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The Effects of *Helicobacter Pylori* Eradication on Liver Function and Metabolic Profile in Non-diabetic Non-alcoholic Steatohepatitis: A 5-year Randomized Clinical Trial

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ABSTRACT

BACKGROUND:

To evaluate the effects of *Helicobacter pylori (HP)* eradication on liver function tests (LFT) and fat content (LFC) in non-diabetic non-alcoholic steatohepatitis (NASH).

METHODS:

This randomized clinical trial included dyspeptic HP infected non-diabetic NASH participants. The intervention arm received HP eradication treatment, while the control arm did not get any HP treatment. In the meantime, the standard management of NASH was performed in both trial arms. Mean alterations in LFT were the primary outcome and the secondary outcomes included the mean changes in LFC and serum metabolic profile. The trial follow-up period was 5 years.

RESULTS:

40 participants (female: 20), with a mean age of 41.58 (±12.31) years, were enrolled in the study. The HP eradication arm included 20 participants (female: 11) with a mean age of 40.25 (±10.59) years, and the control arm consisted of 20 individuals (female: 9) with a mean age of 42.90 (±13.97) years. The tests of within-subjects effects showed a significant decrease in mean serum alanine aminotransferase (ALT; $P=0.007$), triglyceride (TG; $P=0.04$), cholesterol ($P=0.004$), and fasting blood sugar (FBS; $P<0.001$), and an increase in high-density lipoprotein (HDL; $P=0.04$) in both research groups during the study period. The tests of between-subjects effects demonstrated a more significant decrement of FBS in HP eradicated patients than the controls ($P=0.02$). The reduction in waist circumference, aspartate aminotransferase (AST), ALT, alkaline phosphatase, triglyceride, cholesterol, low-density lipoprotein, insulin, and LFC were more prominent in the intervention group than the controls; however, these differences were not statistically significant.

CONCLUSION:

Adding HP eradication treatment to standard NASH treatment showed more therapeutic effect thanthe standard NASH treatment protocol alone regarding the decrement of FBS in participants with dyspeptic non-diabetic NASH. Considering the non-statistically significant improvement in other metabolic indices and LFT in this trial, further studies are recommended.

KEYWORDS:

Non-alcoholic steatohepatitis; *Helicobacter pylori*; Aminotransferase; Fasting blood sugar

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INTRODUCTION

Non-alcoholic steatohepatitis (NASH) has been the leading cause of chronic hepatitis, end-stage liver disease, and liver transplantation in recent years.[1] The burden of disease is growing due to the pandemic of insulin resistance (IR) and metabolic syndrome (MS). Handling the disease complications (such as cardiovascular accidents and cirrhosis) enfaces a great cost for the health care system. A thoughtful approach is to identify and modulate the risk factors involved in the development of steatohepatitis from simple fatty change. The precise mechanisms for this evolution are not clear. However, environmental factors that increase in visceral fat and IR (including diet and bowel microbiome) and genetic backgrounds (that regulate the liver inflammatory responses) are proposed to play a role in the pathogenesis.[2,3]

Helicobacter pylori (HP) is a known pathogen in the gut microbiome. Theoretically, it can damage the gut epithelial barrier and facilitate the entrance of bacterial endotoxins and other hepatotoxic substances to the liver via the portal vein. To define its possible role in NASH establishment, we performed a literature review. A cross-sectional study described the association between active HP infection and NASH in morbidly obese patients.[4] In parallel with the result of the mentioned observation, a meta-analysis concluded the positive association between HP infection and the risk of NASH.[5] On the other hand, our previous short-term trial in patients with dyspeptic NASH showed no correlation between HP eradication and liver function tests and metabolic indices.[6] Meanwhile, a cross-sectional study from Guatemala found no overall relationship between HP seropositivity and NASH.[7] Therefore, we encountered controversial results regarding the relationship between HP and NASH. Heterogeneity in study groups, in view of HP infection phase, the amount of gastric acid output, and degree of IR, would explain the controversial results of published studies. We decided to evaluate the long-term effect of HP eradication on liver function, metabolic indices, and liver fat content (LFC) in a homogenous group of patients with NASH regarding HP infection and metabolic status.

