant or breast feeding were excluded from the study. In addition, patients who consumed tobacco and alcohol, nutritional supplements within the previous 4 weeks or during a 12-week study period, anticoagulant, oral contraceptive and lipid lowering medication were ignored from the study.

The study was conducted from November 2014 to May 2015. Sample size was determined based on the serum Hcy level, which obtained from a pilot study in the beginning of our research by the size of 8 patients per group. Considering $\alpha = 0.05$, power of 80%, a two-tailed test, 18.5% change and Pocock formula, at least 18 samples per group were computed. This number was increased to 23 per group to consider the anticipated dropout rate.

2.2. Study Design

The study was a randomized, double-blind, placebo-controlled trial (RCT), in which turmeric and placebo were compared in patients with NAFLD. After assessing for eligibility, subjects who met the inclusion criteria were randomly assigned into the two groups using a block randomization procedure with matched subjects in each block of size 4 based on age, gender and BMI. Contributors were randomly allocated into the two groups by using a block randomization method, which was generated by the random allocation software (RAS). A computer-generated random sequence was kept in a remote secure location and administered by an independent third party who was not involved with the clinical conduct of the study until all data were collected and verified. Patients and those involved in enrolling participants, administering interventions, and assessing outcomes were blind to group assignments. The turmeric group (n = 21) was given six turmeric capsules daily for 12 weeks. Each capsule contained 500 mg turmeric powder (6 $\times$ 500 mg). The placebo group (n = 21) was given six placebo capsules daily for the same period. Placebo capsules contained starch and were similar in size and color to the turmeric capsules. All of the supplement packs were identical looking. The volunteers were followed up with telephone once a week and number of returned supplements every 2 weeks (Figure 1).

2.3. Ultrasonography

Transabdominal ultrasonography was performed at baseline to confirm NAFLD and its stages. Degree of hepatic steatosis was performed according to the macrovesicular

