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Original Article

Interaction of Endurance Training and Low-Calorie Diet on Homocysteine Levels and Lipid Profile of Plasma in Males with Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Background: Lifestyle change through diet and exercise is first line therapy for non-alcoholic fatty liver disease (NAFLD), which is associated with increase in risk of cardiovascular disease. Therefore the aim of this study was to investigate the effect of endurance training and low calorie diet on levels of homocysteine and plasma lipid profiles in men with NAFLD.

Methods: 70 patients with NAFLD [weight 89.6±5.8 , age 39.2±0.5 years, body mass index (BMI) 29.4±1.9 kg/m^2] were randomly assigned into four groups(training, diet, combined of training & diet, and control). The endurance training program included moderate intensity training with 55-75% of maximal heart rate for 45 min/session, 3 times/week for 8 weeks. Low calorie diet with an energy deficit of 500 calories of daily energy intake was calculated from 3-day food records of the patients. Blood samples were measured before and after intervention. Homocysteine levels and lipid profiles were measured before and after intervention.

Results: Fifty out of the 70 of the participants completed the trial. There were no serious adverse effects. Result exhibited that interaction of endurance training and low calorie diet decrese blood LDL-C (P=0.001), TG (P=0.006), TC (P=0.011) and homocysteine (P=0.001), whereas increased HDL-C (P=0.001) levels significantly.

Conclusion: This study demonstrated that endurance training and low calorie diet interventions are effectiveness in reducing lipid profile and homocysteine levels among patients with NAFLD. However, combined interventions specifically improves NAFLD and has a better effect.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. Given the high prevalence of NAFLD and its high risk of converting to hepatocellular carcinoma as well as increased risk of cardiovascular disease, it is considered a public health concern [1, 2]. Inflammation, oxidative stress, and insulin resistance are among the major pathophysiological mechanisms of NAFLD in inducing cardiovascular disease [1]. Patients with NAFLD have a number of common and abnormal factors for cardiovascular disease including increased total homocysteine and atherogenic dyslipidemia [3]. Dyslipidemia is characterized by elevated TG and low-density lipoprotein cholesterol (LDL-C) levels as well as

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decreased high-density lipoprotein cholesterol (HDL-C) concentrations [4]. Atherogenic dyslipidemia is one of the reasons for increased risk of cardiovascular disease in people with NAFLD [5].

The accumulation of fat in the liver leads to Hyperhomocysteinemia [6]. It causes structural and functional changes in blood vessels in which oxidative stress may play an important role [7]. Additionally, by affecting cardiovascular endothelium and vascular smooth muscle cells, Hyperhomocysteinemia causes cardiovascular complications including stroke and ischemic heart disease [8]. Therefore, the association of homocysteine with various factors increasing the risk of mortality has attracted the attention of many researchers [9]. Accordingly, reducing homocysteine levels can be an effective goal to prevent the development of NAFLD and its cardiovascular complications [8].

Since there are no approved pharmacotherapies for NAFLD, lifestyle modification involving weight loss, initiated by dietary as well as physical activity/exercise behavior change, is the cornerstone of the management of NAFLD [10]. Nutrition and exercise can affect the homocysteine levels and have positive effects on dyslipidemia [9, 11]. In this regard, Subasi et al. did not see any significant changes in the levels of homocysteine and lipid profiles in women after endurance and strength training for 12 weeks [12]. On the other hand, Lee et al. demonstrated that six months of aerobic exercise and resistance training caused a significant decrease in homocysteine levels [13]. However, Habibian et al. reported that intensive continuous and interval training in inactive women caused a significant increase in homocysteine levels [14]. Therefore, this area warrants further and more comprehensive investigations.

Considering the adverse effects of Hyperhomocysteinemia and dyslipidemia on the cardiovascular system of patients with NAFLD [9], the aim of this study was to investigate the effect of endurance training and low-calorie diet on the levels of homocysteine, total cholesterol, triglyceride, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) in males with NAFLD.