MATERIALS AND METHODS

Study design

The protocol of this parallel, open-label randomized clinical trial was registered in "ClinicalTrials.gov" platform (NCT01654549). The Ethics Committee of Tehran University of Medical Sciences reviewed and approved the protocol (registration number: IR.TUMS.DDRI.REC.1397.004). All the participants filled out written informed consent at the entrance to the project.

Patient enrolment protocol: This project was performed in the outpatient gastroenterology clinic of a tertiary referral hospital from April 2012 to September 2017. All participants between 18 to 45 years with dyspepsia, positive HP serology (IgG), persistent serum aminotransferase levels elevation (more than 40 IU/L), and the evidence of fatty liver in abdominal ultrasound were included. The following subjects were excluded from the study: known cases of chronic hepatitis (alcoholic, viral, autoimmune, Wilson disease, and hemochromatosis), hepatotoxic medications, intravenous drug abuse, diabetes mellitus, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, cirrhosis, any known cancer except for skin cancer, upper gastrointestinal symptoms and alarm signs, peptic ulcer disease, and previous HP eradication. A biomedical statistician, who was unaware of the treatment protocol, generated a random allocation sequence using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA). He assigned the enrolled patients, either to the intervention or control arms, based on the mentioned computer-generated block randomization table using 1:1 allocation.

Trial arms: This trial was composed of two "intervention" and "control" arms. The intervention group consisted of 20 HP positive dyspeptic NASH participants, who underwent successful HP eradication, confirmed by a urea breath test. The control group included 20 HP positive dyspeptic NASH participants without HP eradication. All participants in both trial arms were treated based on the standard NASH treatment guideline.[8]

HP eradication protocol: HP eradication in the intervention arm was performed by quadruple therapy

using omeprazole (20 mg twice daily), amoxicillin (1 gram twice daily), bismuth subcitrate (240 mg twice daily), and clarithromycin (500 mg twice daily) for two weeks.[6] We asked the patients to take back the used packages and empty bottles of medications to evaluate their compliance while using the medications. A gastroenterologist followed the patients every week to check for possible side effects or complications during the eradication phase.

Outcome measures: The primary outcome measures were the changes of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels, from baseline up to five years follow-up visits. Secondary outcome measures were the alterations of metabolic profiles and LFC during the trial period. The investigator registered the values of outcome measures every 3 months.

Study Measurements

Trans-abdominal ultrasound (Hitachi EUB 405 apparatus equipped with a convex 3.5 MHz probe) was used to diagnose fatty liver in this research. The radiologist compared the echogenicity of the right kidney (that is voiding of fat) with the right liver lobe in sagittal view. The criteria used for the diagnosis and staging of fatty liver were described in our previous published explorations.[9,10] All the laboratory measurements, including serum AST, ALT, ALP, fasting blood sugar (FBS), triglyceride (TG), cholesterol (CHOL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were made based on the instructions provided by the kits' manufacturers. These investigations were performed in the standard environment of the hospital medical laboratory. To clarify the measurement details [including waist circumference (WC) and body mass index (BMI)] and the standard reporting units, we refer the respect readers to visit our previous studies.[6,9] The estimation of LFC was done by "liver fat score". It seems to be a valid and reliable formula for the detection of liver fat amounts. This formula is constructed by the variables including serum AST, ALT, insulin values, and metabolic and diabetes mellitus status. Please refer to our past publications to find more details, in view of the applied formula.[6,10]

Sample size calculation

To calculate the sample size, the statistical power analysis method was used. Applying two-sided significant level (α) of 0.05 and the power of 90% ($\beta = 0.1$), a total sample size of 40 individuals was appropriate to identify 1% inter-group difference in ALT.

Statistical analysis

Quantitative variables were reported as mean ± standard deviation (SD). Kolmogorov-Smirnov test was used to assess the normal distribution of the continuous variables. A two-sample *t*-test was applied to compare the mean values of continuous variables (age, follow-up duration, and systolic blood pressure) between the trial arms. To evaluate the categorical variables (sex, ultrasound fatty liver grades, smoking status, hypertension, metabolic syndrome, and dyslipidemia) between the study groups, Chi-square test was used. "Mixed Repeated Measure ANOVA" model was used to compare the changes in the mean outcome variables in each trial arm during the study period (the tests of within-subjects effects). The mentioned model defined the differences in alterations in the mean outcome variables between the trial arms (the tests of between-subjects effects). The statistical analysis was performed using IBM SPSS Statistics v23 (IBM, Armonk, NY). The two-sided *P* values less than 0.05 showed a significant probability of diversity between the dependent and independent variables.