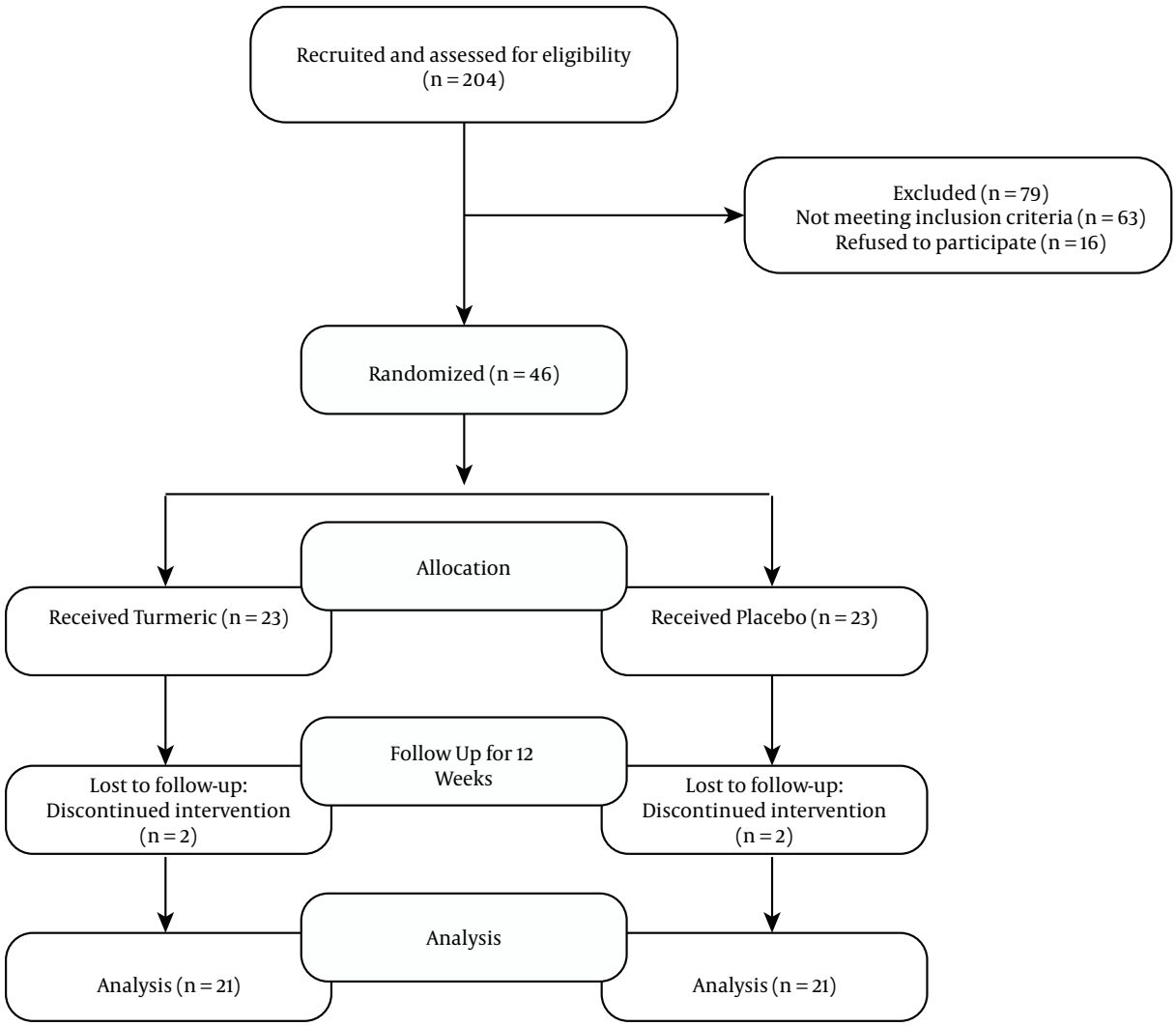

Figure 1. Flow Diagram of Subject Recruitment

steatosis and divided into 4 categories included: no steatosis, grade 1: up to 33% steatosis, grade 2: 33% - 66% steatosis and grade 3: 66% steatosis (17). Another ultrasonography was performed after 12 weeks to evaluate the effect of intervention on NAFLD.

2.4. Herbal Supplement Preparation

Turmeric was purchased locally and were identified and authenticated by the herbarium of the botany department, faculty of pharmacy, Tabriz University of Medical Sciences, Iran. Turmeric rhizomes were lightly washed with water and air dried on filter paper. Then, turmeric was cut into small pieces, crushed and put into 500 mg capsules.

2.5. Anthropometric Assessments

Body weight was measured using a scale (Seca, Hamburg, Germany) with 0.5 kg accuracy, while participants were without shoes and wearing light clothing. A tape was used to measure height with 0.5 cm accuracy, while participants were without shoes. The body mass index was calculated using weight and height measurements (kg/m^2).

2.6. Laboratory Assessment

Blood samples were collected in the morning after a 12-hour overnight fasting at the baseline and 12 weeks after the intervention. The serum glucose was measured using the standard enzymatic methods with a commercially available Pars Azmoon kit (Karaj, Iran). The serum insulin

level was measured by an enzyme-linked immunosorbent assay (ELISA) method using the Monobind kit (USA). Insulin resistance was determined by the homeostatic model assessment (HOMA) index with the formula: HOMA-IR = fasting insulin (μUI/mL) $\times$ fasting glucose (mg/dL) /405. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured by the enzymatic method using a commercial kit (Pars Azmoon, Tehran, Iran). The serum Hcy level was determined using a commercial ELISA kit (Axis Homocysteine EIA, Axis-Shield Diagnostic Ltd, the Technology Park, and Dundee DD2 1Xa, UK) as per manufacturer's instruction. Serum fetuin-A was measured by a commercially available DiaMetra ELISA kit (DiaMetra Co, Milan, Italy).