Methods

This was a randomized trial conducted at University of Mohaghegh Ardabili in Ardabil, Iran. The study was approved by the Research Ethics Committee of Ardabil University of Medical Sciences with the code of IR.ARUMS.REC.1395.93. Informed consent was obtained from all subjects before their participation. The participants were recruited from Diabetes Clinic of Ardabil Imam Khomeini Hospital based on calls between December 2016 and February 2017. The project was implemented in May 2017.

The inclusion criteria were diagnosis of grade 2 & 3 NAFLD, age of 35-45 years, body mass index (BMI)≥ 25 kg/m^2, being sedentary (<2 h/week low-intensity physical activity, no moderate or high intensity activity), no smoking, no alcohol consumption, and male sex, as plasma Hcy concentrations are affected by gender. The exclusion criteria were T2DM, presence of cardiovascular diseases, use of drugs affecting weight, alteration of physical activity levels, use of supplementations, contraindications to exercise, and personal desire to leave the study.

Seventy men with clinical grade 1 & 2 NAFLD were randomly assigned into endurance training (n=17), diet (n=18), endurance training with diet (n=18), and control groups (n=17). The participant flow is shown in Figure 1. In this study, the sample size was determined based on the sample size estimation by Fleiss formula of and by taking into account the test power of 0.8, α=0.05, and average changes of 5 units [15]. Based on the estimation, the sample size included 10.97 people. By considering the probability of dropout of participants, 17 individuals were selected for each of the training and control groups as well as 18 individuals for each of diet and combined groups.

All participants were under the supervision of a nutritionist in order for their diet to be controlled carefully during the study. According to the nutritionist's order, to determine the received energy, the participants recorded the nutrition questionnaires one week before and one week after the study (2 weekdays and 1 weekend day). The data obtained from the nutrition note form was converted to gram using home scales, and then was analyzed using N4 nutrition software by the nutritionist. Fourteen individuals were excluded from the study because of the reasons mentioned in Figure 1.

The participants received a supervised eight-week endurance training and low-calorie diet regimen during this period. The endurance training program was selected according to the World Organization of Gastroenterology guidelines for NAFLD, and involved endurance training in the form of running on treadmill [16]. During the training sessions, the first 5 minutes were used for a warm-up, the next 45 minutes involved endurance training, and the final 5 minutes were reserved for recovery. The training intensity was 60% of the maximum heart rate in the first two weeks, 65% of the maximum heart rate in the third and fourth weeks, 70% of the maximum heart rate in the fifth and sixth weeks, and 75% of the maximum heart rate in the last weeks [16]. The training intensity was measured in terms of the maximum heart rate (HRmax=220-age). The nutritionist diet plan was designed as follows: Every day, 500 kcal less than the calculated energy is required. The share of energy supply from macronutrients includes 60% carbohydrate, 25% fat and 15% protein. Use of all food groups is recommended with an emphasis on fruit consumption, vegetable, reduced consumption of salt and food containing simple sugars [17]. After a familiarization session, they attended the university gymnasium weekly, wearing a heart rate (HR) monitor (Polar, RS100, Finland) and were supervised by a trained exercise physiologist. The participants in the endurance training group performed running training on the ergometer at the intensity of the mentioned protocol. The participants in the low-calorie diet group completed a diet diary regimen as mentioned above. The participants in the combined endurance