RESULTS

A total number of 166 participants suspected of having NASH were evaluated. The run-in period started in April 2012 and was completed in September 2012. The following participants (n = 126) were excluded: those who refused to participate in the study (n = 5), and those with alcoholic hepatitis (n = 15), viral hepatitis (n = 9), auto-immune hepatitis (n = 3), Wilson's disease (n = 0), hemochromatosis (n = 0), hepatotoxic medications use (n = 6), congestive heart failure (n = 1), chronic kidney disease (n = 14), chronic obstructive pulmonary disease (n = 4), cirrhosis (n = 3), intravenous drug abuse (n = 16), diabetes mellitus (n = 17), any known cancer except for skin cancer (n = 1), family history of upper gastrointestinal cancers (n = 2), significant weight loss (n = 1), anemia (n = 3), gastrointestinal bleeding (n = 7), vomiting (n = 1),

peptic ulcer disease (n=6), and previous HP eradication (n=12). Finally, 40 participants, with a mean age of 41.58 (±12.31) years, were enrolled in the study (Figure 1). The mean follow-up time in the trial was 61.25 (±1.19) months. The baseline characteristic of the studied population according to the trial arms is demonstrated in table 1. There were no statistically significant differences regarding age, sex, ultrasound grading of fatty liver, smoking status, dyslipidemia, metabolic syndrome, hypertension, and systolic blood pressure between trial arms at baseline. No side effects of the medications were found in the study. Pill counts in the follow-up visits contemplated reasonable compliance to therapy, with a mean consumption of 92% of expected tablets (range from 88 to 97), leading to an eradication rate of 100% in the intervention arm.

The laboratory measurements and LFC values according to trial arms during the project are provided in table 2. The tests of "within-subjects effects" showed a significant decrease in mean serum ALT ($P=0.007$), TG ($P=0.04$), cholesterol ($P=0.004$), and FBS ($P<0.001$) and an increase in HDL ($P=0.04$) in both HP eradicated and the control arms from baseline to the end of the follow-up time (table 2). The mean changes of other variables, including the WC ($P=0.53$), BMI ($P=0.54$), AST ($P=0.17$), ALP ($P=0.76$), LDL ($P=0.15$), insulin ($P=0.41$), and LFC ($P=0.16$] were not significant in trial arms during the study period (table 2).

The tests of "between-subjects effects" demonstrated that the decrement of FBS was more prominent in HP eradicated participants than the controls ($P=0.02$; Figure 1). The reduction in WC, AST, ALT, ALP, TG, cholesterol, LDL, insulin, and LFC were more prominent in the intervention group than the controls, although not statistically significant (all $P>0.05$; Figure 1).

DISCUSSION

The main finding in this trial was an enhanced improvement of FBS and potential extra improvement in liver function tests, metabolic indices, and LFC in HP eradicated than the control arm during the 5 years of follow-up.

The decrease in serum levels of AST, ALT, and ALP was higher in HP treatment group than the controls in this study, although not statistically significant, which could be attributed to relative small sample size, and therefore our study power. In fact, the improvement in LFT following HP eradication is in accordance with the recent meta-analysis that suggested the association between HP infection and fatty liver disease.[11] The role of HP in the development of liver cell inflammation has been described.[12] One possible mechanism is the HP induction of gut mucosal permeability and the resultant entrance of bacterial endotoxins and similar immunogenic agents to the liver.[4] Meanwhile, an animal model proposed that the damage to the intestine mucosal barrier results in NASH.[13] On the other hand, some studies showed no association between HP and NASH.[14,15] The discrepancy seen in the current pieces of evidence may stem from several reasons. First, serum aminotransferase levels fluctuate in the course of NASH, thus, measuring these markers at a single time point might not reliably predict the inflammatory status of the disease.[16,17] Second, variations in the HP pathogenic genes, including Cag A. and Vac A. may play a role. In fact, these virulence genes are related to severe gastritis.[18] Additionally, Cag A. virulence factor has been reported to change the gut microbiota and permeability.[19] Thus, the variation in the presence of HP virulence is proposed to affect the severity of NASH.[14]