2.7. Statistical Analysis

Statistical analysis was performed using the statistical package for the social sciences (SPSS Inc, Chicago, Illinois, USA) version 13 based on the intention to treat principle. Normal distribution was tested with the Kolmogorov-Smirnov test. Ordinal and nonnormally distributed variables were shown as the median (interquartile range) (MED (IQR)) and numeric normally distributed ones were shown as the mean$\pm$standard deviation. Biochemical parameters of the subjects in both groups at baseline were compared using independent t tests. The paired t test was applied to compare means before and after the intervention in each group. Analysis of covariance (ANCOVA) was used to identify any differences between the groups at the end of the study, adjusting for baseline values and covariates. A probability (P) value less than 0.05 was considered significant in all statistical analyses.

3. Results

A total of 4 patients were excluded from the study for personal reasons (Figure 1). As a result, the data were reported for 42 patients (21 in the turmeric group and 21 in the placebo group). No side effects were reported by consumption of turmeric during the study. General and biochemical values of the subjects at the beginning of the study are shown in Table 1. There were no significant differences in these variables between the two groups at the baseline (Table 1).

Biochemical parameters of the subjects at baseline and after a 12-week intervention are presented in Table 2. No significant differences were observed between the two groups in serum biochemical values at baseline. Serum levels of Hcy were decreased significantly in the turmeric group at the end of the study compared to the baseline values (by 23.14%, P = 0.012). Results of ANCOVA showed a statistically significant difference between the two groups in serum levels of Hcy (by 27.83%, P = 0.034) at the end of the study, adjusted for energy, BMI and baseline values.

Table 1. General and Biochemical Characteristics of the Patients with Nonalcoholic Fatty Liver Disease at Baseline

Variable	Turmeric Group (n=21)	Placebo Group (n=21)	P[a]
Gender, (N) %[b]			0.352
male	(11) 52.4	(8) 38.1	
female	(10) 47.6	(13) 61.9	
Age, y[c]	42.09 (7.23)	40.38 (9.26)	0.391
Weight, kg[c]	85.26 (16.47)	87.40 (15.08)	0.663
BMI, kg/m^2[c]	31.81 (4.58)	32.92 (4.81)	0.447
Energy, kcal/d[c]	2507.19 (598.74)	2409.90 (759.99)	0.647
AST, U/l[c]	24.00 (11.59)	24.33(13.69)	0.933
ALT, U/l[d]	21.00 (15.50, 34.00)	23.00 (15.00, 31.50)	0.967

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BMI, Body Mass Index; NAFLD, Non-Alcoholic Fatty Liver Disease.
[a] P for comparing baseline values based on Independent t test.
[b] Data are tested by κ2 test.
[c] Data are presented as mean (SD).
[d] Data are presented as median (25th percentile 75th percentile).

The mean serum fetuin-A levels in the turmeric group were significantly declined at the end of the

study compared to the baseline values (by 11.27%, P = 0.001). No significant difference was observed between the two groups in serum levels of fetuin-A after the intervention (P > 0.05).

Significant decreases in serum levels of glucose, insulin and HOMA-IR (P < 0.05 for all) were observed in the turmeric group after the intervention compared to the baseline values. Results of ANCOVA showed statistically significant differences between the two groups in serum levels of glucose, insulin and HOMA-IR (by 1.22%, 17.69% and 19.48%, P = 0.039, P = 0.013 and P = 0.001, respectively) at the end of the study, adjusted for energy, BMI and baseline values (Table 2).

4. Discussion

It has been reported that turmeric has hepatoprotective characteristics and useful in prevention of human ailments such as the metabolic syndrome, and inflammatory conditions (18, 19). The nonalcoholic fatty liver disease is the hepatic component of the metabolic syndrome and accounts as an independent risk factor for CVD (20). Based on our knowledge, no study has yet been conducted on the possible cardio metabolic effects of turmeric including serum Hcy and fetuin-A in patients with NAFLD.