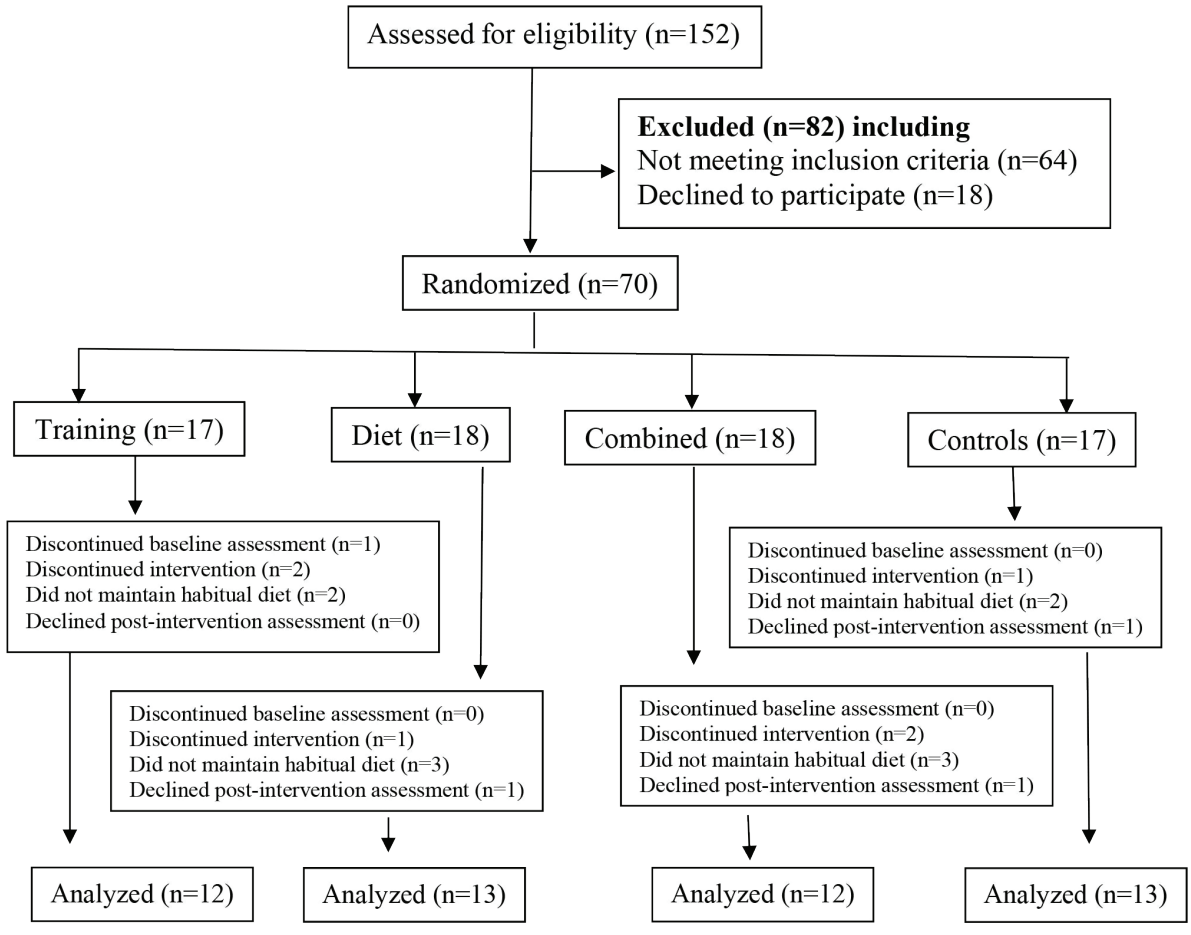

Figure 1: CONSORT diagram showing the flow of participants through the study

training with low calorie diet group performed running training on the ergometer and completed diet regimen simultaneously. Finally, the participants in the control group were asked to maintain their routine activity and eating behaviors for the duration of the intervention.

Biochemical measurements were performed before and after the intervention period. The height and body weight were also recorded (Tanita, Seoul, Korea) and body mass index (BMI) was calculated based on weight (kg)/height (m^2). Blood samples for biochemical and measurements were withdrawn after 12 h of fasting and 48 h after the last training session. The blood samples (20 ml, 10 ml EDTA tube and 10 ml dry tube) were taken from the antecubital vein before the training period and eight weeks after initiation of training. The lipid profile (HDL, LDL, total cholesterol, and triglyceride) was determined using a colorimetric enzymatic method (Bioclin Diagnostic). Homocysteine level was measured using an enzyme-linked immunosorbent assay (Quantikine ELISA) method (R & D System, Minneapolis, USA). All of the above assays were performed according to the manufacturer's instructions.

Data normality was assessed by the Shapiro–Wilk test. Intra-group mean comparisons were made using paired t-test while between-group comparisons were made using two-way ANOVA (version 20.0; SPSS Inc., Chicago, IL). Diet diaries were analyzed by a dietician blinded to group allocation. The average daily intakes of energy and macronutrients were quantified by Foodworks™ (Foodworks 2009, Xyris Software, v6.0.6502). Statistical significance was considered at $p < 0.05$. The values have been reported as means±SE.