The decrement of FBS was more significant in HP eradicated participants than the controls in this investigation. This outcome is in parallel with the previous studies, which showed glycemic improvement after HP eradication in participants with diabetes mellitus type 2.[20,21] Our current trial revealed that the improvement in metabolic indices, including lipid profile, insulin, and LFC was more evident in HP eradicated than the control arm. This is in line with the observed positive relationship between HP and metabolic syndrome.[22] Some studies concluded that HP eradication was associated with the significant normalization of lipid profile, IR, proinflammatory cytokines, and LFC.[23-26] On the opposite side, reports exist that described HP eradication had no effects on the metabolic and inflammatory profiles in NASH.[27,28] In regards to the relation between HP and NASH, the variations in race and genetic factors that are involved in regulating the lipid metabolism and hepatocyte inflammatory responses, dietary patterns, and the cultural variations of studied samples need to be considered.[29]

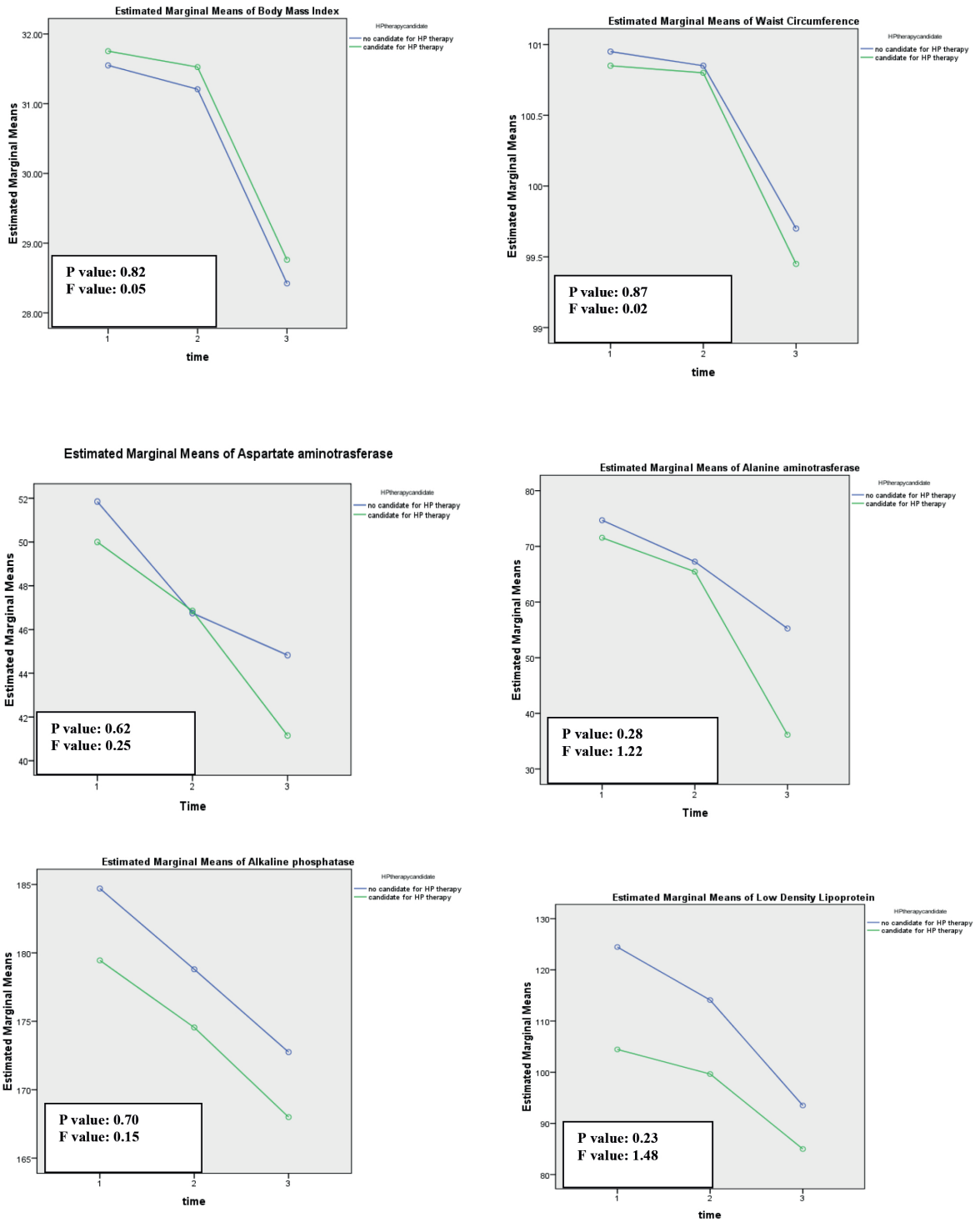

Fig. 1: The laboratory measurements and liver fat content values in trial arms during the study period (tests of between-subjects effects).