Table 2. Serum Biochemical Parameters of Patients with NAFLD Throughout the Study

Variable	Period	Turmeric Group (n = 21)	Placebo Group (n = 21)	P Value[a]
Homocysteine, μmol/L[b]	Before	14.91 (6.69)	14.46 (5.66)	P = 0.812
	After	11.46 (3.56)	15.88 (6.27)	P = 0.034[c]
	MD[d], P value[e]	-3.45 (-6.07 to -0.83), 0.012[f]	1.42 (-1.69 to 4.54), 0.390	
Fetuin-A, μg/mL[b]	Before	182.20 (90.79)	212.77 (82.63)	P = 0.261
	After	161.67 (89.44)	206.46 (74.14)	P = 0.203
	MD[d], P value[e]	-20.52 (-31.19 to -9.86), 0.001[f]	-6.30 (-25.93 to 13.31), 0.510	
FBS, mg/dL[b]	Before	92.80 (22.98)	85.23 (10.06)	P = 0.178
	After	85.23 (13.44)	86.28 (9.34)	P = 0.039[c]
	MD[d], P value[e]	-7.57 (-14.05 to -1.08), 0.024[f]	1.04 (-3.10 to 5.20), 0.605	
Insulin, μu/mL[b]	Before	13.83 (4.20)	14.08 (5.06)	P = 0.875
	After	11.82 (3.97)	14.36 (4.86)	P = 0.013[c]
	MD[d], P value[e]	-2.01 (-3.28 to -0.74), 0.003[f]	0.28 (-0.80 to 1.36), 0.595	
HOMA-IR[b]	Before	3.12 (1.06)	2.97 (1.25)	P = 0.679
	After	2.48 (0.89)	3.08 (1.17)	P = 0.001[c]
	MD[d], P value[e]	-0.64 (-0.98 to -0.30), 0.001[f]	0.10 (-0.14 to 0.36), 0.510	

Abbreviations: Hcy, Homocysteine; FBS, Fasting Blood Sugar; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; NAFLD, Nonalcoholic Fatty Liver Disease.
[a] P value for comparing baseline values based on Independent t test.
[b] Values for quantitative data are expressed as mean (SD).
[c] $P < 0.05$ when the ANCOVA test was used and adjusted for baseline variables, BMI and calorie intake.
[d] Mean difference (95% CI).
[e] P value for comparing baseline with end point values within each group. Paired sample t test was used for parametric comparison.
[f] Statistically significant difference between the two groups before and after the intervention ($P < 0.05$).

Homocysteine is formed as an intermediary in a methionine metabolism through two pathways: remethylation to methionine, which requires folate and vitamin B12 (or betaine in an alternative reaction); and transsulfuration to cystathionine, which requires pyridoxal-5'-phosphate (21). Evidence shows that elevated plasma Hcy, as a risk factor for CVD, alters intracellular lipid metabolism and is associated with hepatic fat accumulation (22).

Based on our results, turmeric consumption decreased serum levels of Hcy in patients with NAFLD. In a study by Kapoor et al., curcumin (200 mg/kg) treatment in methionine-treated rats for 30 days significantly decreased serum Hcy levels (15). Recently, Ramaswami et al. have reported that curcumin effectively reverses the endothelial dysfunction induced by Hcy and blocks Hcy-induced superoxide anion production and down-regulation of nitric oxide synthase in porcine coronary arteries (14). Ataie et al. declared that curcumin improved learning and memory deficits by protecting the nervous system against Hcy toxicity (23). According to the role of insulin in inhibition of hepatic cystathione beta synthase, which is an enzyme involved in methionine metabolism, insulin resistance seems to increase the Hcy levels (24). In the present study, supplementation with turmeric significantly decreased the serum levels of glucose, insulin and HOMA-IR. Therefore, it was possible that beneficial effects of turmeric on serum Hcy status in our subjects might be mediated via regulating glucose and insulin metabolism, in part. Furthermore, it was reported that fresh turmeric rhizomes possessing important probiotic characteristics and three lactic acid bacteria (LAB) strains were isolated from them (25). Due to the ability of LAB to produce folate (26), it was suggested that turmeric as a probiotic may affect monoglutamylated folate production and influence methionine metabolism and subsequently Hcy.