Results

The baseline participant characteristics are presented in Table 1. Fifty of the 70 participants completed the endurance training, low-calorie diet regimen, and combined interventions. The study population had a mean age of 39.3±0.3 years, mean height of 174.9±9.4 cm, mean weight of 91.6±5.8, mean BMI of 26.2±1.3 kg/m^2, and mean energy intake of 2931.3±374.2. The baseline participant characteristics are provided in Table 1. There were no adverse events in the course of the exercise training or low-calorie diet regimen. Further, there were no significant differences in the baseline values between the experimental and control groups.

Within subject effects are reported in Table 2. According to the results, endurance training and combined intervention decreased LDL-C, TG, TC, and Homocysteine levels compared with the control group. Also, the endurance training and combined intervention heightened HDL-C levels compared with the control group.

Between subject effects are outlined in Table 3. There was a significant training * diet interaction for HDL-C (P=0.001), LDL-C (P=0.001), TG (P=0.006), TC (P=0.011), and Homocysteine (P=0.001). After the 8-week intervention, the increase in the concentration

Table 1: The participants' descriptive characteristics

Variables		Group			
		Training	Diet	Combined	Control
Age (years)		40.1±2.6	39.7±3.9	38.1±3.6	39.5±2.2
Height (cm)		178.6±4.3	175±6.7	173.9±5.3	172.4±6.7
Weight (kg)	Baseline	91.7±7.5	92.4±4.8	90.1±4.1	90.4±2.6
	Post	88.3±5.9	87.5±3.9	84.2±2.5	91.7±4.8
BMI (kg/m2)	Baseline	26.3±0.7	25.4±0.1	27.2±2.3	26.1±2.1
	Post	25.5±1.5	24.9±1.5	26.1±1.8	26.2±2.3
Energy intake (kcal)	Baseline	2953.9±116.9	2890.6±113.2	2921.6±417.1	2960.7±108.5
	Post	2987.4±228.4	2402.3±106.9	2415.4±236.3	2983.4±124.7

Values are mean±standard deviation. BMI = body mass index

Table 2: Comparison of changes in the measurement variables, before and after the intervention

Variables	Groups	Baseline	Post	P value
HDL-C (mg/dl)	Training	42.1±6.3	47.8±2.9	0.013
	Diet	38.4±3.7	36.1±1.5	0.071
	Combined	39.5±8.11	52.6±2.7	0.001
	Control	44.8±6.22	41.6±5.1	0.385
LDL-C (mg/dl)	Training	124.7±32.62	113.2±10.7	0.026
	Diet	128.3±17.3	123.9±22.1	0.317
	Combined	122.3±32.6	93.2±21.4	0.001
	Control	125.1±26.5	126.6±23.7	0.579
TG (mg/dl)	Training	202.5±21.6	179.9±17.5	0.001
	Diet	199.4±32.8	190.2±19.3	0.063
	Combined	196.2±32.8	156.2±22.1	0.001
	Control	207.1±36.7	215.2±31.5	0.826
TC (mg/dl)	Training	200.3±26.2	181.2±12.2	0.015
	Diet	210.7±17.3	198±32.8	0.067
	Combined	196.2±32.8	154.2±22.1	0.001
	Control	207.1±36.7	215.2±31.5	0.749
Homocysteine(µg/dl)	Training	18.5±2.2	16.5±0.9	0.032
	Diet	19.7±3.1	19.3±1.7	0.728
	Combined	19.4±2.6	15.1±1.8	0.027
	Control	18.6±3.4	19.2±3.9	0.813

Values are expressed as mean±SD. HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; TG=Triglyceride; TC=Total cholesterol