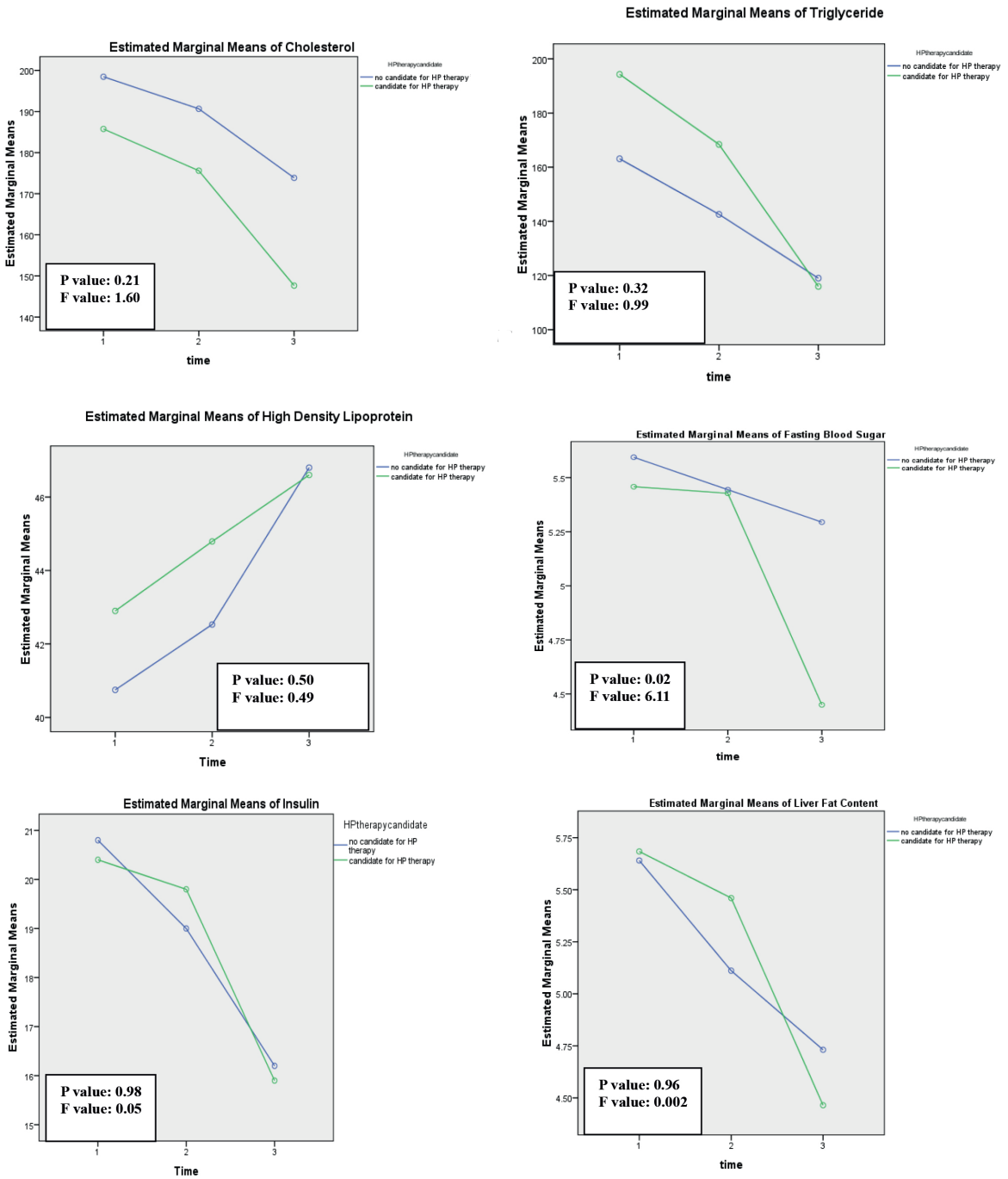

Fig.1: Continued.

The current trial showed that WC and BMI reduction was more prominent in HP eradicated subjects than the controls. This observation is comparable to the finding of a recent meta-analysis, which described the association between HP and overweight/obesity.[30] Contrary to this review, another review indicated a reverse relationship between HP infection and obesity.[31] We believe the controversy between the above-mentioned studies might be in part due to the method used for HP detection, and limitations to match the studied samples, in view of the

Table 1: The baseline characteristics of the studied population according to trial arms

Variables	Intervention arm (n=20)	Control arm (n=20)	P
Age	40.25±10.59	42.90±13.97	0.61
Sex (n, %)			
Male	9 (45.0)	11 (55.0)	0.75
Female	11 (55.0)	9 (45.0)	
Follow-up duration (months)	61.30±1.08	61.20±1.32	0.80
Ultrasound grading of fatty liver (n, %)			
grade 1	16 (80.0)	16 (80.0)	0.76
grade 2	1 (5.0)	2 (10.0)	
grade 3	3 (15.0)	2 (10.0)	
Smoking (n, %)	7 (35.0)	9 (45.0)	0.75
Dyslipidemia (n, %)	17 (85.0)	13 (65.0)	0.27
Metabolic syndrome (n, %)	13 (65.0)	12 (60.0)	1
Hypertension (n, %)	5 (25.0)	7 (35.0)	0.73
Systolic blood pressure			
Baseline (mmHg)	144.3±4.7	142.5±4.4	0.73
At 6 months (mmHg)	131.5±7.5	134.5±9.9	0.29
At 5 years (mmHg)	125.5±6.9	131.5±5.9	0.005**

Values are presented as mean±standard deviation unless specified as number (%).