Fetuin-A is regarded as a key protein in obesity and NAFLD (27). In some studies, hepatic fetuin-A expression and its serum levels increased in obesity and there was a strong association between the serum level of fetuin-A and liver fat accumulation (28, 29). Hepatic expression of fetuin A is related to glucose and lipid metabolism (28). Since fetuin-A is linked with fatty liver and insulin resistance, it may be considered as a new therapeutic target in NAFLD (28, 29).

Our results showed that, turmeric consumption re-

duced the serum fetuin-A level in the intervened group. However, this reduction was not significant compared with placebo. Iyidogan et al. demonstrated that curcumin reduces the serum fetuin-A level in rats fed HFD (16). In another study, liver fetuin-A expression was decreased significantly by the 1.5 g curcumin/kg treatment in rats received HFD. A high-fat diet increased expression of hepatic fetuin-A in rats (27). It was suggested that curcumin may inhibit the expression of hepatic fetuin-A by activating the AMP-activated protein kinase pathway (30). Furthermore, increased serum glucose levels may induce hepatic production of the fetuin-A via activation of ERK-1/2 signaling pathways (31). Taken together, it is possible that curcumin may regulate fetuin-A levels through reducing blood glucose and improvement of insulin resistance.

This study is the first one to investigate the effects of turmeric on serum levels of Hcy and fetuin-A in patients with NAFLD. The main strength of the present study is that it was based on a placebo-controlled, stratification by age, gender and BMI, which make eliminating inter-individual differences and not under concomitant any drug therapy. However, our study had some limitations including small sample size and using fix dose of turmeric. Therefore, the results of the present study are not applicable for other doses or usage durations of turmeric.

4.1. Conclusions

The results of the present study showed that turmeric consumption had beneficial effects on serum Hcy levels. The possible effects of turmeric consumption on serum fetuin-A need other investigations. Further studies with different doses and usage durations of turmeric are also warranted to evaluate its underlying mechanisms of action in patients with NAFLD.

Acknowledgments

This article was written based on data set of Ph.D thesis (NO. D/41) registered in Tabriz University of Medical Sciences, Iran. This study was also supported by Nutrition Research Center, Student Research Committee and the research vice-chancellor of Tabriz University of Medical Sciences, Tabriz, Iran.

Footnote

Conflict of Interests: The authors declare no potential conflicts of interests.