Table 3: Between-subject effects

Variables	Source	Sum of square	Mean square	F	P
HDL-C (mg/dl)	Training	627.3	72.1	17.8	0.006
	Diet	536.2	18.3	5.1	0.091
	Training * Diet	598.7	60.5	29.3	0.001
	Error	12.0	0.2		
LDL-C (mg/dl)	Training	710.9	58.4	26.3	0.013
	Diet	874.2	39.6	17.8	0.231
	Training * Diet	392.7	71.8	5.6	0.001
	Error	391.2	0.5		
TG (mg/dl)	Training	531.02	18.33	6.01	0.02
	Diet	674.49	26.22	13.98	0.07
	Training * Diet	772.11	64.70	5.44	0.006
	Error	17.47	0.16		
TC (mg/dl)	Training	972.66	67.14	36.79	0.01
	Diet	879.43	34.09	31.05	0.13
	Training * Diet	866.50	79.88	12.04	0.011
	Error	15.03	0.71		
Homocysteine(µg/dl)	Training	816.49	75.24	23.02	0.02
	Diet	768.17	83.63	47.19	0.38
	Training * Diet	943.62	51.47	9.28	0.001
	Error	87.03	60.33		

HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; TG=Triglyceride; TC=Total cholesterol

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of HDL-C value was maximum in the combined group as compared with the endurance training group alone or low-calorie diet regimen group alone. Also, after this intervention, the fall in the concentration of LDL-C, TC, TG, and homocysteine levels was highest in the combined group in comparison to the endurance training group alone or low-calorie diet regimen group alone.

Discussion

The aim of this study was to investigate the interaction of endurance training and low-calorie diet regimen on levels of homocysteine, total cholesterol, triglyceride, low-density lipoprotein, and high-density lipoprotein in the males with NAFLD. The results revealed that eight weeks of endurance training and low-calorie diet interaction caused a significant decrease in plasma levels of homocysteine, total cholesterol, TG, LDL-C, and a significant rise in plasma HDL-C in males with NAFLD. Therefore, controlling the energy balance is necessary through diet modification and endurance training to reduce cardiovascular risk in these patients.

In line with the results of this study, Souri et al. revealed that stretch training and aerobic training with an intensity of 50-75% of the maximum heart rate for 10 weeks reduced the mean serum homocysteine in obese and overweight women [12]. Exercise training is likely to contribute to homocysteine level reductions by enhancing the absorption of effective vitamins in the homocysteine cycle, especially vitamins of group B in the intestine [12]. Also, Gondim et al. reported a significant reduction of homocysteine levels after a long-term exercise intervention in obese participants [11]. Possibly, the effect of exercise training on homocysteine levels can be mediated by individual readiness and body response to stress.

Contrary to the results of this study, having investigated the effects of creatinine supplementation on homocysteine metabolism after acute exercise, Deminice et al. reported that plasma levels of homocysteine rose two hours after anaerobic exercise. However, the same result was not found in the acute exercise group [9]. Therefore, creatinine supplementation, independent of the intensity of exercise activity, reduced the levels of homocysteine. Probably, the inhibiting the internal needs of methylation by creatinine reduces the magnitude of homocysteine after doing exercise activity [9]. Habibian et al. reported that intensive interval and continuous training in inactive women resulted in a significant growth in homocysteine. These researchers suggested that the reason was the increased body's need for compounds containing methyl (epinephrine, acetylcholine, creatinine, creatinine), which, together with the methylation reactions, create sufficient induction for methionine metabolism, thereby elevating the homocysteine levels [14].

The possible reason for interaction of the effect of endurance training and low-calorie diet on the reduction of plasma homocysteine levels can be the increased absorption of effective vitamins in the formation of homocysteine and reducing transportation of methyl group for creation of homocysteine [9]. In addition, the conversion of homocysteine to methionine and its reduction can be due to the accelerated activity of coenzyme cobalamin and folic acid due to physical activity. In this regard, s-adenosyl methionine, the most important provider of methyl group agent by obtaining one group of methyl from 5-methyltetrahydrofolate based on a series of biological reactions transfers a methyl root to homocysteine and converts homocysteine to methionine [18]. On the other hand, the conversion of homocysteine to cysteine occurs the sistatyonin beta-sentaz, in which the homocysteine is synthesized by sistatyonin beta-sentaz enzyme with serine whereby the sistatyonin is produced. The produced sistatyonin is degraded irreversibly and convert to cysteine and glutathione [9].

One of factors causing the discrepancy between the results of this study and the previous findings is the health status of participants. Another reason is that during long and heavy exercises, protein metabolism and the blood concentration of certain amino acids change, causing diminished concentration of methionine amino acids. If the quantities of the available methionine decline, it leads to increased methionine production and causes homocysteine accumulation [19].