** $P<0.01$

variables that control the bodyweight, such as ethnicity, smoking, and socioeconomic status. A study proposed that ethnicity influences the effect of obesity in the development of NASH.[32] In spite of the lower frequency of obesity in Asian populations, IR and NASH prevalences are considerable in Asia, suggesting that ethnic diversities in central obesity and visceral fat content could contribute to the variations in the findings of the mentioned study.

The result of our trial showed a significant decrease in serum ALT, TG, cholesterol, FBS, and an increase in HDL in both trial arms during the study period. This finding is in parallel with the previous systematic review results, showing the decrease in aminotransferases and serum metabolic profile in NASH by applying exercise without significant weight changes.[33] These earlier studies suggested that exercise would balance the IR, decrease the entrance of fatty acids to the liver, increase fatty acid oxidation, and reduce liver cell damage.

We believe that the major advantage of our research was the selection of a homogeneous group of participants with regard to IR status. Our previous trial on the effect of HP eradication in NASH included both diabetic and non-diabetic participants.[6] The subgroup analysis in the mentioned study showed promising improvements in LFT and metabolic indices in pre-diabetic individuals. In order to include a homogeneous study sample, we excluded individuals with advanced IR status, and only non-diabetic individuals were enrolled in the current trial. The other strength of this study was the relative long-term follow-up duration, which allowed us to assess the effect of HP eradication on the improvement of metabolic and liver function indices over a longer period.