References

1. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology.* 2012;**55**(6):2005–23. doi: 10.1002/hep.25762. [PubMed: 22488764].
2. Cohen JC, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. *Science.* 2011;**332**(6037):1519–23. doi: 10.1126/science.1204265. [PubMed: 21700865].
3. Misra VL, Khashab M, Chalasani N. Nonalcoholic fatty liver disease and cardiovascular risk. *Curr Gastroenterol Rep.* 2009;**11**(1):50–5. doi: 10.1007/s11894-009-0008-4. [PubMed: 19166659].
4. Lim S, Oh TJ, Koh KK. Mechanistic link between nonalcoholic fatty liver disease and cardiometabolic disorders. *Int J Cardiol.* 2015;**201**:408–14. doi: 10.1016/j.ijcard.2015.08.107. [PubMed: 26310987].
5. Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med.* 1991;**324**(17):1149–55. doi: 10.1056/NEJM199104253241701. [PubMed: 2011158].
6. Mallat SG, Aoun M. Hyperhomocysteinemia and its role in chronic renal failure. *Saudi J Kidney Dis Transpl.* 2002;**13**(3):336–43. [PubMed: 18209429].
7. Ballestri S, Lonardo A, Nascimbeni F, Baldelli E, Meschiari E, Odoardi MR, et al. Non-alcoholic fatty liver disease (NAFLD): a novel cardiovascular risk factor. *Intern Emerg Med.* 2012;**7**:33–46.
8. Dogru T, Genc H, Tapan S, Aslan F, Ercin CN, Ors F, et al. Plasma fetuin-A is associated with endothelial dysfunction and subclinical atherosclerosis in subjects with nonalcoholic fatty liver disease. *Clin Endocrinol (Oxf).* 2013;**78**(5):712–7. doi: 10.1111/j.1365-2265.2012.04460.x. [PubMed: 22676641].
9. Chen HY, Chiu YL, Hsu SP, Pai MF, Lai CF, Peng YS, et al. Association of serum fetuin A with truncal obesity and dyslipidemia in non-diabetic hemodialysis patients. *Eur J Endocrinol.* 2009;**160**(5):777–83. doi: 10.1530/EJE-08-0813. [PubMed: 19228823].
10. Ix JH, Shlipak MG, Brandenburg VM, Ali S, Ketteler M, Whooley MA. Association between human fetuin-A and the metabolic syndrome: data from the Heart and Soul Study. *Circulation.* 2006;**113**(14):1760–7. doi: 10.1161/CIRCULATIONAHA.105.588723. [PubMed: 16567568].
11. Mori K, Emoto M, Yokoyama H, Araki T, Teramura M, Koyama H, et al. Association of serum fetuin-A with insulin resistance in type 2 diabetic and nondiabetic subjects. *Diabetes Care.* 2006;**29**(2):468. doi: 10.2337/diacare.29.02.06.dc05-1484. [PubMed: 16443916].
12. Weikert C, Stefan N, Schulze MB, Pischon T, Berger K, Joost HG, et al. Plasma fetuin-a levels and the risk of myocardial infarction and ischemic stroke. *Circulation.* 2008;**118**(24):2555–62. doi: 10.1161/CIRCULATIONAHA.108.814418. [PubMed: 19029462].
13. Wang Y, Chun OK, Song WO. Plasma and dietary antioxidant status as cardiovascular disease risk factors: a review of human studies. *Nutrients.* 2013;**5**(8):2969–3004. doi: 10.3390/nu5082969. [PubMed: 23912327].
14. Ramaswami G, Chai H, Yao Q, Lin PH, Lumsden AB, Chen C. Curcumin blocks homocysteine-induced endothelial dysfunction in porcine coronary arteries. *J Vasc Surg.* 2004;**40**(6):1216–22. doi: 10.1016/j.jvs.2004.09.021. [PubMed: 15622377].
15. Kapoor P, Ansari MN, Bhandari U. Modulatory effect of curcumin on methionine-induced hyperlipidemia and hyperhomocysteinemia in albino rats. *Indian J Exp Biol.* 2008;**46**(7):534–40. [PubMed: 18807758].
16. Oner-Iyidogan Y, Kocak H, Seyidhanoglu M, Gurdol F, Gulcubuk A, Yildirim F, et al. Curcumin prevents liver fat accumulation and serum fetuin-A increase in rats fed a high-fat diet. *J Physiol Biochem.* 2013;**69**(4):677–86. doi: 10.1007/s13105-013-0244-9. [PubMed: 23430567].
17. Sanyal AJ, American Gastroenterological A. AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology.* 2002;**123**(5):1705–25. doi: 10.1053/gast.2002.36572. [PubMed: 12404245].