In addition to homocysteine levels, total cholesterol, TG, LDL-C, and HDL-C values are also associated with cardiovascular disease [20]. The levels of LDL-C and HDL-C improve after moderate or severe intensive exercise [21]. Further, studies on the combined effects of diet and exercise in NAFLD have reported 23-51% reductions in liver fat [10].

In accordance with the results of this study, Moradi et al. reported that exercise causes significantly reduced total cholesterol, TG, and LDL-C levels [22]. In contrast with the results of this study, Sousa et al. reported that football training and diet did not significantly alter the HDL-C levels [23].

According to the study conducted by Askari et al., after eight weeks of aerobic exercise except for total cholesterol and LDL-C levels, no significant changes were observed in other lipid profiles [24]. The reasons for inconsistency of the results include the type of participants, type of modality (intensity, type of training, low-calorie diet), sample size, the method of assessing risk factors, the type of nutrition, and the age range of participants. Increased received calorie and insulin resistance [25] as well as inactivity have a close relationship with cardiovascular disease.

Obesity and NAFLD lead to increased production of LDL and HDL catabolism [25] as well as elevated risk of heart disease in these patients [10]. For each unit increase in BMI, the risk of cardiovascular disease increases by 8%. In contrast, with increase in the physical activity, the risk of developing these diseases diminishes again by 8% [26]. If exercise training leads to weight loss, it helps to improve fat profile and reduce cardiovascular risk factors. Furthermore, exercise and receiving low-calorie diet reduce the variables related to NAFLD and cardiovascular disease such as glycosylated hemoglobin, resting blood pressure, serum liver enzymes, oxidative

stress, and serum cholesterol values [27]. In addition, increased plasma HDL-C may be due to its production in the liver and reduction of liver lipase activity due to sports training [28]. The liver lipase enzyme plays an important role in converting HDL-2 into HDL-3 and converting VLDL to middle density lipoprotein. The level of this enzyme is low in active individuals, which drops in response to exercise it, thereby maintaining the concentration of HDL at higher levels [28]. Therefore, experts have suggested training and diet modifications as the most effective methods of preventing and treating this condition [27].

Several studies have been conducted on lifestyle modifications and NAFLD. The results of these studies suggested that the interaction of endurance training and low-calorie diet is mainly due to the following mechanisms in regulating liver fat metabolism in patients with NAFLD. These interventions probably occur through the activation of lipolysis, upregulation of uncoupling protein-1 and peroxisome proliferatoractivated receptor γ, and alteration of adipocytokines improving NAFLD and decreasing cardiovascular disease [27]. In addition, these modifications attenuate NAFLD through the regulation of intrahepatic fat composition, oxidative stress, inflammation, apoptosis, and autophagy process [10, 29]. These modifications do not only modulate NAFLD by increasing β-oxidation and reducing lipogenesis, they also mitigate oxidative stress through upregulation of the expression of antioxidant enzymes such as catalase (CAT), GPx, and SOD-1 [29]. For hepatic inflammation, endurance training reduces the expression of pro-inflammatory mediators of TNF-α and IL-1β. In addition, these modifications reduce hepatocyte apoptosis through enhancing the p-AKT level and downregulating the apoptotic markers such as caspase-3 [29]. Finally, these modifications induce hepato-protective autophagy, which further regulates lipid metabolism through lipophagy, modulates oxidative stress by elevating the antioxidant enzymes, inhibits hepatic inflammation by digesting pro-inflammatory mediators, and inhibits apoptosis through caspase-9, ATG5, and Beclin-1 dependent pathways [29].

Conclusion

Lifestyle interventions in the form of caloric restriction and increasing the physical activity level with the aim of weight reduction remain the cornerstone of treatment of patients with NAFLD. The present study revealed that the eight weeks of endurance training and low-calorie diet significantly reduced plasma levels of homocysteine, total cholesterol, TG, and LDL-C, while significantly enhancing plasma HDL-C levels in men with NAFLD. So, controlling the energy balance through dietary modification and endurance training is necessary to reduce cardiovascular risks in these patients.

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Conflict of interest: None declared.

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