The lack of liver biopsy was a shortage in this trial. The other limitation was the lack of upper gastrointestinal endoscopy in the study samples to assess the severity of gastric inflammation. Although we excluded the

Table 2: The anthropometric and laboratory measurements and liver fat content in trial arms during the study period (tests of within-subjects effects)

Variables	Timing	Intervention group	Control group	Tests of within-subjects effects	
				P	F
Body mass index	Baseline	31.75±3.57	31.54±4.71	0.54	0.37
	6 months	31.52±3.39	31.20±4.67		
	5 years	28.76±3.18	28.42±4.50		
Waist circumference	Baseline	100.85±2.77	100.95±2.96	0.53	0.39
	6 months	100.80±2.68	100.85±2.79		
	5 years	99.45±2.62	99.70±2.77		
Aspartate aminotransferase	Baseline	50.00±14.55	51.85±11.36	0.17	1.97
	6 months	46.85±13.79	46.75±10.19		
	5 years	41.15±10.30	44.82±10.82		
Alanine aminotransferase	Baseline	71.55±27.05	74.70±33.77	0.007*	5.35
	6 months	65.45±27.22	67.25±26.96		
	5 years	36.15±10.30	55.25±20.07		
Alkaline phosphatase	Baseline	179.45±9.20	184.7±9.20	0.76	0.90
	6 months	174.55±8.16	178.80±8.16		
	5 years	168.000±8.61	172.75±8.61		
Cholesterol	Baseline	185.75±10.29	198.45±10.29	0.004*	6.02
	6 months	175.60±10.17	190.65±10.17		
	5 years	147.65±10.23	173.85±10.23		
Triglyceride	Baseline	194.30±17.75	163.10±17.75	0.04*	3.30
	6 months	168.40±12.82	142.60±12.82		
	5 years	115.95±10.68	119.00±10.68		
Low-density lipoprotein	Baseline	104.45±10.14	124.45±10.14	0.15	2.13
	6 months	99.65±8.39	114.10±8.39		
	5 years	85.00±7.01	93.50±7.01		
High-density lipoprotein	Baseline	42.9±6.71	40.75±5.97	0.04*	1.80
	6 months	44.79±6.79	42.53±8.71		
	5 years	46.60±5.91	46.80±6.87		
Fasting blood glucose	Baseline	5.46±0.1	5.59±0.1	<0.001***	25.88
	6 months	5.43±0.09	5.44±0.09		
	5 years	4.45±0.13	5.29±0.13		
Insulin	Baseline	20.4±1.3	20.80±1.30	0.41	0.69
	6 months	19.80±1.16	19.00±1.16		
	5 years	15.90±1.19	16.20±1.19		
Liver fat content	Baseline	5.68±2.98	5.64±3.56	0.16	2.05
	6 months	5.46±2.85	5.11±3.05		
	5 years	4.46±2.11	4.73±2.91		

Values are presented as mean±standard deviation
* $P<0.05$, *** $P<0.001$

individuals with high risk for upper gastrointestinal malignancy, the selected participants in trial arms could be heterogeneous regarding the presence of peptic ulcer disease. Some pieces of evidence suggest that the production of more gastric acid in the early phase of HP infection is associated with duodenal ulcers and probable weight gain.[34] The mentioned weight gain would predispose the individuals to IR. On the other hand, a decrease in gastric acid in atrophic gastritis in prolonged infection could cause gastric ulcer and concomitant anorexia and weight loss.[35]

While contemplating the role of HP in the progression of NASH, potential confounders, including those contributed to the severity of HP infection such as duration of HP infection, HP virulence factors, and endoscopic and histologic severity of gastritis, as well as individual characteristics such as ethnicity, sex, age, visceral adiposity, and presence of metabolic syndrome components should be addressed.[36]

CONCLUSION

This study suggests that HP eradication might have a positive effect on liver function tests, metabolic profiles, and LFC in dyspeptic non-diabetic NASH patients.

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AUTHORS' CONTRIBUTIONS

Jamali R. and Jamali A. proposed the idea and designed the research. Jamali R. and Tefagh G. diagnosed NAFLD and enrolled participants. Jamali R., Tefagh G., and Ahmadi A. collected the data. Ahmadi A. and Jamali A. performed the statistical analysis and interpreted the data. Karbalai S., Jamali R. and Jamali A. prepared the draft. All authors read and approved the final manuscript.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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