18. Ahmed MH, Barakat S, Almobarak AO. Nonalcoholic fatty liver disease and cardiovascular disease: has the time come for cardiologists to be hepatologists?. *J Obes.* 2012;**2012**:483135. doi: 10.1155/2012/483135. [PubMed: 23320150].
19. Martin RC, Aiyer HS, Malik D, Li Y. Effect on pro-inflammatory and antioxidant genes and bioavailable distribution of whole turmeric vs curcumin: Similar root but different effects. *Food Chem Toxicol.* 2012;**50**(2):227–31. doi: 10.1016/j.fct.2011.10.070. [PubMed: 22079310].
20. Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. *Nutrients.* 2013;**5**(5):1544–60. doi: 10.3390/nu5051544. [PubMed: 23666091].
21. Selhub J. Homocysteine metabolism. *Annu Rev Nutr.* 1999;**19**:217–46. doi: 10.1146/annurev.nutr.19.1.217. [PubMed: 10448523].
22. de Carvalho SC, Muniz MT, Siqueira MD, Siqueira ER, Gomes AV, Silva KA, et al. Plasmatic higher levels of homocysteine in non-alcoholic fatty liver disease (NAFLD). *Nutr J.* 2013;**12**:37. doi: 10.1186/1475-2891-12-37. [PubMed: 23547829].
23. Ataie A, Sabetkasaei M, Haghparast A, Hajizadeh Moghaddam A, Ataie R, Nasiraei Moghaddam S. An investigation of the neuroprotective effects of Curcumin in a model of Homocysteine - induced oxidative stress in the rat's brain. *Daru.* 2010;**18**(2):128–36. [PubMed: 22615607].
24. Hemati T, Moghadami-Tabrizi N, Davari-Tanha F, Salmanian B, Javadian P. High plasma homocysteine and insulin resistance in patients with polycystic ovarian syndrome. *Iran J Reprod Med.* 2011;**9**(3):223–8. [PubMed: 26396568].
25. Pianpumepong P, Noomhorm A. Isolation of probiotic bacteria from turmeric (Curcuma longa Linn.) and its application in enriched beverages. *Int J Food Sci Nutr.* 2010;**45**(12):2456–62. doi: 10.1111/j.1365-2621.2010.02337.x.
26. Laino JE, Leblanc JG, Savoy de Giori G. Production of natural folates by lactic acid bacteria starter cultures isolated from artisanal Argentinean yogurts. *Can J Microbiol.* 2012;**58**(5):581–8. doi: 10.1139/w2012-026. [PubMed: 22502809].
27. Seyithanoglu M, Oner-Iyidogan Y, Dogru-Abbasoglu S, Tanrikulu-Kucuk S, Kocak H, Beyhan-Ozdas S, et al. The effect of dietary curcumin and capsaicin on hepatic fetuin-A expression and fat accumulation in rats fed on a high-fat diet. *Arch Physiol Biochem.* 2016;**122**(2):94–102. doi: 10.3109/13813455.2015.1120753. [PubMed: 26706937].
28. Haukeland JW, Dahl TB, Yndestad A, Gladhaug IP, Loberg EM, Haaland T, et al. Fetuin A in nonalcoholic fatty liver disease: in vivo and in vitro studies. *Eur J Endocrinol.* 2012;**166**(3):503–10. doi: 10.1530/EJE-11-0864. [PubMed: 22170794].
29. Ismail NA, Ragab S, El Dayem SM, Elbaky AA, Salah N, Hamed M, et al. Fetuin-A levels in obesity: differences in relation to metabolic syndrome and correlation with clinical and laboratory variables. *Arch Med Sci.* 2012;**8**(5):826–33. doi: 10.5114/aoms.2012.31616. [PubMed: 23185191].
30. Ejaz A, Wu D, Kwan P, Meydani M. Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. *J Nutr.* 2009;**139**(5):919–25. doi: 10.3945/jn.108.100966. [PubMed: 19297423].
31. Stefan N, Haring HU. The role of hepatokines in metabolism. *Nat Rev Endocrinol.* 2013;**9**(3):144–52. doi: 10.1038/nrendo.2012.258. [PubMed: 23337953].